Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 24, 2015 1:00 - 5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

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
- 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
- A. Initial Pediatric SSRI High Dose Prior Authorization Criteria — T. Williams (OSU)
  1. Revised Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- B. Codeine PA Criteria Update — A. Gibler (OSU)
  1. Revised Criteria
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA

III. PREFERRED DRUG LIST NEW BUSINESS
- A. Asthma and COPD Class Updates — K. Sentena (OSU)
  1. Asthma and COPD Class Updates
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- B. Diabetes Class Updates — K. Sentena (OSU)
  1. Non-insulin Diabetes Agents Class Updates
  2. Public Comment
  3. Discussion of Clinical Recommendations to OHA
- C. Drug Class Literature Scans — A. Gibler (OSU)
  1. Oral Multiple Sclerosis Drugs
  2. Growth Hormones
  3. Inflammatory Bowel Agents
  4. Alzheimer's Agents
  5. Public Comment
  6. Discussion of Clinical Recommendations to OHA

D. Sacubitril/Valsartan New Drug Evaluation — A. Gibler (OSU)
1. Sacubitril/Valsartan (Entresto™; LCZ696) NDE
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

E. Ivabradine New Drug Evaluation — A. Gibler (OSU)
1. Ivabradine (Corlanor®) NDE
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

F. Influenza Class Update — A. Gibler (OSU)
1. Influenza Antiviral Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS

A. Modafinil/Armodafinil Drug Use Evaluation — K. Ketchum (OSU)
1. Drug Use Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

B. Tetracyclines Drug Use Evaluation — T. Williams (OSU)
1. Drug Use Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. Low Dose Quetiapine Policy Evaluation — K. Ketchum (OSU)
1. Policy Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

D. Clinical Review of Existing Prior Authorization Criteria — A. Gibler (OSU)
1. Tesamorelin for injection
2. Becaplermin topical gel
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	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
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
Vacant	Physician			December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2015
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
Vacant	Physician			December 2015

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 30, 2015 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

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: Cathy Zehrung, RPh; Phillip Levine, PhD; Tracy Klein, PhD., FNP; James Slater, PharmD; William Origer, MD; Caryn Mickelson, PharmD;

Members Present by Phone:

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Amanda Meeker, PharmD; Andrew Gibler, PharmD; Dee Weston; Jamal Furqan; Linnea Saris; Kha Vu, PharmD Candidate

Staff Present by Phone: Sherri Willard Argyres, PharmD

Audience: Jamie Tobitt (Vertex)*; Connie Brooks (Vertex); Gregg Rasmussen (Vertex); Shane Hall (Purdue); Steve Hall (Boehringer Ingelheim)*; Jim Graves (BMS); Don Stecher (Novartis); Mary Kernhus (Novartis)*; Jeana Colabianchi (Sunovion); Stephanie Kendall (J&J); Tina Andrews, PharmD; Lisa Allen (Vertex); Leslie Fox (J&J); David Engen; Dana Evans (Genentech)*; Jody Daniels (GSK); Amy Burns (AllCare Health); Bonnie Jiron (AllCare Health); Jo Choi (AllCare Health); Pat Wiseman (Astra Zeneca)*; Joshua Lee (Astra Zeneca)*; Deron Grothe (Teva); Cheryl Fletcher (AbbVie); Stuart O'Brochta (Gilead)*; Christine Oh (Teva)*; Mark Fledger (Novartis); Rich Thorpe (Astellas)*; Shelly Dhir (VIIV)*; Shawn Madison (VIIV); Mike Powers (OHSU)*; Gopal Allada (OHSU)*; Signe Fransen (BMS)*; Bobbi Joe D (BMS); Chris Conner (BMS); Chris Hoem (Gilead); Stephanie Persaud (OSU); Irena Surina (Pacific U); Mindy Schimpf (UCB); George Dela Corda (Mylan); Soumi Gupta (Janssen)*; Joe Schieck (Allergen); Geoffrey L'Heurrux (HIV Aliance)*; Darlene Halverson (Novartis); Debby Parish; BJ Cavnor (One in Four)*; Timothy McFerron (Alkermes); Brandie Feger (Western Oregon Advanced Health); David Barhoum (Genentech)

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions were made by Committee members and staff.

b. Mr. Citron reported there are no new conflicts of interest to declare.

c. Approval of agenda and minutes presented by Dr. Origer. (pages 5 - 10)

ACTION: Motion, 2nd, All in Favor. Approved.

d. Department updates for OHA.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 11 - 15)
Mr. Citron presented the quarterly utilization report.

b. ProDUR Report (pages 16 - 18)
Mr. Holsapple presented the quarterly ProDUR reports.

c. RetroDUR Report (pages 19 - 22)
Dr. Williams presented the quarterly RetroDUR reports.

III. DUR OLD BUSINESS

a. Ivacaftor Prior Authorization Criteria (pages 23 - 35)
Dr. Herink presented the following criteria changes:

1. Approve use for and include those ages 2 – 5 years with gating mutations in the proposed PA Criteria.
2. Refer PA requests for R117H to Medical Director for manual review.
3. Change the length of authorization on header from 30 days to 60 days and include a 10% change from baseline to the BMI renewal criteria.

Public Comment:
Jamie Tobitt from Vertex presented public comment.
Mike Powers presented public comment.
Gopal Allada presented public comment.

ACTION: Motion, 2nd. Approved.

b. Pediatric SSRI High Dose DUE Clarification (pages 36 - 37)
Dr. Williams presented the following revised criteria:

1. Approve updated PA criteria as presented for children <5 years old.

ACTION: Motion, 2nd. Approved.

c. Rifaximin Prior Authorization Criteria (pages 38 - 39)
Dr. Gibler presented the following clarification and PA criteria update:

1. Approve updated PA criteria as presented. Change approval from lifetime to one year.

ACTION: Motion, 2nd. Majority, 1 opposed. Approved.

d. Codeine Prior Authorization Criteria (pages 40 – 42)
Dr. Gibler presented the following revised criteria:

1. Approve PA criteria as presented for children <18 years old.
2. Change question #2 to #3 and instead ask if it is for an OHP funded condition. Perform RetroDUR for age and prescriber education.

ACTION: Motion, 2nd. Approved.

e. Leuprolide Hormone Therapy Prior Authorization Criteria (pages 43 – 44)
Dr. Gibler presented the proposed updated criteria.

1. The committee rejected the updated PA criteria as presented.
2. Committee asked staff to solicit input from a pediatric endocrinologist and to evaluate cross-sex hormone treatments.

ACTION: Motion not approved, and one abstained.

IV. DUR NEW BUSINESS

a. HIV Class Review / Drug Use Evaluation (pages 45 – 77)
Dr. Gibler and Ms. Ketchum presented the following review and evaluation:

1. Create voluntary Preferred Drug List (PDL) class for all HIV antiretroviral drugs and combination products.
2. Designate all drugs as preferred at this time.
3. Work with established, high Medicaid volume HIV clinics to try and identify ARV regimens with broad tolerability and high viral response rates in most patients and that have favorable or equivalent comparative price (preferred) and try to identify ARV regimens with common tolerability problems or lower viral response rates in most patients and with an unfavorable comparative price (non-preferred).

Public Comment:
Stuart O'Brochta from Gilead provided public comment.
Soumi Gupta from Janssen provided public comment.
Signe Fransen from BMS provided public comment.
Dr. Geoffrey L'Heurex from HIV Alliance provided public comment.
BJ Cavnor from One in Four proved public comment.

ACTION: Motion, 2nd. Approved.

b. Antiplatelet Class Update and Policy Evaluation (pages 78 – 105)
Dr. Herink and Ms. Ketchum presented the following class update and policy evaluation:

1. Continue to PA policy and update with proposed changes.
2. Implement a retrospective safety net program to identify patients that do not start antiplatelet therapy within 14 days for additional transition assistance with a focus on insuring patients qualifying for DAPT are not discontinued prematurely.
3. Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit.
4. Evaluate comparative costs of other antiplatelet drugs in executive session for PDL changes.

***ACTION:** After executive session. All in favor. Approved.

5. *Make cilostazol preferred.
6. *No other changes to PMPDP.

Public Comment:
Joshua Lee from Astrazeneca provided public comment.

c. Tetracyclines Drug Use Evaluation (pages 106 – 116)
Dr. Williams presented the following drug evaluation:

DUE not presented, deferred, will be added to the September P&T agenda.

d. Low Dose Quetiapine Policy Evaluation (pages 117 – 128)
Dr. Meeker and Dr. Herink presented the following policy evaluation:

Policy Evaluation not presented, deferred, will be added to the September P&T agenda.

e. Modafinil / Armodafinil Drug Use Evaluation (pages 129 – 153)
Ms. Ketchum presented the following drug use evaluation:

DUE not presented, deferred, will be added to the September P&T agenda.

f. Clinical Review of Existing Prior Authorization Criteria (pages 154 – 157)
Dr. Gibler presented the following criteria review:

Criteria not presented, deferred, will be added to the September P&T agenda.

V. PREFERRED DRUG LIST NEW BUSINESS

a. Secukinumab New Drug Evaluation (pages 158 – 173)
Dr. Willard presented the following new drug evaluation:

1. Approve modifications to the Oregon Health Plan (OHP) for Prior Authorization (PA) criteria for systemic Biologicals and topical drugs for psoriasis. For ease of administration, PA criteria for topical therapies were removed from the systemic biological PA criteria and incorporated into the topical drugs for proposed psoriasis PA criteria.
2. Incorporate secukinumab into the OHP PA criteria for Biologicals and limit its use to patients with moderate to severe psoriasis, as diagnosed by a dermatologist and defined by the OHA, who have failed first-line therapies as defined by the OHA.
3. Evaluate relative costs in executive session for PDL decision making.

Public Comment:
Mary Kemhus from Novartis provided public comment.

***ACTION:** After executive session. All in favor. Approved.

4. *Maintain secukinumab as non-preferred.
5. *No changes to the PMPDP.

b. Idiopathic Pulmonary Fibrosis (IPF) New Drug Evaluation (pages 174 – 198)

Dr. Gibler presented the following new drug evaluation:

1. Pirfenidone New Drug Evaluation (pages 174 – 187)
   Recommended adopting Idiopathic Pulmonary Fibrosis (IPF) Agents PA criteria and apply to pirfenidone to assure appropriate utilization.

2. Nintedanib New Drug Evaluation (pages 188 – 198)
   Recommend requiring prior authorization for nintedanib to limit use to appropriate patients.

3. Add IPF Class to PMPDP and review comparative costs in the executive session.

***ACTION:** After executive session. All in favor. Approved.

4. *Make pirfenidone and nintedanib non-preferred, no grandfathering necessary.

c. Intranasal Allergy Inhalers Class Review (pages 199 – 215)
   Dr. Gibler presented the following drug class review:

1. Create PDL class for "Intranasal Allergy Drugs" and prefer at least one intranasal corticosteroid due to evidence of effectiveness for OHP-funded conditions.
2. Approve updated PA criteria as presented.
3. Review comparative costs in executive session.

Public Comment:
Christine Oh from Teva provided public comment.

***ACTION:** After executive session. All in Favor. Approved.

4. *Make non-steroid products PDL = N due to lack of data
5. *Make FLUTICASONE PROPIONATE (Legend) PDL = Y
6. *Make all other steroid products PDL = N, no grandfathering

d. Antifungals Class Update (pages 216 – 241)
   Ms. Ketchum presented the following class update:

1. Update the prior authorization criteria as proposed to reflect changes to the OHP prioritized list.
2. Maintain open access to fluconazole.
3. Maintain clinical prior authorization requirement for griseofulvin, itraconazole, and terbinafine.
4. Make ketoconazole non-preferred due to increased risk.
5. Allow hematology, oncology and infectious disease specialty prescribers approval for voriconazole to cover invasive aspergillosis.
6. Review comparative costs in executive session.

Public Comment:
Richard Thorpe from Astellas provided public comment.

***ACTION:** After executive session. All in favor. Approved.

7. *Make ketoconazole non-preferred and no grandfathering.
8. *No other PMPDP changes recommended.

e. Calcium Channel Blockers Class Update (pages 242 – 253)
   Dr. Wu presented the following class update:

1. Create a “Combination Antihypertensive” PDL class to include fixed-dose combination products containing two antihypertensive drugs and combinations containing an antihypertensive drugs with a non-hypertensive drug (e.g., statin)
2. Evaluate comparative costs in executive session.

***ACTION:** After executive session. All in favor. Approved.

3. *Make the following fixed dose combinations preferred:
    - AMLODIPINE-ALMESARTAN
    - ENALAPRIL-HYDROCHLOROTHIAZIDE
    - LISINOPRIL-HYDROCHLOROTHIAZIDE
    - LOSARTAN-HYDROCHLOROTHIAZIDE
    - METOPROLOLSUCCINATE-HYDROCHLOROTHIAZIDE
    - OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE
    - OLMESARTAN-HYDROCHLOROTHIAZIDE
    - PROPRANOLOL-HYDROCHLOROTHIAZIDE
4. *Make all other products in Combination Antihypertensives class non-preferred.
5. *No other PMPDP changes recommended.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

Initial Pediatric SSRI Antidepressant – Daily Dose Limit

Goals:

- Approve only for covered OHP diagnoses.
- Limit risk of new-onset of deliberate self-harm thoughts and behaviors, or suicidality associated with initiation of antidepressant therapy at above recommended doses

Length of Authorization:

- Up to 12 months

Requires PA:

- Any SSRI in children 0-4 years of age.
- Any daily SSRI dose higher than maximum dose in the table below for patients <25 years of age on date of first antidepressant claim (i.e. no claim for any antidepressant in Specific Therapeutic Classes H2H, H2S, H2U, H7B, H7C, H7D, H7E, H7J, H8P or H8T in the 102 days prior)

GSN	SSRI	Age-specific Maximum Initial Daily Dose (mg)			
		Age range (years)			
		5-9	10-15	16-19	20-24
70991, 46206, 46204, 46203, 46205	citalopram	10	10	20	20
50712, 51642, 51698, 50760	escitalopram	5	10	10	10
46219. 46216, 46217, 47571, 46215, 46214, 46213	fluoxetine	10	10	20	20
46222, 46224. 46225, 46223, 46226, 53387, 53390, 53389, 53388,	paroxetine (immediate release)	10	10	20	20
46229, 46228, 46227, 46230	sertraline	25	25	50	50

Note: Paroxetine extended release and fluvoxamine are restricted to use in adults

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the patient under 5 years of age?	Yes: Go to #3	No: Go to #~~5~~4
3. Is the request from a child psychiatrist or was the regimen developed in consultation with a child psychiatrist?	Yes: Approve for 12 months	No: Pass to RPH; Deny Recommend provider seek a consultation with a child psychiatrist, such as the no-cost/same-day consultation service of OPAL-K. www.ohsu.edu/OPALK

Approval Criteria		
4. Is the patientclient being treated for funded diagnosesis on the OHP List of Prioritized Services?	Yes: Go to #5	No: Pass to RPH; Deny, (Diagnosis not funded by OHP)
5. Has the patient been treated previously (within the last 6 months) with antidepressants a SSRI and is the dose at or below the maximum recommended daily dose listed above?	Yes: Approve for 12 months.	No: Go to #6
6. Is the requested dose above the recommended initial dose listed in the table above for the patient's age (i.e. was the days' supply entered correctly, is the patient's age accurate)?	Yes: Pass to RPh. Go to #7.	No: Approve 12 monthsDirect Pharmacy to correct and reprocess
7. Are there clinical circumstances that justify an increased dose?	Yes: RPh to evaluate on a case-by-case basis.	No: Deny for medical appropriateness Recommend provider consider lowering the initial dose and/or seek a consultation with a child psychiatrist, such as the no-cost/same-day consultation service of OPAL-K. www.ohsu.edu/OPALK

P&T/DUR Review: *9/15 (TW); 7/15; 5/15; 11/14*
Implementation: ***TBD***

Codeine

Goal(s):

- Promote safe use of codeine in pediatric patients

Length of Authorization:

Up to 3 days

Requires PA:

- All codeine products for patients under 13 years of age
- All codeine *analgesic* products for patients aged 13 through 17 years

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. What is the age of the patient?	Ages 0-12 years: Pass to RPh. Deny; medical appropriateness	Ages 13-17 years: Go to #3
3. Is the prescription for an OHP-funded condition?	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP
4. Has the patient recently undergone tonsillectomy or adenoidectomy?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #5
5. Does the dose exceed 240 mg per day?	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve no more than 3-day supply

P&T / DUR Review: *7/15 (AG)*
Implementation: *TBD*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
PhCollege of Pharmacy 20 | **Fax** 503-947-1119

Class Update: Asthma / COPD Medications

Month/Year of Review: September 2015 **Date of Last Review:** July 2014

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

Purpose for Class Update:
The asthma/chronic obstructive pulmonary disease (COPD) drug classes will be reviewed for updated evidence to incorporate into the recommendations provided to the Oregon Health Plan (OHP). The last update was in July 2014. Evidence since that time will be reviewed.

Research Questions:

1. Is there new comparative evidence on the efficacy/effectiveness of treatments for asthma or treatments for COPD?
2. Is there new comparative evidence of harms associated with medications used to treat asthma or COPD?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which treatments for asthma or COPD differ in efficacy/effectiveness or frequency of adverse events?

Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of COPD. Evidence-based recommendations in new clinical practice guidelines from The Global Initiative for Chronic Obstructive Lung Disease (GOLD), The American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS), and the Veterans Administration (VA)/Department of Defense (DoD) do not differentiate between drugs within a pharmacological class.[1-3] Therefore, these guidelines cannot be used to support placement of specific therapies on Practitioner-Managed Prescription Drug Plan (PMPDP).[1-3]
- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of asthma. New evidence primarily focuses on the use of omalizumab for severe asthma and continues to support the recommendation to reserve omalizumab to patients with allergic asthma who have failed other treatments.[4-6]
- There is insufficient new comparative safety data for the treatment of COPD or asthma. New evidence primarily focuses on individual treatments and do not support a change to current placement of therapies for asthma or COPD on the Preferred Drug List (PDL).[4,7-12]
- Two new formulations of drug products for COPD previously reviewed by the Pharmacy & Therapeutics Committee were identified. Both products were approved by the FDA based on short-term, 24-week studies that evaluated surrogate outcomes of lung function.
    - Tiotropium/olodaterol (Stiolto™ Respimat®) is indicated for long-term management of COPD. Tiotropium is a preferred inhaled anticholinergic for COPD and olodaterol is a non-preferred long-acting beta-agonist for COPD. Over 5,000 patients from two replicate studies with moderate to very

severe COPD were studied for 52 weeks. Patients were randomized to one of 5 treatment arms: tiotropium 2.5 mcg, tiotropium 5 mcg, olodaterol 5 mcg, tiotropium 2.5 mcg/olodaterol 5 mcg and tiotropium 5 mcg/olodaterol 5 mcg. There is moderate level of evidence that tiotropium/olodaterol fixed-dose combination products are superior compared to its monotherapy components for the outcomes of change from baseline in FEV_1 AUC_{0-3hr} ($p<0.0001$ for all comparisons) and trough FEV_1 ($p<0.05$ for all comparisons) at 24 weeks. There is insufficient evidence of comparative efficacy or safety between tiotropium/olodaterol and other drugs for the management of COPD.[13]

- Fluticasone furoate (Arnuity™ Ellipta®) is an ICS indicated for the maintenance treatment of asthma in patients 12 years and older. Fluticasone furoate demonstrated superiority over placebo with a mean difference in baseline evening trough FEV_1 of 146 mL (95% CI, 36 to 257 mL; p=0.009) at 24 weeks.[14]

- A new indication for asthma in patients 18 years of age or older was identified for fluticasone furoate/vilanterol (Breo® Ellipta®). Approval for asthma by the FDA for the 100/25 mcg and 200/25 mcg dose of fluticasone furoate/vilanterol was based on short-term, 12 to 24-week studies.[27]
  - There is moderate quality evidence that the once-daily fixed dose combination products are more effective than their fluticasone furoate monotherapy counterparts in the ability to improve weighted mean FEV_1 (0-24 hours) from baseline. In addition, fluticasone furoate 100 mcg/vilanterol 25 mcg decreased time to first asthma exacerbation compared to fluticasone furoate 100 mcg alone (HR 0.80; 95% CI, 0.64 to 0.99; p=0.036).[27]

Recommendations:

- No PDL recommendations for the tiotropium/olodaterol, fluticasone furoate or fluticasone furoate/vilanterol products can be made at this time. Evaluate comparative drug costs in the executive session.
- Create new PDL class for long-acting muscarinic antagonist/long-acting beta-agonist (LAMA/LABA) fixed-dose combination inhaler products.
- Re-organize and modify clinical PA criteria to promote step-therapy that is consistent with Oregon Asthma Guidelines and with medical evidence for COPD (see **Appendix 3**):
  - All non-preferred LABA inhalers must go through the LABA PA criteria for appropriate step therapy.
  - All non-preferred inhaled corticosteroids (ICS) must go through the ICS PA criteria for appropriate step therapy.
  - All non-preferred LABA/ICS combination inhalers must go through the LABA/ICS clinical PA criteria for appropriate step therapy.
  - Create new PA criteria for LAMA/LABA products. All LAMA/LABA combination inhalers must go through the LAMA/LABA PA criteria for appropriate step therapy.
  - Remove existing clinical PA for “asthma controllers” and indacaterol. Drugs under these PAs will be incorporated into the ICS or LABA PA criteria.
  - Remove PA for leukotriene inhibitors. Non-preferred leukotriene inhibitors will go through the generic non-preferred PDL PA.
  - Clerical changes to the roflumilast PA criteria.

Previous Conclusions:

- Overall findings from DERP systematic review did not suggest that a single medication within any of the classes evaluated is significantly more effective or harmful than other medications within the same class in the treatment of persistent asthma or COPD.[15]
- There is moderate quality evidence that ICS do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. There are no head trials comparing ICSs in he treatment of COPD.[15]
- For patients with COPD, results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low strength of evidence that treatment with ICS increases the risk of serious pneumonia.[15]

- Umeclidinium demonstrated a statistically and clinically significant increase in mean change from baseline in the change from baseline FEV_1 relative to placebo (115 mL; 95% CI 76 to 155). There is insufficient comparative evidence demonstrating superior efficacy or safety of umeclidinium to other available agents.[16]
- There is low quality evidence that mometasone (Asmanex®) HFA improves change from baseline mean trough FEV_1 at 12 weeks versus placebo (mometasone HFA 100mg difference from placebo 0.12 L; 95% CI 0.05 to 0.2). There is insufficient evidence to determine the efficacy and safety of mometasone HFA compared to mometasone Twisthaler.[17]
- There is moderate quality evidence that once daily umeclidinium/vilanterol is effective at improving lung function in patients with moderate to severe COPD, as measured by the change from baseline in trough FEV_1 compared to placebo (0.17 L; 95% CI 0.13-0.21; $p < 0.001$). Trials have been short-term, and the long-term safety and efficacy of umeclidinium/vilanterol is unknown. There is insufficient evidence to determine the comparative efficacy of umeclidinium/vilanterol. There is insufficient evidence to draw conclusions about the ability of umeclidinium/vilanterol to decrease exacerbations, reduce shortness of breath, or improve quality of life.[18-20]
- Serious adverse events were similar among treatment groups versus placebo. The most common adverse events are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain and chest pain (all ≥1% of patients and more common than with placebo).[18-20]
- There is insufficient evidence for differences in subpopulations in which umeclidinium/vilanterol is more effective or safer.
- There is low quality evidence of no difference in mean change in lung function from baseline to 24 weeks, as measured by trough FEV_1, between olodaterol 5 mcg daily via Respimat inhaler and formoterol 12 mcg twice daily.[21,22]
- There is low quality evidence that once daily olodaterol improves lung function from baseline to 24 weeks in patients with moderate to severe COPD compared to placebo, as measured by FEV_1 and FEV_1 area under the curve from 0 to 3 hours (AUC0-3). This improvement in lung function is not considered clinically meaningful but may be explained in the context that use of other COPD medications were permitted during the study periods.[21,22]
- There is insufficient evidence that olodaterol decreases COPD exacerbations, hospitalizations, mortality or health-related quality of life. There is low quality evidence that olodaterol does not improve dyspnea compared to placebo.[21,22]

Previous Recommendations:

- Due to no evidence demonstrating clinical superiority of umeclidinium/vilanterol over current agents, the Committee recommended making it non-preferred on the PMPDP and applies prior authorization criteria to ensure it is being used appropriately and limit its use to patients with COPD.
- Due to no evidence demonstrating clinical superiority or safety of mometasone HFA over current agents, the Committee recommends making it non-preferred. Due to no evidence demonstrating clinical superiority, the Committee also recommended designating flunisolide HFA as non-preferred on the PMPDP.
- The Committee agreed with the staff to reorganize the PMPDP drug classes into: long-acting bronchodilators, short-acting beta-agonists, anticholinergic inhalers, combination inhalers, inhaled corticosteroids, and miscellaneous pulmonary drugs.
- After comparative cost consideration in executive session, the Committee recommended no changes to the PMPDP.
- Designate olodaterol as non-preferred due to lack of quality evidence demonstrating clinical effectiveness.

Background:

ASTHMA

Asthma is a chronic inflammatory condition of the lungs resulting in airway obstruction, bronchial hyperresponsiveness and airway edema. Genetics and environmental factors are thought to contribute to asthma development. A 2013 report on the Burden of Asthma in Oregon cited 3.5-4% of the OHP population as having an asthma diagnosis.[23] Total National asthma costs were projected to be over $20 billion in 2010.[23]

Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis is confirmed by spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use), airway obstruction that is at least partially reversible and exclusion of other potential diagnoses. Asthma is characterized as being intermittent or persistent (further divided into mild, moderate or severe).[24]

Asthma treatment can be divided into two categories, quick-relief medication and long-term control medications. The Expert Panel Report 3 (EPR3) recommends asthma treatment be approached in a stepwise manner based on the severity of asthma symptoms.[24] Those patients with persistent asthma require long-term control medications to contain the underlying inflammation associated with asthma. Inhaled corticosteroids (ICS) are the preferred maintenance therapy for all patients with persistent asthma. If additional therapy is required to control asthma symptoms, LABAs are recommended in combination with ICS.[24] Other maintenance therapy options include leukotriene inhibitors immunomodulators, methylxanthines, cromolyn sodium and nedocromil. SABAs, anticholinergics and systemic corticosteroids are recommended for acute symptom management.

Outcomes used in asthma trials are FEV_1, asthma exacerbations, hospitalization, emergency room visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used since it is highly reproducible. Minimally important values from research in COPD patients suggest minimally important FEV_1 changes range from 100-140 ml.[25]

COPD

COPD is a chronic respiratory disorder characterized by reduced expiratory flow due to irreversible airway inflammation. Airway narrowing, hyperinflation and impaired gas exchange are pathological changes associated with COPD. The most common cause of COPD is airway irritation, usually from cigarette smoking. In rare cases alpha-1 antitrypsin (AAT) deficiency has been implicated in the development of early onset COPD. It is estimated almost 6% of Oregonians were diagnosed with COPD in 2011.[26] Forty-one percent of these individuals were on at least one daily treatment for COPD.[26]

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of FEV_1/FVC <0.70), symptom severity, risk of exacerbations and comorbidities.[1] COPD is classified into four stages based on spirometric measurements of FEV_1/FVC; grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (very severe) (Table 1). The GOLD guidelines recommend therapeutic approaches based on disease burden as well as FEV_1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations).[1] This type of classification system shifts the focus from including just FEV_1 measurements, as these are not always indicative of COPD status. Important outcomes to access the effectiveness of therapies include: functional capacity, QoL, dyspnea, exacerbation rate and/or severity, mortality and harms. FEV_1 is the most common surrogate outcome used in studies to determine therapy effectiveness. Minimally important FEV_1 values for COPD changes have not been clearly defined but are suggested to range from 100-140 ml.[25]

Table 1. Classification of COPD Based on GOLD Guidelines*[1]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV_1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV_1 < 50% predicted
GOLD 4	Very severe	FEV_1 < 30% predicted

* For patients with a FEV1/FVC < 0.70

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management, usually starting with monotherapy and progressing to combination regimens. SABAs are recommended for acute management and bronchodilator therapy (LABAs and LAMAs) are used as monotherapy or in combination for maintenance treatment for chronic, stable COPD.[1] ICS are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA therapy. SAMAs are appropriate for patients currently well controlled. No treatment has been shown to alter the long-term progression and decline in lung function associated with COPD.[1]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were 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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, 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 drugs, indications, and 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 – Inhaled Corticosteroids in Children with Persistent Asthma: Effects on Growth

A search of the literature ending in January 2014 evaluated the use of ICS in children (up to 18 years) with persistent asthma and the impact on linear growth.[7] Differing aspects of treatment utilization (e.g., dose, length of exposure, age of child, disease severity) were also explored. Twenty-five trials were identified that included 8471 children. Included trials were at least 3 months in duration and up to 6 years. Treatments given at low or medium doses were the following: beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate and mometasone furoate.

In placebo or non-steroidal comparisons of 14 trials, one year of ICS treatment reduced linear growth velocity, MD -0.48 cm/y, 95% CI -0.65 to -0.30, p value <0.0001 (moderate quality of evidence).[7] There was significant heterogeneity across trial results. In children treated for 3-5 months there was no significant difference between ICS and placebo. ICS treatment ranging from 6-8 months in duration demonstrated decreased linear growth velocity, based on 2 trials of 369 participants.

Analysis of 3275 children on ICS for over one year found change in height from baseline to be reduced based on moderate quality of evidence (MD -0.61 cm/y, 95% CI -0.83 to -0.38, $p < 0.00001$).[7] Children treated for 6-8 months were also found to have significant reductions in change in baseline height. Treatment durations less than 6 months were inconclusive on the impact of ICS on change in height from baseline.

Indirect comparisons did not demonstrate a significant difference in daily dose, inhalation device, or age of child on impact of ICS on linear growth velocity with one year of treatment.[7] Linear growth velocity was significantly reduced with all treatments compared to placebo or non-steroidal drugs. Growth suppression was most pronounced during the first year with less of an effect in subsequent years.

COCHRANE – Inhaled Corticosteroids in Children with Persistent Asthma: Dose-Response Effects on Growth

In children with persistent asthma and ICS use of a minimum of 3 months, the effect of increasing the dose of ICS on linear growth velocity, weight gain and skeletal maturation was the subject of a recent Cochrane review.[8] RCTs in children with mild to moderate asthma up to 17 years of age were used to evaluate the different doses of the same ICS using the same device and the effect on growth. Beclomethasone, budesonide, ciclesonide, fluticasone or mometasone monotherapy or in combination with a LABA were studied. Most comparisons were between low dose (50 to 100 µg) and medium dose (200 µg) of hydrofluoroalkane (HFA)-beclomethasone equivalent. Treatment durations ranged from 12 to 52 weeks.

High quality evidence demonstrated ICS treatment (ciclesonide, fluticasone, mometasone) lasting 12 months reduced growth velocity in children treated with higher doses, based on 4 trials (MD 0.20 cm/y, 95% CI 0.02 to 0.39, p=0.03).[8] A significant difference in height change was seen in treatment zero to three months, most pronounced with higher doses of ICS, but no other time points were significantly different between groups. No differences were seen in weight, bone and mass index and skeletal maturation based on low-quality evidence. Magnitude of effect appeared to be unrelated to type of ICS.

COCHRANE - Omalizumab for Asthma in Adults and Children

A 2014 Cochrane review evaluated the use of omalizumab versus placebo or conventional therapy in adults and children with moderate to severe asthma. All participants had a diagnosis of allergic asthma except for one that included severe non-allergic asthma patients.[4] Twenty-five studies met the inclusion criteria, eleven evaluated efficacy. Studies ranged from 8 to 60 weeks. In patients taking concomitant ICS therapy, asthma exacerbations were reduced with subcutaneous omalizumab compared to placebo (OR 0.55, 95% CI 0.42 to 0.60).[4] Omalizumab was shown to have a small effect in patients with severe asthma as demonstrated by wide confidence intervals associated with the findings. Pooled data from four studies showed a significant benefit in hospitalizations due to severe asthma with an absolute risk reduction of 3% with placebo to 0.5% with subcutaneous omalizumab. The ability to withdraw from ICS therapy was higher with omalizumab therapy compared to placebo (OR 2.50, 95% CI 2.00 to 3.13), however no change was seen in the number of patients able to withdraw from oral steroid treatment.[4] A small reduction in ICS dose was seen in patients taking omalizumab compared to placebo, with a more pronounced effect seen in patients with severe asthma. Improvement in asthma symptom scores and health-related quality of life and reduction in rescue medication use was seen with omalizumab use. No significant effect was seen on lung function measurements and mortality.[4]

COCHRANE – Safety of Regular Formoterol or Salmeterol in Adults with Asthma: An Overview of Cochrane Reviews

Serious adverse events associated with the use of formoterol or salmeterol was the focus of a 2014 Cochrane Review.[9] Maintenance formoterol or salmeterol therapy in adults with asthma was compared to placebo or when combined with an ICS in comparison to ICS monotherapy at equivalent doses.[9] Data on 61,366 adult patients was available from six previously reported Cochrane Reviews, four of which focused on the safety and efficacy of formoterol, salmeterol or combination therapy. Direct and indirect comparisons were evaluated separately to preserve the integrity of the data.

Direct comparisons did not demonstrate a significant increase in death from any cause. Monotherapy comparisons of salmeterol and formoterol versus placebo and combination therapy compared to ICS findings could not exclude the possibility of a two-fold increase in mortality based on moderate evidence (Table 2). Absolute risk for mortality demonstrated small differences between monotherapy comparisons, an increase of 7 per 10,000, and for combination therapy comparisons, an increase of 3 per 10,000. Data was insufficient to make a mortality comparison between formoterol and salmeterol and for monotherapy trial risks compared to combination therapy trials. Comparisons of non-fatal adverse events from any cause were significantly higher for patients receiving salmeterol monotherapy (OR 1.14, 95% CI 1.01 to 1.28) but not for any other direct comparisons.[9]

Table 2. Risk of Death of Any Cause in Patients Taking Formoterol or Salmeterol.[9]

Therapy	Odds Ratio	95% Confidence Interval	Trials	Participants
Formoterol monotherapy	4.49	0.24 to 84.80	13	4824
Salmeterol monotherapy	1.33	0.85 to 2.08	10	29,128
Formoterol combination*	3.56	0.79 to 16.03	25	11,271
Salmeterol combination*	0.90	0.31 to 2.6	35	13,447
* Combination therapy includes formoterol or salmeterol and ICS				

COCHRANE – Stopping Long-Acting Beta-Agonists (LABA) for Adults with Asthma Well Controlled by LABA and Inhaled Corticosteroids

A 2015 Cochrane review evaluated the effect of discontinuing LABA therapy in patients with well-controlled asthma. Trials lasting at least eight weeks that evaluated the change from combination ICS/LABA to ICS alone were included (n=2781).[10] Outcomes of interest are loss of asthma control, deterioration in quality of life, increase in asthma attacks or exacerbations, incidence of serious adverse events from any cause upon discontinuation of the LABA.

Exacerbations and the need for oral corticosteroids was increased with the discontinuation of LABA (OR 1.74, 95% CI 0.83 to 3.65), however, the large confidence interval makes these findings uncertain. Small differences in Asthma Control Questionnaire and quality of life scores were shown to benefit those continuing LABA therapy. Conclusions on the effect of discontinuing LABA on serious adverse event risk were not able to be determined due to a low number of events. Discontinuation of LABA therapy showed a non-significant decrease in incidence of adverse events.

COCHRANE- Inhaled Steroids and Risk of Pneumonia for Chronic Obstructive Pulmonary Disease

A Cochrane review of studies lasting at least 12 weeks was done to determine the risk of pneumonia in participants with COPD using fluticasone and budesonide.[11] Placebo comparisons or one of the ICS agents in combination with a LABA compared to LABA monotherapy were included. Twenty-six fluticasone and 17 budesonide studies qualified for inclusion. Forty percent of these had a high degree of bias due to high or uneven dropout rates, however, a sensitivity analysis, which removed studies with high bias risk, did not change the primary outcome findings.

An increase in non-fatal serious adverse pneumonia events requiring hospitalization were increased in both fluticasone and budesonide groups, OR 1.78 [95% CI 1.50 to 2.12, (high-quality evidence)] and OR 1.62 [95% CI 1.00 to 2.62, (moderate-quality evidence)], respectively.[11] The risk of pneumonia was not altered by combining fluticasone with salmeterol or vilanterol or by adjusting the dose, trial duration or baseline severity of COPD. The budesonide findings were less precise which was thought to be due to the use of two different doses. Moderate-quality evidence showed risk of any pneumonia event was higher with fluticasone compared to budesonide (OR 1.86, 95% CI 1.04 to 3.34) based on indirect comparisons and potentially different methods for determining pneumonia diagnosis. Monotherapy indirect comparisons between budesonide and fluticasone found no significant differences in the outcomes of mortality or serious adverse events, including pneumonia (moderate to high-quality evidence for fluticasone and moderate to very low quality evidence for budesonide). High-

quality evidence found no difference in mortality between the ICS agents and the comparison treatments. There was insufficient evidence to determine pneumonia-related deaths.

COCHRANE – Long-Acting Inhaled Therapy (Beta-Agonists, Anticholinergics and Steroids) for COPD: A Network Meta-Analysis

A recent COCHRANE network meta-analysis evaluated the long-term efficacy of treatments for COPD in patients not controlled by short-acting treatments alone.[12] Trials lasting at least 6 months were included. Treatment comparisons are listed in table 3. St George's Respiratory Questionnaire (SGRQ) total score and trough forced expiratory volume in one second (FEV_1) were the efficacy outcomes studied. Seventy-one similar trials were included comprising patients with mostly severe COPD and long history of smoking (40+ pack-years).

Table 3. Treatment Comparisons of Included Studies[12]

Drug Class	Specific Therapies
Long-acting Beta-agonists (LABAs)	Formoterol, salmeterol or indacaterol
Long-acting Muscarinic antagonists (LAMA)	Aclidinium, glycopyrronium or tiotropium
Inhaled Corticosteroids (ICS)	Budesonide, fluticasone or mometasone
Combination LABA/ICS	Formoterol/budesonide, formoterol/mometasone, or salmeterol/fluticasone

For the outcome of SGRQ combination therapy of LABA/ICS demonstrated the greatest improvement at six months when compared to placebo [-3.89 units, 95% credible interval (CrI) -4.70 to -2.97].[12] LAMA, LABA and ICS improvement in SGRQ scores at six months were: -2.63 units, -2.29 units and -2.0 units. Placebo controlled comparisons favored LABA/ICS therapy with trough FEV1 changes of 133.3 mL (95% CrI 100.6 to 164.0) at six months.[12] LAMA and LABAs had similar results with ICS showing less of a benefit. SGRQ and FEV1 differences in treatment seen at six months were less pronounced at twelve months. Individual treatment comparisons were not precise.

New Guidelines:

ACCP/CTS – Prevention of Acute Exacerbations of COPD

The American College of Chest Physicians (ACCP) and Canadian Thoracic Society Guideline (CTS) formed a unique collaboration between two agencies to develop this evidence-based guideline on acute exacerbations of COPD (AECOPD).[2] The quality of the evidence was rated as high to very low, using GRADEpro software. The CHEST grading system was used to grade recommendations as strong (high-quality evidence [1A]) to consensus based. Maintenance pharmacotherapy has shown to: reduce exacerbations of moderate and severe COPD, improve quality of life, improve lung function, reduce hospitalizations, reduce dyspnea and need for rescue medication. Table 4 provides therapy recommendations for maintenance therapy and exacerbation prevention.

Table 4. Treatment Recommendations for Pharmacological Management of COPD.[2]

Recommendation	Grade
In patients with moderate to severe COPD the use of LABAs is recommended over placebo	1B
In patients with moderate to severe COPD the use of LAMAs is recommended over placebo	1A
In patients with moderate to severe COPD the use of LAMAs is recommended over LABAs	1C
In patients with moderate to severe COPD the use of SAMAs are recommended over SABAs	2C
In patients with moderate to severe COPD the use of SAMA + SABA are recommended over SABA alone	2B
In patients with moderate to severe COPD the use of LABA monotherapy is recommended over SAMA monotherapy	2C
In patients with moderate to severe COPD the use of LAMA is recommended over SAMA	1A
In patients with moderate to severe COPD the use of combination SAMA + LABA is recommended over LABA monotherapy	2C
In patients with stable moderate, severe, and very severe COPD the use of maintenance combination ICS/LABA therapy is recommended over the use of placebo	1B
In patients with stable moderate, severe, and very severe COPD the use of maintenance combination ICS/LABA therapy is recommended over the use of LABA monotherapy	1C
In patients with stable moderate to very severe COPD the use of ICS/LABA is recommended over ICS monotherapy	1B
In patients with stable COPD the use of LAMA/LABA or LAMA monotherapy are recommended	1C
In patients with stable COPD the use of maintenance combination ICS/LABA or LAMA are recommended	1C
In patients with stable COPD the use of maintenance combination LAMA/ICS/LABA or LAMA are recommended	2C
In patients with moderate to severe COPD with chronic bronchitis and history of at least one exacerbation in the previous year, roflumilast is recommended	2A
In patients with COPD oral slow-release theophylline twice daily is recommended (if already on maintenance long-acting bronchodilator therapy and ICS)	2B
In patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, N-acetylcysteine is recommended (if already on maintenance long-acting bronchodilator therapy and ICS)	2B
In stable outpatients with COPD the use of oral carbocysteine is recommended in patients who continue to experience exacerbations despite maximal therapy designed to reduce exacerbations	Con-sensus based
Abbreviations: COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroid; LABA – long-acting beta2-agonist; LAMA – long-acting muscarinic antagonists; SABA – short-acting beta2-agonist	

<u>VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease</u>

In December of 2014 the Veterans Administration (VA)/Department of Defense (DoD) updated their 2007 guidance on COPD. Evidence level and quality was considered to formulate best practice clinical guidance recommendations.[3] The strength of the recommendations were based on the GRADE rating for the strength of the evidence as well as desirable versus undesirable outcomes, values and preferences and other considerations to formulate a strength of recommendation as "Strong For", "Weak For", "Strong Against", or "Weak Against". Pharmacotherapy from the following classes were considered: LABAs, SABAs, SAMAs, LAMAs, ICS, PDE4, theophylline, and NAC. Important clinical outcomes of interest were quality of life (QoL), morbidity, dyspnea, functional capacity, exacerbation rate and/or severity, mortality, harms, and healthcare utilization. Twenty-five systematic reviews were evaluated to develop pharmacological recommendations.

Recommendations for COPD Management in the Outpatient Setting:

- SABAs for patients with confirmed COPD for rescue therapy as needed (Strong For)
    - Based on improvements in FEV1, respiratory symptoms, and reduction in exacerbations in COPD exacerbations in stable COPD compared to placebo.

- Long-acting bronchodilators for patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea and cough) (Strong For)
    - LAMAs have been shown to improve FEV1 and QoL and reduce the rate of COPD exacerbations and exacerbations requiring hospitalization. LABAs have been shown to improve FEV1 and QoL.
- Inhaled LAMA tiotropium as first-line maintenance therapy for patients with confirmed, stable COPD, who continue to have respiratory symptoms (e.g., dyspnea, cough) (Weak For)
    - LAMAs have been shown to be superior to LABAs for preventing COPD exacerbations and COPD-related hospitalizations with fewer adverse events.
- Inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1 <50%) or a history of COPD exacerbations (Strong For)
    - LAMAs have been shown to be superior to LABAs for preventing COPD exacerbations and COPD-related hospitalizations with fewer adverse events.
- For patients on SAMA that are clinically stable with a confirmed diagnosis of COPD and who have not had exacerbations, the recommendation is to continue treatment rather than switching to long-acting bronchodilators (Weak For)
    - Ipratropium has been shown to improve FEV1 and respiratory symptoms compared to placebo.
- For patients taking a SAMA who are started on a LAMA, the recommendation is to discontinue the SAMA (Weak For)
    - LAMA have been shown to be superior to SAMA and placebo for the outcomes of FEV1 improvement, exacerbations, respiratory symptoms and COPD –related QoL.
- ICS are not recommended for first-line monotherapy in symptomatic patients with confirmed, stable COPD (Strong Against)
    - ICS has not been shown to be as beneficial as LABAs on lung function.
- Recommend against using a LABA without an ICS in patients with COPD who may have concomitant asthma (Strong Against)
    - LABA monotherapy use in asthma patients has been associated with an increased risk of death.
- Combination therapy of a LABA and LAMA is recommended for patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs and have persistent dyspnea on monotherapy (Strong For)
    - Combination therapy with LAMAs and LABAs has been shown to improve FEV1, QoL, and dyspnea compared to tiotropium alone.
- For patients on a LAMA (tiotropium) and LABA with confirmed, stable COPD and have persistent dyspnea or COPD exacerbations, ICS as a third medication is recommended (Weak For)
    - Limited data suggest improvement in QoL, lung function, and symptoms in patients taking triple therapy.
- Roflumilast is not recommended for patients with confirmed, stable COPD in primary care without the consultation with a pulmonologist (Weak Against)
    - Only modest benefit in FEV1 improvements have been demonstrated when compared to placebo.
- Theophylline is not recommended for patients with confirmed, stable COPD in primary care without the consultation with a pulmonologist (Weak Against)
- There is insufficient evidence to recommend for or against the use of NAC in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough) (Not graded)

<u>GOLD Guidelines</u>

In January of 2015 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were updated.[1] The 2015 guideline builds on the framework established with the 2011 guidelines with the addition of evidenced based updates in 2013, 2014 and now 2015. Treatment recommendations were unchanged from previous updates (Table 5). Evidence to support the use of salmeterol and formoterol, based on decreased exacerbations, was added. Data on increased

exacerbation rates with ICS withdrawal was cited; however, these findings were not reproduced in a second study in patients with severe and very severe COPD. The use of N-acetylcysteine in GOLD stage 2 patients showed decreased exacerbation rates.[1]

Table 5. Initial Pharmacological Management of COPD[1]

Patients	First Choice	Alternative Choice	Other Possible Treatments
Group A: Few symptoms and low risk of exacerbations (GOLD 1 or 2)	Short-acting anticholinergic prn *or* Short-acting beta2-agonist prn	Long-acting anticholinergic *or* Long-acting beta2-agonist *or* Short-acting beta2-agonist and short-acting anticholinergic	Theophylline
Group B: More symptoms and low risk of exacerbations (GOLD 1 or 2)	Long-acting anticholinergic *or* Long-acting beta2-agonist	Long-acting anticholinergic *and* Long-acting beta2-agonist	Short-acting beta2-agonist *and/or* Short-acting anticholinergic *or* Short-acting beta2-agonist *and* Theophylline
Group C: Few symptoms but high risk of exacerbations (GOLD 3 or 4)	Inhaled corticosteroid + Long-acting beta2-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta2-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta2-agonist and phosphodiesterase-4 inhibitor	Short-acting beta2-agonist *and/or* Short-acting anticholinergic *or* Short-acting beta2-agonist *and* Theophylline
Group D: Many symptoms and high risk of exacerbations (GOLD 3 or 4)	Inhaled corticosteroid + Long-acting beta2-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta2-agonist and Long-acting anticholinergic *or* Inhaled corticosteroid + Long-acting beta2-agonist and Phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and Long-acting beta2-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Short-acting beta2-agonist *and/or* Short-acting anticholinergic *or* Short-acting beta2-agonist *and* Theophylline or carbocysteine *or* N-acetylcysteine

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.
**Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed on July 26, 2015.

International ERS/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma

The European Respiratory Society and American Thoracic Society released guidance on the treatment of severe asthma in children and adults.[5] Severe asthma is defined as asthma that requires treatment with high dose ICS and a second controller and/or systemic corticosteroids to prevent symptoms from being uncontrolled or asthma that remains uncontrolled even with this therapy. Pharmacotherapy includes a low (adults) and very low (children) recommendation for the use of anti-IgE antibody therapy (omalizumab) for patients with severe allergic asthma. Candidates for omalizumab therapy should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal treatment with other agents. Exhaled nitric oxide, methotrexate and macrolide antibiotics are not recommended based on low and very low quality of evidence. In adults with asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA) antifungal agents are recommended based on very low quality of evidence.[5]

New Safety Alerts:

Omalizumab (Xolair) – In September of 2014 the FDA released a Drug Safety Communication for omalizumab and the slightly increased risk of cerebrovascular and cardiovascular severe adverse events.[6] These risks have been added to omalizumab labeling. A warning about the uncertain increased risk of cancer with omalizumab therapy has also been added.

New Formulations or Indications:

Tiotropium/olodaterol (Stiolto™ Respimat®)

Combination therapy with an anticholinergic, tiotropium, and a LABA (olodaterol) was approved in May of 2015 for maintenance treatment for airflow obstruction in patients with COPD.[13] The dose of tiotropium/olodaterol is 2 inhalations once daily, at the same time every day. Efficacy data comes primarily from two, 52-week, double-blind, randomized-controlled, confirmatory trials involving 5162 patients. In both studies tiotropium/olodaterol combination therapy was studied using five treatment arms; tiotropium 2.5 mcg, tiotropium 5 mcg, olodaterol 5 mcg, tiotropium 2.5 mcg/olodaterol 5 mcg and tiotropium 5 mcg + olodaterol 5 mcg. Trial participants were COPD patients, mean age of 64, with a smoking history of 10+ pack years and moderate to very severe pulmonary dysfunction (GOLD stage 2-4). Concomitant ICS therapy was used in 47% of patients. The primary outcome measures were change from baseline in FEV_1 AUC $_{0\text{-}3hr}$ and trough FEV_1 measured at 24-weeks of treatment.

For the outcome of FEV_1 AUC $_{0\text{-}3hr}$ tiotropium/olodaterol was superior to tiotropium 5 mcg (difference 0.117 L [95%CI 0.094 to 0.140 L; p≤0.001] in trial 1 and difference 0.103 [95%CI 0.078 to 0.127; p≤0.001] in trial 2). Tiotropium/olodaterol was also superior to olodaterol 5 mcg for the outcome of FEV_1 AUC $_{0\text{-}3hr}$ (difference 0.123 L [95% CI 0.100 to 0.146 L; p≤0.001) for trial 1 and difference 0.132 L [95% CI 0.108 to 0.157 L; p≤0.001) for trial 2].

Fluticasone furoate (Arnuity™ Ellipta®)

The single entity product of Breo Ellipta (fluticasone furoate/vilanterol) was approved in August of 2014.[14] Fluticasone furoate is an ICS indicated for the maintenance treatment of asthma in patients 12 and older.[14] Fluticasone furoate is an inhalation powder dosed as 100 mcg or 200 mcg once daily. There were 4 confirmatory trials in patients with uncontrolled asthma on ICS or LABA/ICS combination therapy. The primary outcome was change in baseline evening trough FEV_1 measured after the final dose of study medication in trials lasting 12 to 24 weeks. Fluticasone furoate 100 mcg was superior to placebo with a mean

difference of 146 mL (95% CI, 36 to 257; p=0.009). Similar results were demonstrated in a second 12 week trial comparing the 100 mcg dose to placebo. In a study of fluticasone furoate 100 mcg and fluticasone 200 mcg, changes in FEV1 from baseline were 208 mL and 284 mL, respectively.

Fluticasone furoate/vilanterol (Breo® Ellipta®)

An indication for the once-daily treatment of asthma in patients 18 years and older was added to the labeling of fluticasone furoate/vilanterol inhalation powder in April of 2015.[27] This ICS/LABA combination was previously approved for COPD maintenance treatment in 2013. The dose for asthma patients is 1 inhalation of fluticasone furoate 100 mcg/vilanterol 25 mcg or fluticasone furoate 200 mcg/vilanterol 25 mcg once-daily.

Four, randomized, double-blind confirmatory trials lasting 12 to 24 weeks and one active-comparator trial lasting 24 weeks provided evidence for the efficacy of fluticasone furoate/vivanterol.[27] Patients received once daily fluticasone furoate 100 mcg/vilanterol 25 mcg, fluticasone furoate 100 mcg, or placebo in the first trial. In the second trial, patients were randomized to once daily fluticasone furoate 100 mcg/vilanterol 25 mcg, fluticasone furoate 200 mcg/vilanterol 25 mcg, or fluticasone furoate 100 mcg. The third study randomized patients to fluticasone furoate 200 mcg/vilanterol 25 mcg, fluticasone 200 mcg or fluticasone proprionate 500 mcg (twice daily). In an active-comparator trial, fluticasone furoate 100 mcg/vilanterol 25 mcg was compared to fluticasone furoate 100 mcg daily on the rate of exacerbations. The primary endpoint in trials 1 and 3 was change from baseline in weighted mean FEV_1 (0-24 hours) and change from baseline trough FEV_1 at approximately 24 hours after the last dose at study endpoint (12 and 24 weeks). In trial 2, the primary endpoint was change from baseline in weighted FEV_1 (0-24 hours) at week 12.[27]

Fluticasone furoate 100 mcg/vilanterol 25 mcg was superior to placebo for the change from baseline in weighted mean FEV_1 (0-24 hours) and for change from baseline in trough FEV_1 in trial 1. Fluticasone furoate 100 mcg/vilanterol 25 mcg was not superior to fluticasone furoate 100 mcg in this same trial. In trials 2 and 3 fluticasone furoate 100 mcg/vilanterol 25 mcg was superior to fluticasone furoate 100 mcg and fluticasone furoate 200 mcg /vilanterol 25 mcg was superior to fluticasone furoate 200 mcg, respectively, in change from baseline in weighted mean FEV_1 (0-24 hours). In the active comparison trial (n=2019), fluticasone furoate 100 mcg/vilanterol 25 mcg decreased time to first asthma exacerbation compared to fluticasone furoate 100 mcg (HR 0.80, 95% CI, 0.64 to 0.99; p=0.036).[27]

Randomized Controlled Trials:

None identified.

References:

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf. Accessed on July 26, 2015.
2. Criner G, Bourbeau J, Diekemper R, et al. Prevention of Acute Exacerbations of COPD – American College of Chest Physicians and Canadian Thoracic Society Guideline. *CHEST*. 2015; 147:894-942.
3. Department of Veterans Affairs/Department of Defense. Va/DoD Clinical Practice Guidelines for the Management of Chronic Obstructive Pulmonary Disease. December 2014. Available at: http://www.healthquality.va.gov/guidelines/CD/copd/. Accessed on: July 9, 2015.
4. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database of Systematic Reviews*. 2014; Issue 1. Art. No.: CD003559. DOI: 10.1002/14651858.CD003559.pub.4.
5. Chung KF, Wenzel S, Jan B, et al. International ERS/ATS guideline on definition, evaluation, and treatment of severe asthma. *Eur Respir J*. 2014; 43: 343-373. DOI: 10.1183/09031936.00202013.
6. US Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. September 26, 2014. Available at: http://www.fda.gov/drugs/drugsafety/ucm414911.htm. Accessed on July 27, 2014.
7. Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. *Cochrane Database of Systematic Reviews*. 2014; Issue 7. Art. No.: CD009471. DOI: 10.1002/14651858.CD009471.pub.2.
8. Pruteanu AI, Chauhan BF, Zhang L, et al. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. *Cochrane Database of Systematic Reviews*. 2014; Issue 7. Art. No.: CD009878. DOI: 10.1002/14651858.CD009878.pub.2.
9. Cates CJ, Wieland LS. Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*. 2014; Issue 2. Art. No.: CD010314. DOI: 10.1002/14651858.CD0010314.pub.2. *Cochrane Database of Systematic Reviews*. 2014; Issue 7. Art. No.: CD009878. DOI: 10.1002/14651858.CD009878.pub.2.
10. Ahamd S, Kew KM, Normansell R. Stopping long-acting beta-agonist (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database of Systematic Reviews*. 2015; Issue 6. Art. No.: CD011306. DOI: 10.1002/14651858.CD011306.pub.2.
11. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2014; Issue 3. Art. No.: CD010115. DOI: 10.1002/14651858.CD010115.pub.2.
12. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 2014; Issue 3. Art No.: CD010844. DOI: 10.1002/14651858.CD010844.pub2.
13. GlaxoSmithKline. US Food and Drug Administration 2014. Arnuity Ellipta. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205625s000lbl.pdf. Accessed July 27, 2015.
14. Boehringer Ingelheim Pharmaceuticals, Inc. Stiolto Respimat Label. US Food and Drug Administration 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206756s001lbl.pdf. Accessed on July 27, 2015.
15. Selph S, et al. Drug Class Review: drugs to treat asthma and chronic obstructive pulmonary disease (COPD). Drug Effectiveness Review Project. May 2014.
16. GlaxoSmithKline. Incruse Ellipta Label. US Food and Drug Administration 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205382s000lbl.pdf. Accessed on July 27, 2015.
17. Merck and Co., Inc. Asmanex Label. US Food and Drug Administration 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205641s000lbl.pdf. Accessed on July 27, 2015.
18. Donohue, J. F. et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respiratory Medicine 107, 1538–1546 (2013).

19. Decramer, M. et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *The Lancet Respiratory Medicine*. 2014;2: 472–486.
20. Celli B, et al. Once-daily umeclidinium/vilanterol 125/25 µg therapy in copd: A randomized, controlled study. *CHEST*. 2014;145: 981–991.
21. 1. Koch, A. *et al.* Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat® versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* **9,** 697–714 (2014).
22. 2. Ferguson, G. T. *et al.* Efficacy and safety of olodaterol once daily delivered via Respimat® in patients with GOLD 2-4 COPD: results from two replicate 48- week studies. *Int J Chron Obstruct Pulmon Dis* **9,** 629–645 (2014).
23. The Oregon Asthma Program 2013. The Burden of Asthma in Oregon; 2013. Available at: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Documents/burden/OR_Asthma_2013.pdf. Accessed July 27, 2014.
24. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94-138.
25. Cazzola M, Macknee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008; 31: 416-469.
26. Center for Disease Control. Chronic Obstructive Pulmonary Disease. COPD among adults in Oregon. Available at: http://www.cdc.gov/copd/maps/docs/pdf/OR_COPDFactSheet.pdf. Accessed July 27, 2015.
27. GlaxoSmithKline. Breo Ellipta Label. US Food and Drug Administration 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204275s001lbl.pdf. Accessed on August 25, 2015.

Appendix 1: Current Status on Preferred Drug List

Anticholinergics, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	AMPUL-NEB	DUONEB	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	AMPUL-NEB	IPRATROPIUM-ALBUTEROL	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	CAP W/DEV	SPIRIVA	TIOTROPIUM BROMIDE	Y
INHALATION	HFA AER AD	ATROVENT HFA	IPRATROPIUM BROMIDE	Y
INHALATION	MIST INHAL	COMBIVENT RESPIMAT	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	Y
INHALATION	AER POW BA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	N
INHALATION	BLST W/DEV	ANORO ELLIPTA	UMECLIDINIUM BRM/VILANTEROL TR	N
INHALATION	BLST W/DEV	INCRUSE ELLIPTA	UMECLIDINIUM BROMIDE	N
INHALATION	MIST INHAL	SPIRIVA RESPIMAT	TIOTROPIUM BROMIDE	N
INHALATION	MIST INHAL	STIOLTO RESPIMAT	TIOTROPIUM BR/OLODATEROL HCL	

Beta-agonists, Inhaled Long-acting

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	SEREVENT DISKUS	SALMETEROL XINAFOATE	Y
INHALATION	CAP W/DEV	FORADIL	FORMOTEROL FUMARATE	Y
INHALATION	CAP W/DEV	ARCAPTA NEOHALER	INDACATEROL MALEATE	N
INHALATION	MIST INHAL	STRIVERDI RESPIMAT	OLODATEROL HCL	N
INHALATION	VIAL-NEB	BROVANA	ARFORMOTEROL TARTRATE	N
INHALATION	VIAL-NEB	PERFOROMIST	FORMOTEROL FUMARATE	N

Beta-agonists, Inhaled Short-acting

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	HFA AER AD	PROAIR HFA	ALBUTEROL SULFATE	Y
INHALATION	HFA AER AD	PROVENTIL HFA	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	ALBUTEROL SULFATE	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	PROVENTIL	ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	VENTOLIN	ALBUTEROL SULFATE	Y
INHALATION	VIAL-NEB	AIRET	ALBUTEROL SULFATE	Y
INHALATION	VIAL-NEB	ALBUTEROL SULFATE	ALBUTEROL SULFATE	Y
INHALATION	AER POW BA	PROAIR RESPICLICK	ALBUTEROL SULFATE	N
INHALATION	AER REFILL	ALBUTEROL	ALBUTEROL	N
INHALATION	AER W/ADAP	ALUPENT	METAPROTERENOL SULFATE	N
INHALATION	AEROSOL	PROVENTIL	ALBUTEROL	N
INHALATION	AEROSOL	VENTOLIN	ALBUTEROL	N
INHALATION	HFA AER AD	ALBUTEROL SULFATE HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	PROAIR HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	VENTOLIN HFA	ALBUTEROL SULFATE	N
INHALATION	HFA AER AD	XOPENEX HFA	LEVALBUTEROL TARTRATE	N
INHALATION	SOLUTION	ALUPENT	METAPROTERENOL SULFATE	N
INHALATION	VIAL-NEB	LEVALBUTEROL CONC	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	LEVALBUTEROL HCL	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	XOPENEX	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	XOPENEX CONCENTRATE	LEVALBUTEROL HCL	N
INHALATION	VIAL-NEB	LEVALBUTEROL CONC	LEVALBUTEROL HCL	
INHALATION	VIAL-NEB	LEVALBUTEROL HCL	LEVALBUTEROL HCL	

Corticosteroids, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	AER POW BA	PULMICORT FLEXHALER	BUDESONIDE	Y
INHALATION	AER W/ADAP	FLOVENT HFA	FLUTICASONE PROPIONATE	Y
INHALATION	AER W/ADAP	QVAR	BECLOMETHASONE DIPROPIONATE	Y
INHALATION	BLST W/DEV	FLOVENT DISKUS	FLUTICASONE PROPIONATE	Y
INHALATION	AER POW BA	ASMANEX	MOMETASONE FUROATE	N
INHALATION	AER W/ADAP	AEROBID	FLUNISOLIDE	N
INHALATION	AER W/ADAP	AEROBID-M	FLUNISOLIDE/MENTHOL	N
INHALATION	AER W/ADAP	AZMACORT	TRIAMCINOLONE ACETONIDE	N
INHALATION	AMPUL-NEB	BUDESONIDE	BUDESONIDE	N
INHALATION	AMPUL-NEB	PULMICORT	BUDESONIDE	N
INHALATION	BLST W/DEV	ARNUITY ELLIPTA	FLUTICASONE FUROATE	N
INHALATION	HFA AER AD	AEROSPAN	FLUNISOLIDE	N
INHALATION	HFA AER AD	ALVESCO	CICLESONIDE	N
INHALATION	HFA AER AD	ASMANEX HFA	MOMETASONE FUROATE	N

Corticosteroids/LABA Combination, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	ADVAIR DISKUS	FLUTICASONE/SALMETEROL	Y
INHALATION	HFA AER AD	ADVAIR HFA	FLUTICASONE/SALMETEROL	Y
INHALATION	HFA AER AD	SYMBICORT	BUDESONIDE/FORMOTEROL	Y
INHALATION	BLST W/DEV	BREO ELLIPTA	FLUTICASONE/VILANTEROL	N
INHALATION	HFA AER AD	DULERA	MOMETASONE/FORMOTEROL	N

Miscellaneous Pulmonary Agents

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TAB CHEW	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TAB CHEW	SINGULAIR	MONTELUKAST SODIUM	Y
ORAL	TABLET	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TABLET	SINGULAIR	MONTELUKAST SODIUM	Y
SUB-Q	VIAL	XOLAIR	OMALIZUMAB	N
ORAL	TABLET	DALIRESP	ROFLUMILAST	N
ORAL	GRAN PACK	MONTELUKAST SODIUM	MONTELUKAST SODIUM	N
ORAL	GRAN PACK	SINGULAIR	MONTELUKAST SODIUM	N
ORAL	TABLET	ACCOLATE	ZAFIRLUKAST	N
ORAL	TABLET	ZAFIRLUKAST	ZAFIRLUKAST	N
ORAL	TABLET	ZYFLO	ZILEUTON	N
ORAL	TBMP 12HR	ZYFLO CR	ZILEUTON	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to July Week 3 2015

Search Strategy:

#	Searches	Results
1	Ipratropium/	749
2	tiotropium.mp.	1007
3	aclidinium.mp.	83
4	umeclidinium.mp.	29
5	salmeterol.mp.	2113
6	formoterol.mp.	1561
7	indacaterol.mp.	214
8	olodaterol.mp.	28
9	arformoterol.mp.	29
10	albuterol.mp. or Albuterol/	5613
11	metaproteranol.mp.	1
12	levalbuterol.mp. or Levalbuterol/	120
13	budesonide.mp. or Budesonide/	3890
14	fluticasone.mp.	3156
15	beclomethasone diproprionate.mp.	26
16	mometasone.mp.	672
17	flunisolide.mp.	191
18	triamsinolone.mp.	2
19	budesonide.mp. or Budesonide/	3890
20	fluticasone furoate.mp.	141
21	ciclesonide.mp.	274
22	montelukast.mp.	1707
23	omalizumab.mp.	1066
24	roflumilast.mp.	336
25	zafirulukast.mp.	1
26	zileuton.mp.	402
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	16473
28	limit 27 to (english language and yr="2014 -Current")	905
29	limit 28 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	313

Inhaled Corticosteroids (ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage for non-preferred ICS products:
  - Asthma: inhaled short-acting beta-agonist.
  - COPD: short-acting and long-acting bronchodilators (inhaled anticholinergics and beta-agonists). Preferred short-acting and long-acting bronchodilators do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • 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 in class.	No: Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD9 493.xx)?	Yes: Go to #7	No: Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD9 496), chronic bronchitis (ICD9 491.x) and/or emphysema (ICD9 492.x)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *9/15 (KS/AG)*
Implementation: *TBA*

Long-acting Beta-agonists (LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage of non-preferred LABA products:
  - Asthma: inhaled corticosteroid and short-acting beta-agonist.
  - COPD: inhaled short-acting bronchodilator.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • 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 in class	No: Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD9 493.xx)?	Yes: Go to #6	No: Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD9 496), chronic bronchitis (ICD9 491.x) and/or emphysema (ICD9 492.x)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *9/15 (KS/AG); 5/12; 9/09; 5/09*
Implementation: *8/12; 1/10*

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting and long-acting bronchodilators (inhaled anticholinergics and beta-agonists). Preferred short-acting and long-acting bronchodilators do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class	No: Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD9 493.xx)?	Yes: Go to #7	No: Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD9 496), chronic bronchitis (ICD9 491.x) and/or emphysema (ICD9 492.x)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist) or does the patient have documented severe (GOLD 3) or very severe (GOLD 4) COPD?	Yes: Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.	No: Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	Yes: Go to #8	No: Pass to RPh; Deny, medical appropriateness
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have documented severe persistent asthma (Step 4 or higher per NIH EPR 3)?	Yes: Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.	No: Pass to RPh; Deny, medical appropriateness

P&T/DUR Review: *9/15 (KS/AG); 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist Combination (LAMA/LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage:
  - COPD: short-acting, long-acting bronchodilators (inhaled anticholinergics and beta-agonists) and inhaled corticosteroid. Preferred short-acting, long-acting bronchodilators and inhaled corticosteroids do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of preferred LAMA and LABA products in each class	No: Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD9 493.xx)?	Yes: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	No: Go to #4
4. Does the patient have a diagnosis of COPD (ICD9 496), chronic bronchitis (ICD9 491.x) and/or emphysema (ICD9 492.x)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an inhaled corticosteroid?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness.
7. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist) or does the patient have documented severe (GOLD 3) or very severe (GOLD 4) COPD?	Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *9/15 (KS/AG); 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/15; 1/14; 9/12; 1/10*

Roflumilast

Goals:

- Decrease the number of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and with a history of exacerbations.

Length of Authorization:

Up to 12 months

Covered Alternatives:

Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not covered by the OHP
3. Does the patient have documented severe (GOLD 3) or very severe (GOLD 4) COPD?	Yes: Go to #4	No: Pass to RPh. Deny for medical appropriateness
4. Does the patient have a diagnosis of chronic bronchitis (ICD9 491.x)?	Yes: Go to #5	No: Pass to RPh. Deny for medical appropriateness
5. Does the patient have documented prior COPD exacerbations?	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness
6. Does the patient have an active prescription for a long-acting bronchodilator (long-acting anticholinergic agent or long-acting beta-agonist) and inhaled corticosteroid (ICS)?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; recommend trial of preferred long-acting bronchodilator and ICS

P&T/DUR Review: *9/15 (KS/AG); 5/13; 2/12*
Implementation: *TBD; 1/14; 5/12*

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

Class Update: Non-insulin Antidiabetic Agents

Month/Year of Review: September 2015
Last Review: September 2014
End date of literature search: June 2015

PDL Classes:
- DPP-4 Inhibitors
- GLP-1 Receptor Agonists
- Oral Hypoglycemics (sulfonylureas and meglitinides)
- SGLT-2 Inhibitors
- Thiazolidinediones
- Miscellaneous Antidiabetic Agents

Current Status of PDL Class:
- See Appendix 2

Reasons for the Review:
The purpose of this review is to evaluate new evidence on each of the antidiabetic agents, and if appropriate, update therapy recommendations and therapy placement on the Oregon Health Plan (OHP) Preferred Drug List (PDL). Prior authorization criteria for each class will be reviewed and revised based on the evidence.

Research Questions:
1. Is there any new comparative evidence for non-insulin diabetes treatments pertaining to important intermediate (e.g., hemoglobin A1C [A1C]) and long-term clinical outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new evidence about comparative harms among the available non-insulin diabetes treatments?
3. Are there subpopulations of patients with diabetes mellitus for which specific therapies may be more effective or associated with less harm?

Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for type 2 diabetes mellitus (T2DM). Evidence-based recommendations in new clinical practice guidelines from the American Diabetes Association (ADA),[1] Institute for Clinical Systems Improvement (ICIS),[2] and the National Institute for Health and Care Excellence (NICE),[4] American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)[5,6] and a systematic review draft report from the Agency for Healthcare Research and Quality (AHRQ),[3] support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL) (see Appendix 2).
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a dipeptidyl peptidase-4 (DPP-4) inhibitor, or metformin plus a sodium-glucose cotransporter-2 (SGLT-2) inhibitor have similar rates of all-cause mortality based on one systematic review.[3]
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of hemoglobin A1c (A1C) based on one systematic review.

- There is moderate quality evidence that DPP-4 inhibitors lower A1C less than metformin and glimepiride based on two systematic reviews (one for each comparison).[3,14]
- Moderate quality evidence from one fair and one good quality trial suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Data from the EXAMINE and TECOS found these drugs to be non-inferior to placebo when a composite of CV outcomes were evaluated.[9,10]
- Moderate quality evidence from two meta-analyses showed a statistically significant increase in HF outcomes with DPP-4 inhibitors compared to placebo or active treatment.[10,11] Studies included in the meta-analyses were of short duration and the majority of included outcomes were limited to 2 trials only [SAVORTIMI53 (saxagliptin) and EXAMINE (alogliptin)].
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews.[3,13,14] Evidence from a recent systematic review and meta-analysis found glyburide to be associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).[13]
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease based on one systematic review. Evidence from this review suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2) without increased risk of lactic acidosis, based on evidence from primarily non-clinical trial data.[8] The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.[8]
- In December of 2014 liraglutide injection (Saxenda) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity.[15] Treatments for weight loss are not funded by the OHP.

Recommendations:
- Include at least one GLP-1 RA on the PDL as a preferred third-line option for T2DM after metformin and a SU.
- Make GLYXAMBI® (empagliflozin and linagliptin) a non-preferred drug subject to current PA for SGLT-2 inhibitors.
- No additional changes to the PDL are recommended. Consider comparative drug pricing in the executive session.
- Reorganize PDL classes for non-insulin antidiabetic agents to the following:
    - DPP-4 Inhibitors
    - GLP-1 Receptor Antagonists
    - Miscellaneous Antidiabetic Agents (metformin, pramlintide, meglitinides, others).
    - SGLT-2 Inhibitors
    - Sulfonylureas
    - Thiazolidinediones
- No longer require prior authorization (PA) for pramlintide due to low overall market share and because the FDA-mandated Risk Evaluation Mitigation Strategy (REMS) in place already promotes safe use through education. Continue clinical PA criteria for all DPP-4 inhibitors, all SGLT-2 inhibitors, and non-preferred GLP-1 RAs as shown in **Appendix 4**.

Previous Conclusions:
- A recent systematic review found insufficient evidence to compare health outcomes of the newer diabetes medications and combinations.[16] Intermediate endpoints, including hemoglobin A1c (A1c) and weight, found low SOE that exenatide XR weekly was superior to exenatide daily, liraglutide was superior to exenatide and sitagliptin, exenatide was superior to sitagliptin, and canagliflozin was similar in efficacy to metformin. In a comparison between metformin and dapagliflozin there was low SOE of a trend favoring dapagliflozin for HbA1c lowering, but it was not deemed clinically significant, -0.11% and -0.12%,

respectively. There was moderate SOE that metformin was superior to linagliptin, alogliptin and sitagliptin. The addition of metformin to alogliptin, linagliptin or sitagliptin resulted in greater glucose lowering than monotherapy dose comparisons.[16]

- In a phase 4, placebo-controlled, randomized trial of over 16,000 patients there was moderate evidence that saxagliptin therapy neither conferred a CV risk or benefit compared to placebo (HR 1.00 (95% CI, 0.89 to 1.12, P<0.001 for noninferiority). Hospitalization rates in patients with heart failure were found to be higher in those patients treated with saxagliptin compared to placebo (HR 1.27 [95% CI, 1.07 to 1.51, P=0.007]).[17]
- A systematic review and meta-analysis on SGLT2 inhibitors, including canagliflozin and dapagliflozin, demonstrated A1C lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]).[18] The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90)] and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to7.45]).[18]
- Oral hypoglycemic scan summary from the Drug Effectiveness Review Project (DERP) found limited new evidence since the last review; no further review or research needed.[19]

Previous Recommendations:

- The current PA criteria align with the conclusions of a recent systematic review by the DERP. No changes to the PDL are recommended.
- Continue to require a prior authorization for saxagliptin therapy. No changes to the PDL are recommended.
- Evidence on SGLT2 inhibitors supports the current PA criteria. Dapagliflozin should be added to the criteria and made non-preferred. No changes to the PDL are recommended.
- There is no new evidence on the comparative efficacy/effectiveness or safety for the oral hypoglycemic PDL class. Evaluate comparative costs in executive session

Reasons for the Review:

The purpose of this review is to evaluate new evidence on each of the antidiabetic agents, and if appropriate, update therapy recommendations and therapy placement on the Oregon Health Plan (OHP) PDL. Prior authorization criteria for each class will be reviewed and revised based on the evidence.

Background:

Type 2 diabetes mellitus (T2DM) is a prevalent disease affecting an estimated 25.6 million people in the United States, based on 2013 data.[20] In Oregon, it is estimated that 287,000 adults have T2DM, in which 38,000 are estimated to be OHP members.[21] OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[21] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[22] Despite a variety of treatment options, a significant number of patients fail to meet A1C goals; within 3 years of being diagnosed, 50% of patients require combination therapy to control their disease.[1,2] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and the addition of pharmacotherapy for persistent hyperglycemia.[1,2] Guidelines recommend a goal A1C of < 7% for most patients but a range of <6.5% to <8% is reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[1,2] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT-2 inhibitors, SUs, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. Hemoglobin A1C is often used as a surrogate marker to assess comparative efficacy of different AHA therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well.[1,2] Available data for most newer drugs are limited to short-term studies, which prevents the assessment of the durability of most available AHAs to control glucose levels long-term and to compare their impact on

microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of CV disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[1] UKPDS data also shows reduced incidence of microvascular risk with SU therapy and insulin.

Methods:

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

Systematic Reviews:

AHRQ – Diabetes Medications for Adults with Type 2 Diabetes: An Update Focused on Monotherapy and Add-On Therapy to Metformin – Draft

A report in process from the Agency for Healthcare Research and Quality (AHRQ) reviews the effectiveness and safety of monotherapy and metformin-based combination therapy for adults with T2DM.[3] Studies on therapy with metformin, SUs, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors or metformin combination therapies were included. Outcomes of interest were the following: intermediate (e.g., A1C), long-term clinical outcomes (e.g., all-cause mortality), and safety (e.g., hypoglycemia).

Two hundred twenty nine studies were included in the analysis. The correlation of microvascular disease to A1C levels makes this outcome particularly important. Metformin, SU and TZDs were shown to have similar ability to lower A1C.[3] Metformin is associated with superior A1C lowering than DPP-4 inhibitors (absolute difference of 0.4%). Monotherapy comparisons were based on high strength of evidence (SOE). Most combination therapies (metformin plus one other agent) lower A1C to the same extent, by an additional 0.7% to 1% (intermediate SOE). However, the combination of metformin plus a GLP-1 RA decreased A1C more than metformin plus a DPP-4 inhibitor. No other combination therapy comparisons demonstrated A1C changes that were either clinically meaningful or statistically significant.

Metformin use was shown to result in less weight gain with a difference of approximately 2.5 kg compared to treatment with a SU or TZD (high SOE). Use of a TZD results in a weight difference of +2.5 kg compared to use of a DPP-4 inhibitor and +3.5 kg compared to use of a GLP-1 RA. Weight loss favored metformin when compared to DPP-4 inhibitors and SU were shown to have less associated weight gain compared to TZDs. SGLT-2 inhibitors decrease weight more than metformin and DPP-4 inhibitors (moderate SOE). Metformin plus a GLP-1 RA and metformin plus a SGLT-2 inhibitor were associated with less weight gain compared to metformin plus a DPP-4 inhibitor. Metformin plus SU were shown to have less of an effect on weight compared to metformin and insulin.

There is moderate to high evidence that the SGLT-2 inhibitors and the GLP-1 RAs decrease systolic blood pressure by up to 5 mmHg and 3 mmHg, respectively.[3] All-cause mortality data are primarily based on studies lasting only 1 year or less, and many agents have insufficient data to make conclusions regarding mortality. All-cause mortality rates are similar between metformin and pioglitazone monotherapy, and for the combinations of metformin/DPP-4 inhibitor and metformin/SGLT-2 inhibitor, based on moderate to high SOE. There are limited data on CV morbidity and CV mortality for most treatments. Metformin use is associated with decreased CV morbidity and mortality compared to SU use. Metformin and pioglitazone have similar rates of CV morbidity. No conclusions on microvascular outcomes, such as retinopathy, nephropathy and neuropathy can be made due to insufficient evidence.

SU therapy is associated with more mild, moderate and total (risk of any type of) hypoglycemia compared to all other treatments. SU therapy had a1.5-fold risk for more severe hypoglycemia compared to TZDs and metformin.[3] The combination of metformin/DPP-4 inhibitor or metformin/SGLT-2 inhibitor is associated with less risk of severe hypoglycemia compared to metformin combined with a SU (moderate SOE). The DPP-4 inhibitors have little risk for severe hypoglycemia events when compared to metformin monotherapy or metformin/TZD therapy (moderate SOE). Gastrointestinal side effects are more common with metformin and GLP-1 RAs (moderate to high SOE). Congestive heart failure is more common with TZDs compared to metformin or SU (low SOE). Risk of pancreatitis is similar between metformin and the combination of metformin/DPP-4 inhibitor, although rare in both groups. Metformin plus a SGLT-2 inhibitor is associated with a 3-fold increase in genital mycotic infections compared to metformin alone, and 6-fold higher risk when compared to metformin plus a SU (high SOE).[3] The risk of urinary tract infections is similar between SGLT-2 inhibitors alone and in combination therapy when compared to metformin or metformin plus a SU (moderate to high SOE).

Metformin in Patients with Type 2 Diabetes and Kidney Disease

A meta-analysis on the risk of lactic acidosis in patients taking metformin with kidney disease included sixty-five studies on the following: pharmacokinetic/metabolic investigations, case series, cross-sectional, observational, pharmacosurveillance studies, meta-analyses and a clinical trial.[8] Metformin concentrations were found to remain in safe therapeutic levels in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2), despite reduced metformin clearance. Additionally, circulating lactate levels were normal in patients with kidney dysfunction receiving metformin. Limited data suggests that patients who developed metformin-related lactic acidosis previously had normal renal function, questioning the utility of using renal function values as a determinant for appropriate use.[8] The incidence of lactic acidosis ranges from 3 per 100,000 person-years to 10 per 100,000 person-years in patients taking metformin, which is similar to the overall diabetic population. Observational studies have shown the use of metformin in patients with renal dysfunction have improved macrovascular outcomes. However, there is insufficient evidence from randomized controlled trials in this population. The authors recommend a revised dosing strategy to metformin labeling that outlines use in patients with CKD stage 1-3B (eGFR ≥90 to 30 mL/min per 1.73 m^2).

Dipeptidyl Peptidase-4 Inhibitors and Heart Failure: A Meta-analysis of Randomized Clinical Trials

The evidence that saxagliptin increased hospitalizations due to heart failure has prompted additional research of the DPP-4 inhibitors to determine if this is a class effect.[11] The meta-analysis by Monami, et al included 84 randomized clinical trials in patients with T2DM lasting at least 24 weeks. Included treatments were the following: vildagliptin, saxagliptin, sitagliptin, alogliptin, linagliptin and dutogliptin. Of the 84 trials, 45 reported no HF events and therefore 37 trials were included in the primary analysis. Eighty-seven percent of the HF events were from SAVOR-TIMI53 (saxagliptin) and EXAMINE (alogliptin).
In placebo and active comparison studies, the risk of acute HF was higher in the DPP-4 inhibitor-treated groups (OR: 1.19 (95% CI, 1.03 to 1.37; p=0.015). When trials with and without HF events were analyzed, the incidence of HF was the same for DPP-4 inhibitors and comparators (0.9%). When individual DPP-4 inhibitors were analyzed separately, only saxagliptin demonstrated a significant increase in HF risk.

Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Outcomes: Meta-analysis of Randomized Clinical Trials with 55,141 Participants

A meta-analysis and systematic review studied the CV safety and efficacy of DPP-4 inhibitors.[12] Fifty trials with a mean follow-up of 45.3 weeks and minimal study period of 24 weeks provided data on 55,141 patients. Alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin were the included search terms. Studies meeting the inclusion criteria had to have at least one CV outcome, a minimum of 100 patients, a randomized study design and in participants with T2DM. All-cause mortality, CV mortality, acute coronary syndrome or strokes were similar for DPP-4 inhibitors and comparators (placebo and active). The incidence in heart failure outcomes was significantly higher with DPP-4 inhibitors than with comparators (RR 1.16; 95% CI, 1.01 to 1.33; p=0.04). Like with other meta-analyses, the majority of HF outcomes came from SAVORTIMI53 (66.2%) and EXAMINE (21.3%).

A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events: comparison of glyburide with other secretagogues and with insulin

This systematic review was done to investigate the hypoglycemia and cardiovascular risk of glyburide.[13] Twenty one studies lasting 1 month to 10 years were included in the analysis. Glyburide was compared with other secretagogues and with insulin, in separate analyses. In a subgroup analysis glyburide was compared to other SUs. Glyburide was found to have a higher risk of at least one episode of hypoglycemia compared to other secretagogues (RR 1.52, 95% CI 1.21 to 1.92). Results of the comparison of glyburide to other SU demonstrated similar results with a RR of 1.83 (95% CI 1.35 to 2.49). Total hypoglycemia episodes were also higher with gluyburide compared to other secretagogues, however there was high heterogeneity between the studies. Weight, A1c and cardiovascular events were not statistically different between glyburide and comparators.

Effectiveness and Safety of Glimepiride and iDPP4, Associated with Metformin in Second Line Pharmacotherapy of Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis

A systematic review and meta-analysis was done to analyze trial data on the efficacy and safety of combination of DPP-4 inhibitors/metformin compared to glimepiride/metformin as second line therapy in the treatment patients with T2DM.[14] Four studies involving 5637 patients with endpoints presented as primary variables (no composite endpoints) were included in the review. Three of the four studies were non-inferiority design. Participants were a mean age of 58 years, mean weight o f 87 kg, and mean A1c of 7.5%. Sitagliptin, vildagliptin, and linagliptin were the DPP-4 inhibitors included in the study. Comparisons favored glimepiride/metformin use compared to DPP-4 inhibitors/metformin for A1C lowering [weighted mean difference (WMD) -0.12 (CI-0.16 to -0.07). More patients taking the glimepiride combination met A1C goals <7% compared to DPP-4 inhibitors combination. Dropouts due lack of effectiveness was lower with glimepiride than DPP-4 inhibitors combinations and need for rescue treatment was 20% less in the glimepiride group. Weight loss of -0.23 to -1.4 kg was seen with DDP-4 inhibitor combinations compared to weight gain with glimepiride combinations, ranging from 0.73 to 1.76 kg. Adverse effects were high with combinations of glimepiride and DPP-4 inhibitors, 78.3% and 71.9%, respectively. The risk of hypoglycemia was higher with glimepiride combination therapy compared to DPP-4 inhibitors (OR 5.07, 95% CI 4.33 to 5.93), mostly due to mild to moderate episodes of hypoglycemia. Discontinuations due to adverse events was higher with glimepiride combinations compared to DPP-4 inhibitors (OR 1.34, 95% CI 1.17 to 1.81).

New Guidelines:

Standards of Medical Care in Diabetes – 2015: Summary of Revisions

The annual update of the *Clinical Practice Recommendations* by the ADA have been renamed *Standards of Medical Care in Diabetes.*[1] Changes relevant to our update include the inclusion of all available therapies for diabetes management. As with previous recommendations, initial treatment with metformin should be used if pharmacotherapy is warranted. Patients presenting with markedly elevated blood glucose levels, A1C or severe symptoms should be considered for insulin therapy alone or in combination with other agents. If combination therapy is required, data suggests that all non-insulin therapy combinations lower A1C

by a similar level of approximately 0.9-1.1%.[1] Suggested add-ons to metformin include: SUs, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs or basal insulin. Patients unable to take SU therapy due to irregular meal schedules or hypoglycemia may benefit from a rapid-acting secretagogue (meglitinides). Other antidiabetic agents that aren't routinely recommended due to efficacy or tolerability issues are: α-glucosidase inhibitors, colesevelam, bromocriptine, or pramlitide. A patient-centered approach is emphasized, factoring in efficacy, side effects, cost, hypoglycemia risk, weight, comorbidities and patient preferences.

Institute for Clinical Systems Improvement (ICSI) – Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

In July of 2014 the Institute for Clinical Systems Improvement (ICIS) published guidance on the management of adults with T2DM.[2] Guideline recommendations are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Metformin and insulin were the only glucose lowering therapies specifically included in guidelines. Metformin is strongly recommended based on high strength of evidence as first-line therapy. Failure to obtain A1C goals with metformin should have treatment modified. No additional oral treatment recommendations are discussed. Insulin therapy for hospitalized patients is discussed but not graded.

NICE Guidance – Empagliflozin in Combination Therapy for Treating Type 2 Diabetes

The National Institute for Health and Care Excellence (NICE) reviewed the efficacy and safety data of empagliflozin use in combination with other treatments for patients with T2DM.[4] NICE recommends empagliflozin as dual therapy for patients if a SU is contraindicated or not tolerated or the person is at significant risk of hypoglycemia. The use of empagliflozin as part of a triple therapy regimen is recommended for patients taking metformin and a SU, or metformin and a TZD. Empagliflozin may also be offered as an option with insulin, with or without other antidiabetic agents. The guidance suggests that empagliflozin would be best suited for overweight patients with good renal function requiring assistance in lowering blood glucose levels and not susceptible to genitourinary infections. Meta-analysis data show the clinical effectiveness of empagliflozin was similar to other SGLT-2 inhibitors and sitagliptin.

AACE/ACE – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan – 2015

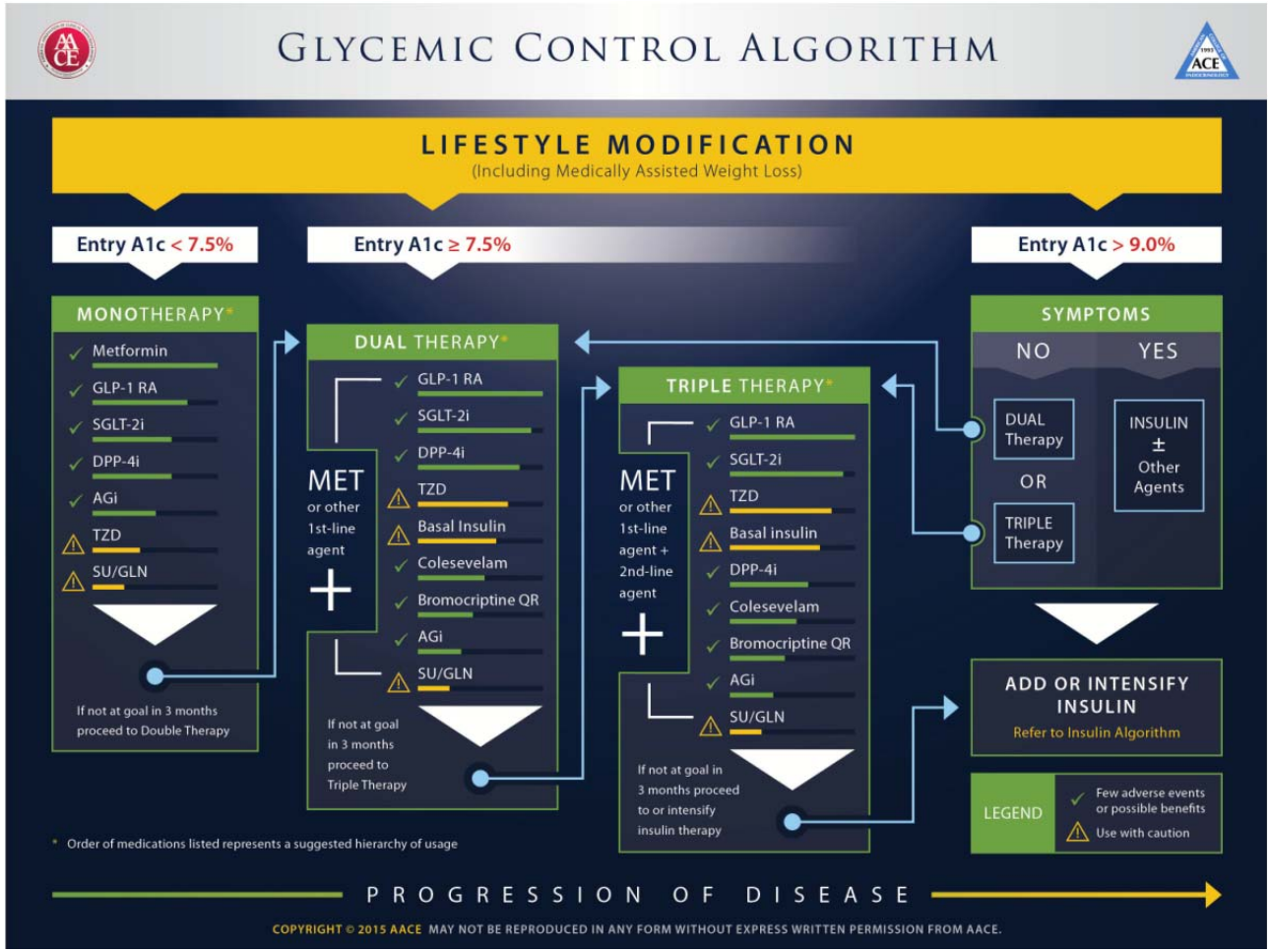
The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) updated their 2011 guidance with new recommendations for individuals with DM.[5] Guidelines development is based on expertise from AACE members integrating objective and subjective data. Evidence is graded and incorporated into recommendation grades (strong to not evidence based). New recommendations include management of comorbidities and a focus on safety as well as efficacy. A comprehensive approach to patient management is suggested, with the specific recommendations of: an education resource for the comprehensive management of patients with DM that involves all relevant practitioners, guidance on coping with issues inherent to DM care, and electronic sharing of patient information to facilitate decision making.

Blood glucose goals are recommended based on patient specific factors, with a general A1C target of ≤6.5% for most adults. Pharmacotherapy should be tailored to the patient's characteristics, such as A1C lowering, comorbidities and risk of hypoglycemia. The guidelines recommend that patients presenting with an A1C less than 7.5% be started on one of the following agents: metformin, GLP-1 RA, SGLT-2 inhibitor, DPP-4 inhibitor or an α-glucosidase inhibitor, based on a weak recommendation due to weak evidence.[5] Other options are SUs, TZDs or glinides since adverse effects may not allow these drugs to be universally recommended for everyone. Dual therapy is recommended for those with A1C greater than 7.5%. Metformin and an additional agent with low risk of hypoglycemia and weight neutral or weight negative (i.e., GLP-1 RA, SGLT-2 inhibitors, DPP-4 inhibitors) are weakly recommended based on weak evidence. TZDs and basal insulin may also be appropriate as an add-on agent. Other treatments, such as colesevelam, bromocriptine, or α-glucosidase inhibitors, have low glucose lowering ability but also low risk of adverse events, which make them appropriate for a small subset of DM patients. Intermediate evidence suggests use of SUs and glinides be monitored regularly due to the risk of hypoglycemia. Symptomatic patients with A1C greater than 9% are candidates for insulin alone or combined with metformin or another oral treatment (strongly recommended). The addition of pramlintide or a GLP-1 RA to prandial insulin is recommended to

reduce postprandial hyperglycemia and weight (intermediate evidence). Long-acting insulin is strongly recommended if non-insulin therapy is unable to control glucose levels in patients with DM. Rapid-acting insulin is recommended for elevated postprandial glucose levels based on intermediate evidence.

AACE/ACE Comprehensive Diabetes Management Algorithm 2015

The AACE algorithm serves as a quick reference guide for physicians and reiterates management described in the comprehensive care plan for DM patients as described above.[6]



Abrahmson M, Barzilay J, Blonde L, et al. AACE/ACE Comprehensive Diabetes Management Algorithm. *Endocr Prac*. *2015;21:438-447.*

Safety Alerts:

In May of 2015, the FDA issued a warning pertaining to the use of SGLT-2 inhibitors and the risk of ketoacidosis.[23] Patients should be monitored for signs and symptoms of acidosis. The FDA is still evaluating the risk and no labeling changes have been issued at this time.

New Formulations or Indications:

GLYXAMBI® (empagliflozin and linagliptin) is a combination of an SGLT-2 inhibitor and a DPP-4 inhibitor approved in January of 2015 by the FDA to be used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when the treatment of both empagliflozin and linagliptin is appropriate.[24] The empagliflozin/linagliptin combination was approved based on one study in patients with T2DM (n=686). Patients were randomized to empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg compared to treatment with the individual components. All groups were on baseline metformin therapy. The combination of empagliflozin 10 mg or 25 mg and linagliptin 5 mg was superior at reducing A1c after 24 weeks compared to either empagliflozin or linagliptin alone.[22]

Randomized Controlled Trials:

Forty-five potentially relevant clinical trials were evaluated from the literature search. After further review, only one trial was included. Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trial is briefly described in the table below. The full abstract is included in Appendix 2.

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Primary Outcome	ARR/NNT	Quality Rating
1. Zannad, et al (EXAMINE)[9,25] RCT, DD, DB, Phase 3	1. Alogliptin (A) 25 mg PO daily* 2. Placebo (P) * Dose was 12.5 mg PO daily for eGFR 30-60 mL/min per 1.73m^2 and for eGFR <30 mL/min per 1.73m^2 the dose was 6.25 mg PO daily Treatment duration: 18 months	Demographics: Age: 61 years Male: 65% Hx of HF: 29% NYHA Class II: 56% A1C: 8.1% Key Inclusion Criteria: T2DM Currently on DM therapy (excluding GLP-1 RA and DPP-4 inhibitors) ACS event within 15-90 days before randomization A1C of 6.5 – 11% or insulin therapy Key Exclusion Criteria:	ITT: 1.2701 2.2679 PP: 1. 2128 2. 2057 Attrition: 1. 573 (21%) 2. 622 (23%)	**Composite of CV death, non-fatal MI, and non-fatal stroke:** A: 305 (11.3%) vs. P: 316 (11.8%); HR 0.96 (95% CI, ≤1.16; P= 0.315) **Composite of CV death, non-fatal MI, non-fatal stroke, and urgent revascularization due to unstable angina:** A: 344 (12.7%) vs. P: 359 (13.4%); HR 0.95 (95% CI, ≤1.16; P=0.258) **First occurrence of all-cause mortality, non-fatal MI, non-fatal stroke, urgent revascularization due to unstable angina, and hospital admission**	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Patients were randomized in a 1:1 ratio. No details on randomization methods were given. Performance: Trial was double-blind design but no details on blinding were provided. Double-dummy design masked treatment allocation. Detection: Outcome assessment was done by an independent committee, blinding was not described. Attrition: Overall attrition was 22% off the study drug at the end of the trial and similar between groups. ITT analysis was used for all data. **Applicability**: Patients: Patients were well matched except for those patients with heart failure at baseline tending to be older, female, higher BNP concentrations, and lower eGFR levels compared to those without heart failure. Intervention: Alogliptin 6.25 mg – 25 mg daily depending on renal function. Comparator: Matched placebo. Outcomes: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated

		NYHA Class IV Unstable heart disease, uncontrolled blood pressure or dialysis within 14 days of screening		**due to HF*:** A: 433 (16.0%) vs. P: 441 (16.5%); HR 0.98 (95% CI, 0.86 to 1.12; P=0.728) Hospital admission for HF*: A: 85 (3.1%) vs. P: 79 (2.9%); HR 1.07 (95% CI, 0.79 to 1.46; P=0.657) All-cause mortality*: A: 106 (3.9%) vs. P: 131 (4.9%); HR 0.80 (95% CI, 0.62 to 1.03; P=0.081) * Component of a predefined exploratory endpoint Post-hoc analysis of Hospital admission for HF: A: 106 (3.9%) vs. P: 89 (3.3%); HR 1.19 (95% CI, 0.90 to 1.58; P=0.220)	NS NS NS NS	with unacceptable levels of cardiac risk. In this study the rate of hospitalizations for heart failure, which has recently been shown to be elevated with saxagliptin, was a post-hoc analysis limiting the applicability of the findings. Setting: Forty-nine countries and 898 centers. **Analysis**: In patients with T2DM, alogliptin demonstrated a similar risk of heart failure as placebo, based on short-term data. Subgroup analysis of patients with preexisting heart failure showed no increased risk of adverse cardiac events for patients taking alogliptin compared to placebo.
1. Green, et al (TECOS)[10] RCT, DB, Phase 3	1. Sitagliptin (S) 100 mg PO daily*† 2. Placebo (P) † * Dose was 50 mg PO daily for eGFR ≥30 to <50 mL/min per 1.73m^2 † Patients also received usual care with metformin, pioglitazone, sulfonylurea or insulin Median follow-up: 3 years	Demographics: Age: 65.5 years Female: 29.3% Hx of HF: 18.0% NYHA Class 3 or higher: 2.5% A1C: 7.2% Key Inclusion Criteria: T2DM Currently on DM therapy (metformin, pioglitazone, sulfonylurea, or insulin) Established coronary artery disease A1C of 6.5 – 8.0% or insulin therapy Key Exclusion	ITT: 1.7332 2.7339 PP: 1. 5682 2. 5633 Attrition: 1. 360 (22.5%) 2. 622 (23.2%)	**Composite of CV death, non-fatal MI, and non-fatal stroke or hospitalization for unstable angina (PP population):** S: 839 (11.4%) vs. P: 851 (11.6%); HR 0.98 (95% CI 0.88 to 1.09; P<0.001 for noninferiority) Supporting analysis of ITT population: HR 0.98 (95% CI, 0.89 to 1.08; P= 0.65 for superiority) **Composite of CV death, non-fatal MI or non-fatal stroke (PP population):** S: (12.7%) vs. P: (13.4%); HR 0.99 (95% CI 0.89 to 1.11; P<0.001 for	NA NS NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized in a 1:1 ratio. Randomized via an interactive voice-response system. Performance: Trial was double-blind design but with packaging to maintain blinding. Detection: Outcome assessment was done by an independent classification committee, blinded to treatment assignment. Attrition: Overall attrition was approximately 23% in both groups. Per protocol population was used for the primary analysis and ITT analysis was done as a supporting analysis. **Applicability**: Patients: Patients with were well matched with similar usage of diabetic and cardiovascular therapies. Patients had moderately elevated A1Cs and preexisting cardiovascular disease. No patients with severe renal insufficiency were included. Intervention: Sitagliptin 50-100 mg daily depending on renal function. Comparator: Matched placebo. Outcomes: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated

		Criteria: Previous use of DPP-4 inhibitor, GLP-1 RA, or TZD (other than pioglitazone) within previous 3 months Severe hypoglycemia eGFR < 30 mL/min per 1.73 m^2		noninferiority) Supporting analysis of ITT population: HR 0.99 (95% CI, 0.89 to 1.10; P= 0.84 for superiority) Hospital admission for HF (ITT population): s: 228 (3.1%) vs. P: 229 (3.1%); HR 1.00 (95% CI, 0.83 to 1.20; P=0.98) All-cause mortality (ITT population): S: 547 (7.5%) vs. P: 537 (7.3%); HR 1.01 (95% CI, 0.90 to 1.14; P=0.88) A1C at 48 months: S: 7.20 P: 7.49 LSMD -0.29 (95% CI -0.32 to -0.27)	 NS NS NS NS	with unacceptable levels of cardiac risk. In this study the rate of hospitalizations for heart failure, which has recently been shown to be elevated with saxagliptin, was included as a secondary endpoint and therefore results could be do to chance. Setting: Thirty-eight countries and 673 centers. **Analysis**: In patients with T2DM, alogliptin demonstrated a similar risk of heart failure as placebo, based on short-term data. Subgroup analysis of patients with preexisting heart failure showed no increased risk of adverse cardiac events for patients taking alogliptin compared to placebo.
Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DD = double-dummy; eGFR = estimated glomular filtration rate; FAS = full analysis set; HF = heart failure; HR = hazard ratio; ITT = intention to treat; kg = kilogram; LSMD = least-squares mean difference; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; NYHA = New York Heart Association; PO = by mouth; PP = per protocol;						

References:

1. American Diabetes Association. 2015 standards of medical care in diabetes. *Diabetes Care*. 2015;38(Suppl.1):S4. Doi: 10.2337/dc15-s003.
2. Redmon B, Caccamo D, Flavin P, et al. Institute for Clinical Systems Improvement. Diagnosis and Management of type 2 diabetes mellitus in adults. Updated July 2014. Available at: https://www.icsi.org/_asset/3rrm36/Diabetes.pdf.
3. Agency for Healthcare Research and Quality. Diabetes medications for adults with type 2 diabetes: an update focused on monotherapy and add-on therapy to metformin – draft report 2015. Draft Comparative Effectiveness Review. www.ahrq.gov.
4. National Institute for Health and Care Excellence. Empagliflozin in combination therapy for treating type 2 diabetes. Nice Technology Appraisal Guidance [TA336]. March 2015. Available at: https://www.nice.org.uk/guidance/ta336.
5. Handelsman Y, Bloomgarden Z, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care plan – 2015. *Endocr Pract*. 2015;21(Suppl 1). Available at: https://www.aace.com/files/dm-guidelines-ccp.pdf.
6. Abrahmson M, Barzilay J, Blonde L, et al. AACE/ACE Comprehensive Diabetes Management Algorithm. *Endocr Prac*. 2015;21:438-447. Available at: https://www.aace.com/publications/algorithm.
7. Drug Use Research and Management Programs. Abbreviated class update: newer diabetes medications. Oregon drug use review/Pharmacy and Therapeutics Committee Meeting. September 26, 2013. Available at http://www.orpdl.org/durm/meetings/meetingdocs/2013_09_26/finals/2013_09_26_PnT_Complete.pdf. Accessed on July 27, 2015.
8. Inzucchi S, Lipska K, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease. *JAMA*. 2014;312(24):2668-2675. Doi:10.1001.jama.2014.15298.
9. Zannad F, Cannon C, Cushman W, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a mulitcentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-76.
10. Green J, Bethel A, Armstrong P, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. NEJM 2015;373:232-42. Doi: 10.1056/NEJMoal1501352.
11. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: A meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc*. 2014;24:689-697.
12. Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovasc Ther 2014;32:147-158. Doi: 10.1111/1755-5922.12075.
13. Gangji A, Cukierman T, Gerstein H, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events. Diabetes Care 2007; 30; 389-394.
14. Amate JM, Lopez-Cuadrado T, Almendro N, et al. Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis. Int J Clin Pract 2015; 69:292-304.
15. US Food and Drug Administration. FDA approves weight-management drug Saxenda. FDA News Release. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm427913.htm. Accessed on August 12, 2015.
16. Feltner C, Wines R, Simon J, et al. Drug class review: Newer diabetes medications and combinations. Prepared by the RTI-UNC Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University. Portland, OR. 2014.
17. Scirica B, Bhatt D, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1317-26. Doi:10.1056/NEJMoal1307684.
18. Vasilakou D, Karagiannis T, Athanasiasou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159:262-274.

19. Thakurta, S. Drug Effectiveness Review Project: Drug Class Review on Oral Hypoglycemics. Preliminary Scan Report #6. Pacific Northwest Evidence Practice Center. May 2014.
20. National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics. NIH Publication. Accessed July 2, 2013. Accessed at: http://www.diabtetes.niddk.nih.gov/dm/pubs/statistics/#Diagnosed20.
21. Oregon Health Authority. Oregon Diabetes Report – A report on the burden of diabetes in Oregon and progress on the 2009 strategic plan to slow the rate of diabetes. January 2015. Available at: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf. Accessed June 9, 2015.
22. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. 2010. Accessed July 23, 13. Available at: http://www.cdc.gov/media/pressrel/2010/r101022.html.
23. US Food and Drug Administration. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Drug Safety Communication May 15, 2015. Available at: http://www.fda.gov/drugs/drugsafety/ucm446845.htm. Accessed June 30, 2015.
24. Boehringer Ingelheim Pharmaceuticals, Inc. Glyxambi Label. US Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206073s000lbl.pdf. Accessed June 15, 2015.
25. White W, Bakris G, Bergenstal R, et al. Examination of Cardiovascular OutcoMes with AlogliptIN versus standard of CarE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J*. 2011;162:620-626.

Appendix 1: Current Status on Preferred Drug List

Diabetes, Dipeptidyl Peptidase-4 Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**JANUMET**	**SITAGLIPTIN PHOS/METFORMIN HCL**	**Y**
ORAL	**TABLET**	**JANUVIA**	**SITAGLIPTIN PHOSPHATE**	**Y**
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN /METFORMIN HCL	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN MONOHYDRATE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N

Diabetes, GLP-1 Receptor Agonists & Amylin Analogs

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN INJCTR	SYMLINPEN 120	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	SYMLINPEN 60	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	BYETTA	EXENATIDE	N
SUB-Q	PEN INJCTR	VICTOZA 2-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-Q	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-Q	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-Q	PEN INJCTR	TRULICITY	DULAGLUTIDE	N

Diabetes, Oral Hypoglycemic

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**DIABETA**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLYBURIDE**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLIPIZIDE**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**GLUCOTROL**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**AMARYL**	**GLIMEPIRIDE**	**Y**
ORAL	**TABLET**	**GLIMEPIRIDE**	**GLIMEPIRIDE**	**Y**
ORAL	**TAB ER 24H**	**GLUCOPHAGE XR**	**METFORMIN HCL**	**Y**
ORAL	**TAB ER 24H**	**METFORMIN HCL ER**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**GLUCOPHAGE**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**METFORMIN HCL**	**METFORMIN HCL**	**Y**
ORAL	TABLET	TOLBUTAMIDE	TOLBUTAMIDE	N
ORAL	TABLET	CHLORPROPAMIDE	CHLORPROPAMIDE	N
ORAL	TABLET	TOLAZAMIDE	TOLAZAMIDE	N
ORAL	TAB ER 24	GLIPIZIDE ER	GLIPIZIDE	N
ORAL	TAB ER 24	GLIPIZIDE XL	GLIPIZIDE	N
ORAL	TAB ER 24	GLUCOTROL XL	GLIPIZIDE	N
ORAL	TABLET	GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	GLYNASE	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	PRANDIN	REPAGLINIDE	N
ORAL	TABLET	REPAGLINIDE	REPAGLINIDE	N
ORAL	TABLET	NATEGLINIDE	NATEGLINIDE	N
ORAL	TABLET	STARLIX	NATEGLINIDE	N
ORAL	SOLUTION	RIOMET	METFORMIN HCL	N
ORAL	TAB ER 24	FORTAMET	METFORMIN HCL	N
ORAL	TAB ER 24	METFORMIN HCL ER	METFORMIN HCL	N
ORAL	TABERGR24H	GLUMETZA	METFORMIN HCL	N
ORAL	TABLET	ACARBOSE	ACARBOSE	N
ORAL	TABLET	PRECOSE	ACARBOSE	N
ORAL	TABLET	GLYSET	MIGLITOL	N
ORAL	TABLET	GLUCOVANCE	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLYBURIDE-METFORMIN	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	N
ORAL	TABLET	PRANDIMET	REPAGLINIDE/METFORMIN HCL	N

Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N

Diabetes, Thiazolidiniones

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**PIOGLITAZONE HCL**	**PIOGLITAZONE HCL**	**Y**
ORAL	TABLET	AVANDIA	ROSIGLITAZONE MALEATE	N
ORAL	TABLET	AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	N
ORAL	TABLET	DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	N
ORAL	TABLET	PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	N
ORAL	TBMP 24HR	ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	N

Appendix 2: Abstracts of Clinical Trials

Zannad F, Cannon C, Cushman W, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a mulitcentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-76.

Background: The EXAMINE trial showed non-inferiority of the DPP-4 inhibitor alogliptin to placebo on major adverse cardiac event (MACE) rates in patients with type 2 diabetes and recent acute coronary syndromes. Concerns about excessive rates of in-hospital heart failure in another DPP-4 inhibitor trial have been reported. We therefore assessed hospital admission for heart failure in the EXAMINE trial. Methods: Patients with type 2 diabetes and an acute coronary syndrome event in the previous 15–90 days were randomly assigned alogliptin or placebo plus standard treatment for diabetes and cardiovascular disease prevention. The prespecified exploratory extended MACE endpoint was all-cause mortality, non-fatal myocardial infarction, non- fatal stroke, urgent revascularization due to unstable angina, and hospital admission for heart failure. The post-hoc analyses were of cardiovascular death and hospital admission for heart failure, assessed by history of heart failure and brain natriuretic peptide (BNP) concentration at baseline. We also assessed changes in N-terminal pro-BNP (NT-pro-BNP) from baseline to 6 months. Findings: 5380 patients were assigned to alogliptin (n=2701) or placebo (n=2679) and followed up for a median of 533 days (IQR 280–751). The exploratory extended MACE endpoint was seen in 433 (16·0%) patients assigned to alogliptin and in 441 (16·5%) assigned to placebo (hazard ratio [HR] 0·98, 95% CI 0·86–1·12). Hospital admission for heart failure was the first event in 85 (3·1%) patients taking alogliptin compared with 79 (2·9%) taking placebo (HR 1·07, 95% CI 0·79–1·46). Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the

post hoc analysis (HR 1·00, 95% CI 0·82–1·21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups. Interpretation: In patients with type 2 diabetes and recent acute coronary syndromes, alogliptin did not increase the risk of heart failure outcomes.

Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015 Jul 16;373(3):232-42.

Background: Data are lacking on the long-term effect on cardiovascular events of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease. Methods: In this randomized, double-blind study, we assigned 14,671 patients to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, aimed at reaching individually appropriate glycemic targets in all patients. To determine whether sitagliptin was noninferior to placebo, we used a relative risk of 1.3 as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Results: During a median follow-up of 3.0 years, there was a small difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, -0.29 percentage points; 95% confidence interval [CI], -0.32 to -0.27). Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98). There were no significant between-group differences in rates of acute pancreatitis (P=0.07) or pancreatic cancer (P=0.32).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to June Week 3 2015

Search Strategy:

#	Searches	Results
1	sitagliptin {No Related Terms}	807
2	alogliptin {No Related Terms}	158
3	saxagliptin {No Related Terms}	233
4	linagliptin {No Related Terms}	189
5	pramlintide {No Related Terms}	233
6	exenatide {No Related Terms}	928
7	liraglutide {No Related Terms}	603
8	albiglutide {No Related Terms}	35
9	dulaglutide {No Related Terms}	16
10	glyburide {No Related Terms}	3791
11	glipizide {No Related Terms}	532
12	glimepiride {No Related Terms}	742
13	metformin {No Related Terms}	9524
14	tolbutamide {No Related Terms}	1565
15	chlorpropamide {No Related Terms}	208
16	tolazamide {No Related Terms}	21
17	repaglinide {No Related Terms}	499
18	nateglinide {No Related Terms}	366
19	acarbose {No Related Terms}	1338
20	miglitol {No Related Terms}	151
21	dapagliflozin {No Related Terms}	145
22	canagliflozin {No Related Terms}	93
23	empagliflozin {No Related Terms}	57
24	pioglitazone {No Related Terms}	3242
25	rosiglitazone {No Related Terms}	4148
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	26318
27	limit 26 to (english language and yr="2014 -Current")	2029
28	limit 27 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	554

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to June Week 3 2015

Search Strategy:

#	Searches	Results
1	pramlintide.mp.	278
2	limit 1 to (english language and yr="2012 -Current")	34
3	limit 2 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	6

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All DPP-4 inhibitors

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #4	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class	No: Approve for up to 12 months

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *TBD; 1/15; 9/14; 1/14; 2/13*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred GLP-1 receptor agonists

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class	No: Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the patient currently taking insulin?	Yes: Go to #6	No: Approve for up to 12 months
6. Is the patient requesting exenatide, liraglutide or albiglutide and using basal insulin?	Yes: Approve for up to 12 months	No: Go to #7
7. Is the patient requesting dulaglutide and using prandial insulin?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *9/15 (KS); 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *TBD; 2/15; 1/14*

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All SGLT-2 inhibitors

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #4	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
4. Is the patient requesting the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2 ?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #5
5. Has the patient tried and failed all of the following drugs, or have contraindications to these drugs? • Insulin • Thiazolidinedione • DPP-4 inhibitor • GLP-1 agonist • Amylin analog	Yes: Approve for up to 12 months.	No: Pass to RPh; deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *9/15 (KS); 1/15; 9/14; 9/13*
Implementation: *TBD; 2/15*

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

Literature Scan: Oral Multiple Sclerosis Drugs

Date of Review: September 2015
PDL Class: Multiple Sclerosis

Date of Last Review: September 2014
Literature Search: July 2014 – June 2015

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

Conclusions:

- There is insufficient comparative evidence between oral disease modifying drugs for multiple sclerosis (MS) and other oral or injectable disease-modifying therapies.
- Moderate-quality evidence demonstrates the proportion of patients who experience at least one relapse over 2 years is reduced with use of dimethyl fumarate compared to placebo (relative risk [RR] = 0.58; 95% CI, 0.50 to 0.67, p<0.00001) but not when compared to glatiramer acetate (RR=0.91; 95% CI, 0.72 to 1.13);[1] however, the quality of the evidence to support benefit of dimethyl fumarate to slow worsening disability versus placebo is low (RR = 0.66; 95% CI, 0.53 to 0.81).[2]
- According to the National Institute for Health and Clinical Excellence (NICE), there is low quality evidence fampridine (ie, dalfampridine), which is not a disease-modifying drug, may be more effective than placebo in response outcomes to different walking ability parameters are assessed; however, there is low quality evidence that there is no difference in efficacy between fampridine and placebo in time to walk 8 meters and there is insufficient evidence to determine if fampridine improves gait speed versus placebo.[3] In addition, there is low quality evidence that there is no difference in the MS walking scale (MSWS-12) scores with fampridine compared to placebo.[3] The NICE recommends against the use of dalfampridine due to poor cost effectiveness.[3]
- There is low-quality evidence, based on one phase 3 trial, that a daily dose of 7 mg and 14 mg of terflunomide may reduce time to first relapse in patients with a first clinical episode suggestive of MS (14 mg vs. placebo: hazard ratio [HR]=0.574 [95% CI, 0.379-0.869; p=0.0087] and 7 mg vs. placebo: HR=0.628 [95% CI, 0.416-0.949; p=0.0271].[4] It is currently FDA-approved to treat relapsing-remitting forms of multiple sclerosis (RRMS).[5]
- A follow-up phase 3 trial of fingolimod confirms results from previous phase 3 trials, and provides moderate-quality evidence the drug significantly reduces relapse rates versus placebo in patients with RRMS (fingolimod 0.5 mg: rate ratio [RR]=0.52 (95% CI, 0.40-0.66; p<0.0001).[6] It is currently FDA-approved to treat RRMS, to reduce the frequency of clinical exacerbations, and to delay the accumulation of physical disability in these patients.[7]

Recommendations:

- Maintain current prior authorization criteria for oral MS drugs (see **Appendix 5**). No further review or research needed at this time.
- Evaluate comparative drug costs of oral disease modifying therapies (dimethyl fumarate, fingolimod, teriflunomide) in the executive session.

Previous Conclusions:

- There is moderate strength of evidence that glatiramer 40 mg three times a week (tiw), a recently approved dosage and new formulation, reduced annualized relapses compared to placebo by 34% (mean ARR = 0.331 vs. 0.505; RR 0.66 [95% CI 0.539 to 0.799], p < 0.0001) based on one 12-month, good quality study. Limited data suggests similar efficacy to glatiramer 20 mg daily, however, no direct comparisons are available.
- There is low-moderate strength of evidence that fingolimod 0.5 mg reduced the mean annualized relapse rate by 48% in patients with relapsing-remitting multiple sclerosis (MS) compared to placebo, 0.21 versus 0.40, respectively (rate ratio 0.52, 95% CI 0.40 to 0.66; p<0.001) as demonstrated by one fair quality study.
- There is moderate strength of evidence from one good-quality study that peginterferon beta-1a significantly reduced relapses in patients with relapsing-remitting MS when given every 14 or 29 days compared to placebo. Annualized relapse rates at 48 weeks were 0.397 for placebo, 0.256 for peginterferon beta-1a every 2 weeks and 0.288 for peginterferon beta-1a every 4 weeks. The most common adverse event with active treatment were injection site reactions which were higher in the peginterferon beta-1a groups receiving injections every 2 weeks.
- There is low strength of evidence indicating dimethyl fumarate 720 mg daily reduced the risk of relapse (RR 0.75, 95% CI 0.59 to 0.96) and improved annualized relapse rate (rate ratio 0.69, 95% CI 0.51 to 0.96) compared with glatiramer 20 mg. This was based on one fair quality 2-year, placebo-controlled trial comparing dimethyl fumarate and glatiramer with placebo. The study was not designed to directly compare dimethyl fumarate with glatiramer and there was no difference in preventing disability progression.
- There is insufficient evidence that dimethyl fumarate is more effective than other treatment options in slowing disability progression in patients with RRMS.
- Based on an indirect study, there is low quality evidence that dimethyl fumarate is associated with more adverse events than glatiramer, but no differences in serious adverse events or withdrawals due to adverse events.
- The evidence supports a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes (1.51, 95% CI 1.11 to 2.07; NNT 6). There is conflicting evidence on disease progression outcomes.
- Three head to head trials suggest a benefit of interferon beta-1a SC over interferon beta-1a IM in relapse outcomes, with no differences in disease progression.
- There is insufficient evidence to identify any differences between interferon beta-1b SC and interferon beta-1a SC.
- There is no head to head evidence available for teriflunomide and insufficient evidence to determine its efficacy and safety.

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), Cochrane Collection, 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[1] aimed to conduct a meta-analysis after assessing the efficacy and safety of dimethyl fumarate for the treatment of RRMS. Eligible studies were published, blinded RCTs evaluating dimethyl fumarate monotherapy compared to placebo or an active control for the treatment of RRMS in adults (≥18 years of age).[1] Evaluation of efficacy was based on the annualized relapse rate at 2 years, the proportion of patients who relapsed, or proportion of patients who had confirmed progression of disability by 2 years.[1] Safety evaluations were based on the proportion of patients who experienced any adverse event, any serious adverse event, or proportion of patients who discontinued treatment due to adverse events or died from any cause.[1] Only 3 RCTs were identified and eligible for qualitative review; only 2 of these RCTs were eligible for meta-analysis.[1] In brief, the two 96-week studies (n=2,651) included in the meta-analysis were phase 3, double-blind placebo-controlled RCTs which evaluated the effectiveness of dimethyl fumarate 240 mg twice daily and three times daily as monotherapy in adult patients with RRMS; a third arm in one of the studies also assessed a third group of patients who received subcutaneous daily injections of glatiramer acetate.[1] In this review, only the FDA-approved twice daily dose will be discussed.[1] The annualized rate of relapse at 2 years was significantly reduced with dimethyl fumarate when compared to placebo ($p<0.001$).[1] In patients with one or no relapse in the year prior to study entry, the annualized rate of relapse with dimethyl fumarate was reduced by 50%; in patients with 2 or more relapses in the year prior to study entry, the annualized rate of relapse was decreased by 47%.[1] The difference between dimethyl fumarate and glatiramer acetate was not significantly different.[1] In both RCTs, the proportion of patients who had at least 1 relapse of MS by 2 years was significantly reduced with dimethyl fumarate (relative risk [RR] = 0.58; 95% CI, 0.50 to 0.67, $p<0.00001$).[1] However, there was no statistically significant difference in the proportion of patients with a relapse by 2 years between dimethyl fumarate and glatiramer acetate (RR = 0.91; 95% CI, 0.72 to 1.13).[1] Dimethyl fumarate was also associated with reduced risk of confirmed progression of disability over 2 years compared to placebo (RR = 0.66; 95% CI, 0.53 to 0.81).[1] Overall, there was no significant difference in the frequency of any adverse events between dimethyl fumarate and placebo (RR = 1.02; 95% CI, 1.00 to 1.05).[1] Adverse events that occurred more frequently with dimethyl fumarate in both trials compared to placebo included: flushing and gastrointestinal events (e.g., diarrhea, nausea, and upper abdominal pain).[1] However, glatiramer acetate was associated with significantly fewer adverse events compared to dimethyl fumarate (RR = 1.09; 95% CI, 1.04 to 1.14).[1]

A recent systematic review[2] from the Cochrane Collaboration specifically aimed to review the evidence of dimethyl fumarate as monotherapy or combination therapy compared to placebo or other disease modifying therapies for MS. All parallel-group RCTs with a length of follow-up of at least 1 year were included. The 2 placebo-controlled Phase 3 trials previously assessed by Kawalec, et al.[1] were the only trials identified in the Cochrane review; the data from the Cochrane meta-analysis were similar and will not be reported again. The authors concluded there is "moderate-quality evidence to support that dimethyl fumarate at a dose of 240 mg orally three times daily or twice daily reduces both the number of patients with a relapse and the annualized rate over 2 years of treatment in comparison to placebo. However, the quality of the evidence to support the benefit in reducing the number of patients with disability worsening is low."[2]

Both systematic reviews of dimethyl fumarate found flushing and gastrointestinal events to be the most common adverse effects associated with the drug.[1,2] Both lymphocytopenia (abnormally low level of lymphocytes in the blood) and leukopenia (decreased number of white blood cells) were significantly more common with dimethyl fumarate than with placebo.[2] The FDA approved the twice daily regimen because it had similar efficacy and safety as the three times daily regimen in the Phase 3 trials.[8]

New Guidelines:
The NICE updated their clinical guideline for the management of multiple sclerosis symptoms in October 2014.[3] This specific guideline does not address the use of disease-modifying treatments.[3] Relevant outcomes identified by in this guideline to assess management of MS symptoms were: quality of life; changes in disability or impairment scales assessing motor function, fatigue, spasticity, and walking speed; and incidence of adverse events.[3] Dalfampridine was the only drug in the OHP PDL addressed in this guideline. It is an oral drug approved in the U.S. and previously reviewed by this P&T committee. It is formerly known as fampridine,[9] and was specifically evaluated for its efficacy in improving mobility in MS patients. In total, 4 parallel RCTs and 4 crossover RCTs were identified. In terms of assessing walking ability, "low quality evidence from 3 studies (n=738) showed fampridine was clinically effective compared to placebo at obtaining a positive response to treatment. Moderate quality evidence from 1 study (n=8) showed that there was no difference between fampridine and placebo in time to walk 8 meters. Very low quality evidence from 2 studies (n=334) showed there was no difference in clinical effectiveness between fampridine and placebo in terms of gait speed."[3] When the MS walking scale (MSWS-12) was used, there was very low to low quality evidence that there was no difference in MSWS-12 scores between low, medium and high doses of fampridine compared to placebo.[3] Very low quality evidence showed that fampridine was clinically harmful compared to placebo in terms of a higher rate of adverse events, but without a difference in clinical harm between fampridine and placebo in terms of discontinuation due to adverse events.[3] Safety comparisons suffered from serious imprecision and no comparison was made with active controls.[3] The NICE recommends not using fampridine to treat lack of mobility in people with MS because of lack of cost effectiveness from the perspective of the English National Health Service.[3]

The NICE provided guidance on the use of dimethyl fumarate in 2014.[10] Currently, dimethyl fumarate is recommended as an option for treating adults with RRMS if "they do not have highly active or rapidly evolving severe RRMS" and if the manufacturer provides dimethyl fumarate at a discounted cost.[10]

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
<u>Tecfidera (dimethyl fumarate)</u>
The FDA issued new contraindication labeling in December 2014 for patients with known hypersensitivity to dimethyl fumarate or any of its excipients. Reactions have included anaphylaxis and angioedema.[11]

<u>Gilenya (fingolimod)</u>
The FDA issued a drug safety alert in August 2015 that warns about cases of rare brain infection. One confirmed case of progressive multifocal leukoencephalopathy (PML) and one case of probable PML have been reported. These are the first cases of PML reported in patients taking Gilenya who had not previously been treated with an immunosuppressant drug for MS or any other medical condition.[12]

References:

1. Kawalec P, Mikrut A, Wisniewska N, Pilc A. The Effectiveness of Dimethyl Fumarate Monotherapy in the Treatment of Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Current Neuropharmacology*. 2014;12:256-268.

2. Xu Z, Zhang F, Sun F, Gu K, Dong S, He D. Dimethyl fumarate for multiple sclerosis. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD011076. DOI: 10.1002/14651858.CD011076.pub2.

3. Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care; NICE Clinical Guideline 186, October 2014. National Institute for Health and Care Excellence (NICE). Available at guidance.nice.org.uk/cg186. Accessed June 11, 2015.

4. Miller A, Wolinsky J, Kappos L, et al. Oral terflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-986.

5. Aubagio (teriflunomide) [prescribing information]. Cambridge, MA: Genzyme Corporation (Sanofi), October 2014.

6. Clabresi P, Radue E, Goodin D, et al. Safety and efficacy of fingolimid in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:545-556.

7. Gilenya (fingolimod) [prescribing information]. East Hanover, MJ: Novartis Pharmaceuticals, May 2015.

8. Drugs at FDA. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed July 6, 2015.

9. Dalfampridine [application no: 22-250s000]. FDA Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_SumR.pdf. Accessed June 11, 2015.

10. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 320, August 2014. National Institute for Health and Care Excellence (NICE). Available at http://www.nice.org.uk/guidance/ta320. Accessed June 11, 2015.

11. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Safety Information: Tecfidera (dimethyl fumarate) delayed-release capsules, for oral use. The U.S. Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm429768.htm. Accessed June 12, 2015.

12. Gilyena (fingolimod): Drug Safety Communication. MedWatch, The FDA Safety Information and Adverse Event Reporting System. The U.S. Food and Drug Administration. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm457183.htm. Accessed August 8, 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	KIT	AVONEX	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	
INTRAVEN	VIAL	TYSABRI	NATALIZUMAB	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
INTRAVEN	VIAL	NOVANTRONE	MITOXANTRONE HCL	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	N
SUB-Q	VIAL	BETASERON	INTERFERON BETA-1B	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	**TAB ER 12H**	**AMPYRA**	**DALFAMPRIDINE**	**N**
ORAL	**CAPSULE**	**GILENYA**	**FINGOLIMOD HCL**	**N**
ORAL	**TABLET**	**AUBAGIO**	**TERIFLUNOMIDE**	**N**
ORAL	**CAPSULE DR**	**TECFIDERA**	**DIMETHYL FUMARATE**	**N**

Appendix 2: New Clinical Trials

Thirty-once potentially relevant clinical trials were evaluated from the literature search. After further review, only 2 interventional, prospective trials evaluating an oral MS drug were identified. These trials are briefly described in the table below. Full abstracts are included in Appendix 3.

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Miller AE, et al.[4] MC, DB, PG, PC, RCT, Phase 3 (n=618) 108 weeks Genzyme (Sanofi)	Teriflunomide 14 mg once daily vs. placebo Teriflunomide 7 mg once daily vs. placebo	Adults 18-55 years of age w/ clinically isolated syndrome (first acute or subacute neurological event consistent w/ demyelination (optic neuritis, spinal cord syndrome, or brainstem or cerebellar syndromes)	Time to relapse, indicating conversion to clinically definite MS	Reported as hazard ratios (HR) vs. placebo: Teriflunomide 14 mg: HR=0.574 (95% CI, 0.379-0.869; p=0.0087) Teriflunomide 7 mg: HR=0.628 (95% CI, 0.416-0.949; p=0.0271)
Calabresi PA, et al.[6] MC, DB, PG, PC, RCT, Phase 3 (n=1083) 24 months Novartis	Fingolimod 0.5 mg once daily vs. placebo Fingolimod 1.25 mg once daily vs. placebo	Adults 18-55 years of age diagnosed w/ RRMS, ≥1 confirmed relapses in preceding 1 year, and EDSS score of 0.5-5.5.	Reduction in annualized relapse rates in patients with RRMS	Reported as rate ratios (RR) vs. placebo: Fingolimod 0.5 mg: RR=0.52 (95% CI, 0.40-0.66; p<0.0001) Fingolimod 1.25 mg: RR=0.50 (95% CI, 0.39-0.65; p<0.0001)

Abbreviations: DB = double-blind; EDSS = Expanded Disability Status Scale; MC = multi-centered; PC = placebo-controlled; PG = parallel group; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis.

Appendix 3: Abstracts of Clinical Trials

Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-986.

Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis. We aimed to assess the efficacy and safety of teriflunomide in patients with a first clinical episode suggestive of multiple sclerosis.
Methods: In this randomised, double-blind, placebo-controlled, parallel-group study, we enrolled patients aged 18–55 years with clinically isolated syndrome (defined as a neurological event consistent with demyelination, starting within 90 days of randomisation, and two or more T2-weighted MRI lesions ≥3 mm in

diameter) from 112 centres (mostly hospitals) in 20 countries. Participants were randomly assigned (1:1:1) in a double-blind manner (by an interactive voice response system) to once-daily oral teriflunomide 14 mg, teriflunomide 7 mg, or placebo, for up to 108 weeks. Patients, staff administering the interventions, and outcome assessors were masked to treatment assignment. The primary endpoint was time to relapse (a new neurological abnormality separated by ≥30 days from a preceding clinical event, present for ≥24 h in the absence of fever or known infection), which defined conversion to clinically definite multiple sclerosis. The key secondary endpoint was time to relapse or new gadolinium-enhancing or T2 lesions on MRI, whichever occurred first. The primary outcome was analysed for the modified intention-to-treat population; safety analyses included all randomised patients who were exposed to the study drug, as treated. This trial is registered with ClinicalTrials.gov, number NCT00622700.
Findings: Between Feb 13, 2008, and Aug 22, 2012, 618 patients were enrolled and randomly assigned to teriflunomide 14 mg (n=216), teriflunomide 7 mg (n=205), or placebo (n=197). Two patients in each of the teriflunomide groups did not receive the study drug, so the modified intention-to-treat population comprised 214 patients in the teriflunomide 14 mg group, 203 in the teriflunomide 7 mg group, and 197 in the placebo group. Compared with placebo, teriflunomide significantly reduced the risk of relapse defining clinically definite multiple sclerosis at the 14 mg dose (hazard ratio [HR] 0·574 [95% CI 0·379–0·869]; p=0·0087) and at the 7 mg dose (0·628 [0·416–0·949]; p=0·0271). Teriflunomide reduced the risk of relapse or a new MRI lesion compared with placebo at the 14 mg dose (HR 0·651 [95% CI 0·515–0·822]; p=0·0003) and at the 7 mg dose (0·686 [0·540–0·871]; p=0·0020). During the study, six patients who were randomly assigned to placebo accidently also received teriflunomide at some point: four received 7 mg and two received 14 mg. Therefore, the safety population comprised 216 patients on teriflunomide 14 mg, 207 on teriflunomide 7 mg, and 191 on placebo. Adverse events that occurred in at least 10% of patients in either teriflunomide group and with an incidence that was at least 2% higher than that with placebo were increased alanine aminotransferase (40 [19%] of 216 patients in the 14 mg group, 36 [17%] of 207 in the 7 mg group vs 27 [14%] of 191 in the placebo group), hair thinning (25 [12%] and 12 [6%] vs 15 [8%]), diarrhoea (23 [11%] and 28 [14%] vs 12 [6%]), paraesthesia (22 [10%] and 11 [5%] vs 10 [5%]), and upper respiratory tract infection (20 [9%] and 23 [11%] vs 14 [7%]). The most common serious adverse event was an increase in alanine aminotransferase (four [2%] and five [2%] vs three [2%]).
Interpretation: TOPIC is to our knowledge the first study to report benefi ts of an available oral disease-modifying therapy in patients with early multiple sclerosis. These results extend the stages of multiple sclerosis in which teriflunomide shows a beneficial effect.

Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:545-556.

Background: Fingolimod has shown reductions in clinical and MRI disease activity in patients with relapsing-remitting multiple sclerosis. We further assessed the effi cacy and safety of fingolimod in such patients.
Methods: We did this placebo-controlled, double-blind phase 3 study predominantly in the USA (101 of 117 centres). Using a computer-generated sequence, we randomly allocated eligible patients—those aged 18–55 years with relapsing-remitting multiple sclerosis—to receive fingolimod 0·5 mg, fingolimod 1·25 mg, or placebo orally once daily (1:1:1; stratified by study centre). On Nov 12, 2009, all patients assigned to fingolimod 1·25 mg were switched to the 0·5 mg dose in a blinded manner after a review of data from other phase 3 trials and recommendation from the data and safety monitoring board, but were analysed as being in the 1·25 mg group in the primary outcome analysis. Our primary endpoint was annualised relapse rate at month 24, analysed by intention to treat. Secondary endpoints included percentage brain volume change (PBVC) from baseline and time-to-disability-progression confirmed at 3 months. This trial is registered with ClinicalTrilals.gov, number NCT00355134.
Findings: Between June 30, 2006, and March 4, 2009, we enrolled and randomly allocated 1083 patients: 370 to fingolimod 1·25 mg, 358 to fingolimod 0·5 mg, and 355 to placebo. Mean annualised relapse rate was 0·40 (95% CI 0·34–0·48) in patients given placebo and 0·21 (0·17–0·25) in patients given fingolimod 0·5 mg: rate ratio 0·52 (95% CI 0·40–0·66; p<0·0001), corresponding to a reduction of 48% with fingolimod 0·5 mg versus placebo. Mean PBVC was –0·86 (SD 1·22)

for fingolimod 0·5 mg versus –1·28 (1·50) for placebo (treatment difference –0·41, 95% CI –0·62 to –0·20; p=0·0002). We recorded no statistically significant between-group difference in confirmed disability progression (hazard rate 0·83 with fingolimod 0·5 mg vs placebo; 95% CI 0·61–1·12; p=0·227). Fingolimod 0·5 mg caused more of the following adverse events versus placebo: lymphopenia (27 [8%] patients vs 0 patients), increased alanine aminotransferase (29 [8%] vs six [2%]), herpes zoster infection (nine [3%] vs three [1%]), hypertension (32 [9%] vs 11 [3%]), first-dose bradycardia (five [1%] vs one [<0·5%]), and first-degree atrioventricular block (17 [5%] vs seven [2%]). 53 (15%) of 358 patients given fingolimod 0·5 mg and 45 (13%) of 355 patients given placebo had serious adverse events over 24 months, which included basal-cell carcinoma (ten [3%] patients vs two [1%] patients), macular oedema (three [1%] vs two [1%]), infections (11 [3%] vs four [1%]), and neoplasms (13 [4%] vs eight [2%]).
Interpretation: Our findings expand knowledge of the safety profile of fingolimod and strengthen evidence for its beneficial effects on relapse rates in patients with relapsing-remitting multiple sclerosis. We saw no effect of fingolimod on disability progression. Our findings substantiate the beneficial profile of fingolimod as a disease modifying agent in the management of patients with relapsing-remitting multiple sclerosis.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to June Week 1 2015
1 dalfampridine.mp. 56
2 fingolimod.mp. 1399
3 teriflunomide.mp. 139
4 dimethyl fumarate.mp. 327
5 1 or 2 or 3 or 4 1825
6 exp Multiple Sclerosis/ 46930
7 5 and 6 547
8 limit 7 to (english language and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 31

Oral Multiple Sclerosis Drugs

Goal(s):

- Promote safe and effective use of oral disease-modifying Multiple Sclerosis drugs
- Promote use of preferred Multiple Sclerosis drugs.

Length of Authorization:

Up to 12 months

Requires PA:

- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of relapsing remitting Multiple Sclerosis (MS) (ICD9 340)?	**Yes:** Go to #3	**No:** Pass to RPH; Deny, medical appropriateness.
3. Will the prescriber consider a change to a preferred MS product? Message: • Preferred products do not require a PA or a copay. • 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 in class.	**No:** Go to #4

Approval Criteria		
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5	**No:** Pass to RPH; Deny, medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPH; Deny, medical appropriateness.
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPH; Deny, medical appropriateness.	**No:** Go to #7
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10.
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year.
9. Is the patient currently on a documented use of reliable contraception?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny, medical appropriateness.
10. Is the prescription fingolimod?	**Yes:** Go to #11	**No:** Go to #14
11. Does the patient have evidence of macular edema (ICD9 362.07)?	**Yes:** Pass to RPH; Deny, medical appropriateness.	**No:** Go to #12
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13	**No:** Approve up to 1 year.
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 1 year.	**No:** Pass to RPH; Deny, medical appropriateness.
14. Is the prescription for dimethyl fumarate?	**Yes:** Approve up to 1 year.	**No:** Pass to RPH; Deny, medical appropriateness.

Fingolimod Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs, electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

Teriflunomide Clinical Notes:

- Before starting Terinflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check BP, obtain a complete blood cell count within the 6 months prior to starting therapy, instruct patients receiving Terinflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Terinfluomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Terinflunomide is given with other potentially hepatotoxic drugs, consider stopping Teriflunomide if serum transaminase levels increase (>3 times the ULN), monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction, stop TER and start accelerated elimination in those with suspected TER-induced liver injury and monitor liver tests weekly until normalized, check BP periodically and manage elevated BP, check serum potassium level in TER-treated patients with hyperkalemia symptoms or acute renal failure, monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from TER to another agent with a known potential for hematologic suppression, because systemic exposure to both agents will overlap.

P&T / DUR Review: *9/15 (AG); 9/13; 5/13; 3/12*
Implementation: *1/1/14; 6/21/2012*

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

Literature Scan: Growth Hormone

Date of Review: September 2015

Date of Last Review: September 2014
Literature Search: August 2014 – August 2015

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

Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (ie, Growth Hormone, GH) products and formulations.
- There is insufficient new evidence that further described efficacy outcomes associated with use of GH.
- There is low quality evidence that use of GH in childhood may increase all-cause mortality as an adult but has no significant effect on malignancy-related mortality or cardiovascular-related mortality.
- There is low quality evidence that use of GH in childhood may increase incidence of cancer as an adult and increase secondary malignancies in cancer survivors.

Recommendations:
- No further review or research needed. Evaluate comparative drug costs in the executive session.

Previous Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin products and formulations.

Previous Recommendations:
- No further review or research needed. Evaluated comparative drug costs in the executive session.

Methods:
Evidence in this literature scan is limited to conditions outlined in Guideline Note 74 of the Health Evidence Review Commission's (HERC) Prioritized List of Health Services, titled GROWTH HORMONE TREATMENT[1]: "*Treatment with growth hormone is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stage 3 or higher) and those with renal transplant. Treatment with growth hormone should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults".* Growth hormone studied for conditions not funded by the Oregon Health Plan (OHP) will be otherwise noted in abstract form only in **Appendix 3**.

Author: Date:

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 clinical trial results of studied conditions funded by the OHP are available in **Appendix 2**. 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), 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:
Only one new systematic review that evaluated use of GH in populations with possible conditions funded by the OHP was identified.[2] The review did not evaluate efficacy but rather examined the evidence whether use of GH treatment during childhood may be associated with a higher risk of all-cause, cancer-related and cardiovascular-related mortality and morbidity.[2] The primary efficacy outcome was the all-cause, cancer and cardiovascular mortality, using the standardized mortality ratio (SMR), defined as the number of observed deaths divided by the number of expected deaths.[2] The secondary efficacy outcomes were incidence of primary cancer or secondary cancer in cancer survivors.[2] The standardized incidence ratio (SIR), defined as the number of observed cancer cases divided by the number of expected cases and the risk of second cancers, was used to assess incidence of malignancy.[2] Second cancer incidence in cancer survivors was described by relative risk (RR), defined as the incidence of a second malignancy in patients exposed to GH divided by the incidence among patients not exposed to GH.[2]

Twelve studies were identified that included mortality data, but 8 studies were excluded because the studies only observed deaths (n=4) or used indices different than SMR (n=4).[2] Four studies (n=24,456 patients; mean age 32.6 years) that used SMR rates to evaluate mortality were included in the review.[2] The overall all-cause SMR in GH treated patients, which was evaluated in 3 studies and mostly in children, was significantly increased at 1.19 (95% Confidence Interval [CI], 1.08 to 1.32; p<0.001).[2] Four studies reported SMRs for cancer-related mortality in patients treated with GH.[2] The overall mean malignancy SMR was not significantly different at 0.95 (95% CI, 0.74 to 1.19; p=0.61).[2] Mortality due to cardiovascular events was analyzed in 3 studies.[2] The mean cardiovascular SMR derived from all these studies was also not significantly different at 1.39 (95% CI, 0.76 to 2.55; p =0.28).[2]

Seven studies were identified that included primary cancer incidence data, but 3 studies were excluded because the studies only observed cancer incidence (n=2) or used indices other than SIR (n=1).[2] The overall mean malignancy SIR from the remaining 4 studies was significantly increased at 1.36 (95% CI, 1.00 to 1.85; p=0.05).[2] The incidences of second malignancies were captured in 5 studies which used RR to evaluated incidence of secondary tumors.[2] The overall mean RR of second malignancy in cancer survivors was also significantly higher at 1.99 (95% CI, 1.28 to 3.08; p=0.002).[2]

The results of this systematic review are limited by the heterogeneous populations studied, which comprised of both adult and pediatric cohorts, and patients of different diagnoses.[2]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
New warnings and precautions for malignancies in patients treated with somatotropin products were applied to labeling in September 2014.[3] These warnings stem from evidence that shows an increased risk of second neoplasm in childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent Growth Hormone deficiency and were treated with somatropin.[3] It is unknown if there is any relationship between GH replacement therapy and brain tumor recurrence in adults.[3] Because children with certain rare genetic causes of short stature have an increased risk of developing cancer, the risks and benefits of starting GH should be carefully considered in these patients.[3]

References:

1. Prioritized List of Health Services, January 1, 2015. Health evidence Review Commission, Oregon Health Plan. Available at http://www.oregon.gov/oha/herc/PrioritizedList/1-1-2015%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed 6 August 2015.

2. Deodati A, Ferroli B, Cianfarani S. Association between growth hormone therapy andmortality, cancer and cardiovascular risk: Systematic review and meta-analysis. *Growth Hormone & IGF Research*. 2014;24:105-111. doi:10.1016/j.ghir.2014.02.001.

3. MedWatch Safety Information. U.S. Food and Drug Administration. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258783.htm. Accessed 12 August 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND NAME	GENERIC NAME	PDL
SUB-Q	CARTRIDGE	OMNITROPE	SOMATROPIN	Y
SUB-Q	CARTRIDGE	SAIZEN	SOMATROPIN	Y
SUB-Q	PEN INJCTR	NORDITROPIN FLEXPRO	SOMATROPIN	Y
SUB-Q	PEN INJCTR	NORDITROPIN NORDIFLEX	SOMATROPIN	Y
SUB-Q	VIAL	SAIZEN	SOMATROPIN	Y
INJECTION	CARTRIDGE	HUMATROPE	SOMATROPIN	N
INJECTION	VIAL	HUMATROPE	SOMATROPIN	N
SUB-Q	CARTRIDGE	GENOTROPIN	SOMATROPIN	N
SUB-Q	CARTRIDGE	NUTROPIN AQ	SOMATROPIN	N
SUB-Q	CARTRIDGE	NUTROPIN AQ NUSPIN	SOMATROPIN	N
SUB-Q	SYRINGE	GENOTROPIN	SOMATROPIN	N
SUB-Q	VIAL	OMNITROPE	SOMATROPIN	N
SUB-Q	VIAL	SAIZEN	SOMATROPIN	N
SUB-Q	VIAL	SEROSTIM	SOMATROPIN	N
SUB-Q	VIAL	ZORBTIVE	SOMATROPIN	N

Appendix 2: New Clinical Trials

A total of 110 citations were manually reviewed from the literature search. After further review, all studies were excluded because of wrong study design (observational), comparator (placebo, different doses, not FDA-approved drug), or outcome studied (non-clinical; not funded by the OHP).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 5 2015

1 exp Growth Hormone/ 21514
2 somatotropin.mp. 3175
3 somatropin.mp. 120
4 1 or 2 or 3 22671
5 limit 4 to (english language and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or multicenter study or pragmatic clinical trial or randomized controlled trial) and last year) 110

Growth Hormones

Goal:

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

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

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- All GH products require prior authorization for OHP coverage. GH treatment for adults is not funded by the OHP.
- Preferred alternatives are listed at www.orpdl.org/drugs/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the patient an adult (~~>~~≥18 years of age)?	Yes: Pass to RPh. Deny; not funded by the OHP	No: Go to #3
3. Is this a request for initiation of growth hormone?	Yes: Go to #4	No: Go to Renewal Criteria
4. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
5. Is the diagnosis promotion of growth delay in a child with 3rd degree burns (ICD9 941.3-949.3)?	Yes: Document and send to DHS Medical Director for review and pending approval	No: Go to #6
6. Is the diagnosis one of the following? • Turner's syndrome (ICD9 758.6) • Noonan's syndrome (ICD9 759.89) • ~~Pre-transplant chronic renal insufficiency (CRI) (593.9)~~ • Prader-Willi syndrome (PWS) (ICD9 759.81) • ~~Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6)~~ • ~~X-linked Hypophosphotemia~~ • Pituitary dwarfism (ICD9 253.3) • Short stature homeobox-containing gene (SHOX) (ICD9 783.43) • Chronic kidney disease (CKD, Stage ≥3) (ICD9 585.2-5) • Renal transplant (ICD9 V42.0)	Yes: Document and go to #7	No: Pass to RPh. Deny; not funded by the OHP.
7. If male, is bone age <16 years? If female, is bone age <14 years?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Is there evidence of non-closure of epiphyseal plate?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness
9. Is the product requested preferred?	Yes: Approve for up to 12 months	No: Go to #10

Initial Approval Criteria		
10. Will the prescriber consider a change to a preferred product? Message: • Preferred products to not require a copay. • 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 in class and approve for up to 12 months.	No: Approve for up to 12 months

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is male bone age <16 years or female bone age <14 years?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the product requested preferred?	Yes: Approve for up to 12 months	No: Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a copay. • 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 in class and approve for up to 12 months	No: Approve for up to 12 months

P&T / DUR Review: *9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03*
Implementation: *1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03*

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

Literature Scan: Inflammatory Bowel Agents (oral, rectal)

Date of Review: September 2015

Date of Last Review: May 2014
Literature Search: April 2014 – August 2015

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

Conclusions:

- There is low-quality evidence based on retrospective observational studies that 5-aminosalicylates (5-ASA) use may be associated with a reduced risk of colorectal cancer in patients with ulcerative colitis (Odds Ratio [OR] 0.63; 95% Confidence Interval [CI], 0.48 to 0.84).
- There is moderate-quality evidence 8 weeks of oral budesonide 9 mg daily is more effective than placebo for induction of remission of Crohn's disease (47% vs. 22%, respectively; Relative Risk [RR] 1.93; 95% CI, 1.37 to 2.73) but at the expense of more adverse effects.
- There is low quality evidence that budesonide is superior to placebo for short-term maintenance of remission of Crohn's disease (64% vs. 52%, respectively; RR 1.25; 95% CI, 1.00 to 1.58) but at the expense of more adverse effects. Longer-term remission rates (>3 months) do not differ between oral budesonide and placebo.
- There is moderate-quality evidence oral budesonide is less effective than traditional corticosteroids (ie, prednisone, prednisolone) for induction and maintenance of remission of Crohn's disease, but budesonide is associated with significantly fewer adverse effects.
- There is insufficient evidence to determine differences in efficacy or safety between budesonide and other oral agents for induction and maintenance of remission of Crohn's disease.
- There is low-quality evidence a rectal foam formulation of budesonide may induce remission in patient with mild to moderate distal ulcerative colitis compared to placebo based on 2 identical 6-week studies (response was 38.3% and 44.0% vs. 25.5% and 22.4%, respectively). However, most patients treated with budesonide did not respond to treatment with a 61.7% and 56.6% non-response rate in both studies).

Recommendations:

- No changes to current preferred 5-ASA products on the Oregon Health Plan (OHP) Preferred Drug List (PDL) are needed.
- At least one oral corticosteroid formulation should be available on the PDL for adjunctive management of mild Crohn's disease.
- Budesonide rectal foam should not be a preferred agent at this time due to limited short-term evidence.
- No further review of research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions:

- There is high quality evidence that 5-aminosalicylic acid is superior to placebo in inducing clinical remission (RR 0.86; 95% CI 0.81 to 0.91; NNT 9) and relapse (RR 0.69; 95% CI 0.62 to 0.77; NNT 5-8).
- There is moderate quality evidence of no difference between 5-aminosalicylate products and sulfasalazine in failure to induce clinical remission (RR 0.90; 95% CI 0.77 to 1.04) and high quality evidence of superiority of sulfasalazine in maintaining clinical remission (RR 1.14; 95% CI 1.03 to 1.27), with a higher rate or relapse associated with aminosalicylates.
- However, when including only the studies with outcomes at 12 months or taking the olsalazine trials out of the analysis, there was no difference between sulfasalazine and aminosalicylic acid in maintenance of clinical remission.
- There is moderate quality evidence of less withdrawals due to adverse events with oral 5-aminosaylciates compared to sulfasalazine (RR 0.40; 95% CI 0.24 to 0.69).
- There is moderate quality evidence of no difference between once daily dosing and conventional dosing in failure to induce clinical remission, maintaining clinical remission or adverse events and withdrawals due to adverse events.
- There is moderate quality evidence of no difference between different formulations of oral aminosayliclates in induction of clinical remission (RR 0.94; 95% CI 0.86 to 1.02) or adverse events and withdrawals due to adverse events (RR 0.94; 95% CI 0.57 to 1.54), and low quality evidence of no difference in maintaining clinical remission (RR 1.01; 95% CI 0.80 to 1.28).
- There is evidence that higher doses (≥ 3g/day) of aminosalicylate are more likely to induce clinical remission than lower doses.
- There is low quality evidence of no difference in maintenance of remission between rectal and oral formulations of 5-aminosalicylic acid (RR 1.24; 95% CI 0.92 to 1.66; p=0.15) for distal ulcerative colitis.

Previous Recommendations:

- Continue to maintain topical and oral options as preferred on the PDL.
- No further review of research needed at this time and review comparative costs to determine PDL placement of these agents.

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**. The Medline search strategy used for this literature scan 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), 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[1] was conducted to identify and update the association between 5-ASA use in patients with ulcerative colitis and colorectal neoplasia (CRN), which included low- and high-grade dysplasia, and colorectal cancer (CRC). 5-ASA drugs approved in the U.S. for ulcerative colitis include balsalazide, mesalamine and sulfasalazine. All published studies that evaluated the effect of 5-ASA use on the risk of CRN were examined.[1] Seventeen studies (6 retrospective cohort studies and 11 case-control studies) containing 1,508 cases of CRN and 20,193 subjects published between 1994 and 2012 were analyzed.[1] Of the 1,508 cases of CRN, at least 75% of the cases were cases of CRC.[1] When data from all studies were pooled, 5-ASA use was associated with a reduced risk of CRC (OR 0.63; 95% CI, 0.48 to 0.84).[1] Reduction in CRN was primarily driven by case-control studies (OR 0.64; 95% CI, 0.45 to 0.90) because the retrospective cohort studies were underpowered to see a significant reduction (OR 0.59; 95% CI, 0.34 to 1.03).[1] However, significant heterogeneity between the studies was found (I^2=34.8%, p<0.001).[1] Different sensitivity analyses yielded non-significant reduction of CRN in the following: population-based studies (hospital-based studies showed a significant reduction); studies based in North America (European studies showed a significant protective benefit); patients with irritable bowel disease; and patients with extensive ulcerative colitis (proximal to splenic flexure).[1] Studies that evaluated a higher average daily dose of 5-ASA (sulfasalazine ≥2 g/day, mesalamine ≥1.2 g/day) found a lower associated risk of CRN (OR 0.51; 95% CI, 0.35 to 0.75).[1]

A Cochrane Review[2] evaluated the efficacy and safety of oral budesonide for induction of remission in Crohn's disease. Induction of remission was defined as Crohn's Disease Activity Index [CDAI] <150 or Pediatric Crohn's Disease Activity Index [PCDAI] <10 by 8-16 weeks of therapy.[2] Randomized controlled trials that compared budesonide to a control (active or placebo) were evaluated.[2] Fourteen studies (n=1805) were included in the review: 3 studies compared budesonide to placebo; 9 studies compared budesonide to traditional corticosteroids; and 2 studies compared budesonide to mesalamine.[2] Moderate quality evidence showed that budesonide 9 mg daily was significantly more effective than placebo after 8 weeks for reduction of clinical remission (47% vs. 22%, respectively; Relative Risk [RR] 1.93; 95% CI, 1.37 to 2.73; I^2=0%).[2] However, moderate quality evidence showed budesonide was significantly inferior to traditional corticosteroids (ie, prednisone, prednisolone, etc.) for reduction of clinical remission at 8 weeks (61% vs. 52%, respectively; RR 0.85; 95% CI, 0.75 to 0.97; I^2=0%), though risk of bias was judged to be high with these studies.[2] There was significant heterogeneity between the 2 studies that compared budesonide to mesalamine (I^2=81%) so data were not pooled.[2] Both studies had conflicting results: 1 study demonstrated significant superiority for budesonide 9 mg daily for reduction of remission at 8 weeks compared to mesalamine 4 g daily (RR 1.63; 95% CI, 1.23 to 2.16) but another study did not a difference between these interventions at 8 weeks (RR 1.12; 95% CI, 0.95 to 1.32), though a significant benefit was observed at 12 and 16 weeks.[2] Budesonide was similarly tolerated as mesalamine, but budesonide was better tolerated than traditional corticosteroids with fewer reported adverse events (RR 0.64; 95% CI, 0.54 to 0.76).[2] In addition, abnormal adrenocortical stimulation tests (ACTH) were significantly lower with budesonide than with traditional corticosteroids (RR 0.65; 95% CI, 0.55 to 0.78).[2]

A Cochrane Review[3] evaluated the efficacy and safety of oral budesonide for maintenance of remission (CDAI ≤150) following initiation of maintenance therapy in Crohn's disease. Randomized controlled trials that compared budesonide to a control (active or placebo), or that compared 2 doses of budesonide, were evaluated.[3] Twelve studies (n=1273) were included in the review: 8 studies compared budesonide to placebo; 1 study compared budesonide to 5-ASA, 1 study compared budesonide to traditional corticosteroids, 1 study compared budesonide to azathioprine, and 1 study compared 2 different doses of budesonide.[3] Budesonide 6 mg daily was not more effective than placebo for maintenance of remission at 3 months or anytime thereafter.[3] Low quality evidence showed at 3 months 64% of budesonide treated patients remained in remission compared to 52% of placebo patients (RR 1.25; 95% CI, 1.00 to 1.58).[3] The quality of evidence was judged to be low due to moderate heterogeneity (I^2=56%) and the limited amount of overall events.[3] At 6 months, moderate quality evidence showed 61% of budesonide treated patients remained in remission compared to 52% of placebo patients (RR 1.15; 95% CI, 0.95 to 1.39) but the quality of evidence was limited by the small number of events.[3] The results at 12 months between budesonide treated patients and placebo were similar to results observed at 6 months (RR 1.13; 95% CI, 0.94 to 1.35).[3] Current recommended dosing of oral budesonide for maintenance of remission is congruent with the evidence demonstrated in

these studies: "continued treatment beyond 3 months has not demonstrated to result in substantial benefit".[4] Low quality evidence (due to limited data from one study) showed there was no significant difference in continued remission at 3, 6, or 12 months between budesonide 9 mg daily and prednisolone 40 mg daily with a weaning schedule (50% vs. 64%, respectively; RR 0.79; 95%CI 0.55 to 1.13).[3] Very low quality evidence suggested budesonide 6 mg daily was superior to mesalamine 3 g daily when remission rates were assessed at 12 months (45% vs. 18%, respectively; RR 2.51; 95% CI, 1.03 to 6.12), but this was based on one small, open-labeled study.[3] Very low quality evidence also suggested budesonide was equal to azathioprine at 12 months (64% vs. 79%, respectively; RR 0.81; 95% CI 0.61 to 1.08) based on 1 small, single-blinded study without appropriate concealment of allocation.[3] The number of adverse drug events was similar in patients treated with budesonide compared to placebo (RR 1.51; 95% CI 0.90 to 2.52) and did not result in increased rates of study withdrawal.[3] The more commonly reported events were similar to those seen with systemic corticosteroids and included acne, moon facies, hirsutism, mood swings, insomnia, weight gain, striae, and hair loss.[3] Abnormal ACTH tests were more frequently observed in patients who received budesonide 6 mg daily (RR 2.88; 95% CI, 1.72 to 4.82) compared to placebo.[3]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
Uceris (budesonide) 2 mg rectal foam was approved in October 2014 to induce remission in patients with active mild to moderate distal ulcerative colitis (ie, ulcerative proctitis [UP] or ulcerative protcosigmoiditis) extending up to 40 cm from the anal verge.[5] Budesonide 2 mg rectal foam has topical anti-inflammatory properties, weak mineralocorticoid activity and undergoes significant first-pass elimination.[6] These properties result in limited systemic bioavailability, which theoretically reduce systemic adverse effects commonly observed with traditional corticosteroids.[6] This particular formulation is an emulsion provided in an aluminum container with an aerosol propellant.[6]

BACKGROUND: In contrast to more extensive ulcerative colitis, UP typically follows a more benign course with less severe symptoms but will often extend proximally and eventually involve more medication.[6] Topical medication with rectally administered 5-ASA and corticosteroid suppositories or enemas are effective treatment for most patients with UP.[6] The combination of topical 5-ASA and oral 5-ASA or topical steroids is considered when escalation of treatment is required.[6] Patients refractory or intolerant to 5-ASAs and corticosteroids may eventually require immunomodulators or biological therapy.[6]

EFFICACY/SAFETY: There were 2 replicate 6-week, phase 3, multi-centered, randomized, double-blind, placebo-controlled trials (BUCF 3001 and BUCF 3002) designed to assess the efficacy of budesonide 2 mg rectal foam (dosed twice daily for 2 weeks, followed by once daily for 4 weeks) in patients with mild to moderate distal ulcerative colitis.[6] Patients included in the trials had baseline Modified Mayo Disease Activity Index (MMDAI) scores of 5 through 10 with a score of ≥2 on the MMDAI rectal bleeding component and ≥2 on the MMDAI endoscopy or sigmoidoscopy component.[6] The primary outcome was the proportion of patients who achieved remission at the end of 6 weeks.[6] Remission was defined as components of an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency sub-scales of the MMDAI at the end of 6 weeks of treatment or withdrawal.[6] Baseline characteristics were similar between the groups in both studies (ie, extent of disease, stools per day, duration of disease).[6] Over half of the patients studied were concomitantly on oral 5-ASA. Remission rates for the 2 studies are described in Table 1.[6]

Table 1. Remission Rates After 6 Weeks of Budesonide Rectal Foam or Placebo (Studies BUCF 3001 and BUCF 3002).[6]

	Study BUCF 3001			Study BUCF 3002		
Efficacy Endpoint	Budesonide Foam (n=133)	Placebo (n=132)	p-value	Budesonide Foam (n=134)	Placebo (n=147)	p-value
Achieved Remission						
Responder	51 (38.3%)	34 (25.8%)	p=0.03	59 (44.0%)	33 (22.4%)	p<0.001
Non-Responder	82 (61.7%)	98 (74.2%)		75 (56.0%)	114 (77.6%)	

Results demonstrate a significant difference between budesonide foam and placebo at induction of remission; however, there were also a very large number of non-responders.[6] There was also a trend towards higher remission rates that correlated with greater extent of disease activity – higher baseline MMDAI scores were associated with greater response with budesonide rectal foam.[6]

The safety profile of budesonide rectal foam is similar to that observed with the oral formulation of Uceris (budesonide).[6]

New FDA Safety Alerts:
None identified.

References:

1. Zhao L, Li J, Yu T, Chen G, Yuan Y, Chen Q. 5-aminosalicylates reduce the risk of colorectal neoplasia in patients with ulcerative colitis: an updated meta-analysis. *PLoS ONE*. 9(4):e94208. doi:10.1371/journal.pone.0094208.

2. Rezaie A, Kuenzig M, Benchimol E, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;6:Art. No. CD000296. doi:10.1002/14651858.CD000296.pub4.

3. Kuenzig M, Rezaie A, Seow C, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014;8:Art. No. CD002913. doi:10.1002/14651858.CD002913.pub3.

4. ENTOCORT EC (budesonide) [prescribing information]. Sodertalje, Sweden: AstraZeneca AB, December 2011.

5. UCERIS (budesonide) [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc., October 2014.

6. Uceris (budesonide) Rectal Foam 2 mg Summary Review. Application No: 205613Orig1s000. Center for Drug Evaluation and Research, Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205613Orig1s000SumR.pdf. Accessed 5 August 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRANDE NAME	GENERIC NAME	PDL
ORAL	CAP ER 24H	APRISO	MESALAMINE	Y
ORAL	CAPSULE	BALSALAZIDE DISODIUM	BALSALAZIDE DISODIUM	Y
ORAL	CAPSULE	COLAZAL	BALSALAZIDE DISODIUM	Y
ORAL	CAPSULE	DIPENTUM	OLSALAZINE SODIUM	Y
ORAL	TABLET	AZULFIDINE	SULFASALAZINE	Y
ORAL	TABLET	SULFASALAZINE	SULFASALAZINE	Y
ORAL	TABLET	SULFAZINE	SULFASALAZINE	Y
ORAL	TABLET DR	ASACOL	MESALAMINE	Y
ORAL	TABLET DR	AZULFIDINE	SULFASALAZINE	Y
ORAL	TABLET DR	LIALDA	MESALAMINE	Y
ORAL	TABLET DR	SULFASALAZINE	SULFASALAZINE	Y
ORAL	TABLET DR	SULFASALAZINE DR	SULFASALAZINE	Y
ORAL	TABLET DR	SULFAZINE EC	SULFASALAZINE	Y
RECTAL	SUPP.RECT	CANASA	MESALAMINE	Y
ORAL	CAPSULE DR	DELZICOL	MESALAMINE	N
ORAL	CAPSULE ER	PENTASA	MESALAMINE	N
ORAL	TABDR & ER	UCERIS	BUDESONIDE	N
ORAL	TABLET	GIAZO	BALSALAZIDE DISODIUM	N
ORAL	TABLET DR	ASACOL HD	MESALAMINE	N
RECTAL	ENEMA	MESALAMINE	MESALAMINE	N
RECTAL	ENEMA	SFROWASA	MESALAMINE	N
RECTAL	ENEMA KIT	MESALAMINE	MESALAMINE W/CLEANSING WIPES	N
RECTAL	ENEMA KIT	ROWASA	MESALAMINE W/CLEANSING WIPES	N
RECTAL	FOAM/APPL	UCERIS	BUDESONIDE	N
ORAL	CAPDR - ER	BUDESONIDE EC	BUDESONIDE	
ORAL	CAPDR - ER	ENTOCORT EC	BUDESONIDE	

Appendix 2: New Clinical Trials

No relevant comparative clinical trials published since April 2014 were identified for this literature scan.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2015

1 exp Colitis, Ulcerative/ 13899
2 balsalazide.mp. 102
3 exp Mesalamine/ 2084
4 exp Sulfasalazine/ 1563
5 exp Budesonide/ 3063
6 2 or 3 or 4 or 5 6432
7 1 and 6 1134
8 limit 7 to (yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 16

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2015
1 exp Budesonide/ 3063
2 exp Crohn Disease/ 18412
3 1 and 2 190
4 limit 3 to (yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 2

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

Literature Scan: Alzheimer's Drugs

Date of Review: September 2015
PDL Class: Alzheimer 's disease (AD) Drugs

Date of Last Review: September 2014
Literature Search: July 2015

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

Conclusions:

- While acetylcholinesterase inhibitors and memantine have demonstrated modest but persistent improvements in cognition, activities of daily living, and behavior, none of the approved medications have been shown to stop or reverse the underlying process or any impact on important clinical outcomes such as mortality, disability, or institutionalization in patients with moderate to severe Alzheimer's disease (AD).
- There is low quality evidence that cholinesterase inhibitors can reduce neuropsychiatric symptoms in patients with AD but there is no effect with memantine.[1]
- There was moderate quality evidence that rivastigmine is associated with better outcomes for cognitive function, activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27), and deterioration (OR 0.68; 95% CI 0.58 to 0.80) compared to placebo. However, these effects were small and of uncertain clinical significance. There is moderate level evidence of no difference in behavioral change or impact on caregivers with rivastigmine compared to placebo.[2]
- There is moderate quality evidence of a small but significant benefit of combination therapy with cholinesterase inhibitors and memantine on behavior and cognitive functions, with no difference in activities of daily living or serious adverse events.[3]
- There is moderate quality evidence that the new fixed-dose combination of memantine ER and donepezil (Namzaric®) is bioequivalent to co-administered memantine ER and donepezil but no clinical efficacy data are available. Generic formulations of both individual products are currently available.

Recommendations:

- There is no new comparative efficacy or safety data resulting in changes to the current PDL; maintain Namzaric® (memantine ER/donepezil) as non-preferred.
- Review comparative costs in executive session.

Previous Conclusions and Recommendations:

- There remains insufficient evidence for the treatment of AD beyond 6 months and on important clinical outcomes such as mortality, disability, or institutionalization.
- There is moderate quality evidence that cholinesterase inhibitors can alleviate AD symptoms and there is no strong evidence that one agent is more efficacious or safer than others.

- There is low quality and conflicting evidence that the combination of memantine with cholinesterase inhibitors may provide a small improvement in cognition and behavior. However, the magnitude of effect is low and the clinical significance is unknown. There is no evidence of an improvement in function with the combination compared to monotherapy.
- Make Aricept 23 mg non-preferred due to an increased risk of adverse drug events.

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**. The Medline search strategy used for this literature scan 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), 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 recent systematic review from the Cochrane Collaboration was completed to determine the clinical efficacy and safety of rivastigmine for patients with Alzheimer's dementia.[2] A total of 7 randomized, double-blind trials of 12 weeks or more were included in the review (n=3450). The main comparison was rivastigmine 6 to 12 mg/day orally or 9.5 mg/day transdermally to placebo. All of the studies included patients with mild to moderate disease with a mean age of about 75 years. There was moderate level evidence that rivastigmine was associated with better outcomes for cognitive function measured with the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (mean difference [MD] -1.79; 95% CI -2.21 to -1.37) and the mini mental state examination (MMSE) score (MD 0.74; 95% CI 0.52 to 0.97), activities of daily living (SMD 0.20; 95% CI 0.13 to 0.27), and deterioration (OR 0.68; 95% CI 0.58 to 0.80) compared to placebo. However, these effects were small and of uncertain clinical significance. A standard mean difference of 0.2 in the activities of daily living scale is considered a small effect size, as well as the differences in the cognitive function scores. There were no differences found in behavioral change with rivastigmine compared to placebo (SMD -0.04; 95% CI -0.14 to 0.06). There was no difference in impact on caregivers or in the clinician's global assessment. Patients taking rivastigmine were more likely to withdraw from trials (OR 2.01; 95% CI 1.71 to 2.37) or experience an adverse event (OR 2.16; 95% CI 1.82 to 2.57), but no significant difference in withdrawals due to adverse events (OR 1.20; 95% CI 0.68 to 2.13) was found. There was a significant difference between oral rivastigmine and the patch, favoring the patch, in total adverse events (OR 0.59; 95% CI 0.43 to 0.82). There is insufficient data beyond 12 months on the long term treatment outcomes of AD.

Due to recent conflicting evidence for the efficacy and safety of pharmacological agents used for the treatment of neuropsychiatric symptoms in patients with AD, a systematic review and meta-analysis of RCTs was done to compare agents on Neuropsychiatric Inventory (NPI) and safety outcomes in patients with AD and neuropsychiatric symptoms.[1] The NPI is a validated inventory used to assess neuropsychiatric symptoms and behavioral disturbances in patients with AD.[4] Thirty two studies were included in the review; 8 evaluating memantine and 15 with cholinesterase inhibitors. The remaining trials included atypical antipsychotics and antidepressants. All of the included trials were randomized, double-blinded, and placebo-controlled. Meta-analysis data demonstrated a significant benefit on neuropsychiatric symptoms with cholinesterase inhibitors compared to placebo (standard mean difference [SMD] -0.12; 95% CI -0.23 to -

0.02) and no difference between memantine and placebo (SMD -0.12; 95% CI -0.27 to 0.03). In the donepezil subgroup, there were no significant effects seen on neuropsychiatric symptoms. There were no significant differences in the number of dropouts for any reason between any treatment group and placebo but a significantly higher number of withdrawals due to adverse events in the cholinesterase inhibitor treatment group compared to placebo (RR 1.64; 95% CI 1.12 to 2.42).

A good quality systematic review and meta-analysis by Tan, et al. evaluated the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. [5] A systematic literature search through 2013 for double-blind, placebo-controlled RCTs identified 23 trials that met inclusion criteria. Trials were assessed for quality using the GRADE tool and demonstrated poor reporting of allocation concealment and randomization methods. Of these, 10 donepezil, 4 galantamine, 3 rivastigmine, and 6 memantine trials were included. There was a statistically significant benefit in cognitive outcomes on the ADAS-cog subscale with all agents compared to placebo, with a pooled weighted MD between intervention and placebo ranging from -1.29 points (95% CI -2.30 to -0.28) in the memantine trials to -3.20 points (95% CI -3.28 to -3.12) in the galantamine group. However, both memantine and galantamine had no effect on the Clinicians' Global Impression of Change scale. Overall, there was no significant difference on behavioral outcomes.

New Guidelines:
The European Federation of Neurological Societies (EFNS) and European Neurological Society (ENS) developed guidelines for the concomitant use of cholinesterase inhibitors and memantine in AD.[3] Results of their meta-analysis showed moderate level evidence of significant overall benefits of combination therapy over cholinesterase inhibitor therapy alone for behavior (SMD -0.19; 95% CI -0.31 to -0.07), cognitive function (SMD -0.27; 95% CI -0.37 to -0.17) and global clinical impression (SMD -0.20; 95% CI -0.31 to -0.09). There was low level evidence of no overall differences between combination and monotherapy in activities of daily living (SMD -0.08; 95% CI -0.18; 95% CI 0.02). Overall, the guideline panel gave a weak recommendation for the combination therapy in patients with moderate to severe AD.

New FDA Drug Approvals:
In December 2014, the FDA approved a fixed-dose combination of extended-release (ER) memantine 28 mg, an NMDA-receptor antagonist, and donepezil 10 mg, an acetylcholinesterase inhibitor for the treatment of moderate to severe Alzheimer's type dementia in patients previously stabilized on both drugs.[6,7] Generic formulations of both individual products are currently available.[8] Previous trials of combination therapy with both agents have had conflicting results. Some have shown an improvement in measures of cognition and function compared to treatment with an acetylcholinesterase inhibitor alone, while others have not.

No efficacy data were required for approval of the combination product. Two single-dose, randomized, open-label, cross over studies in 74 healthy volunteers 18-45 years of age evaluated the combination capsule formulation for bioequivalence with co-administered memantine ER and donepezil.[9] Both studies demonstrated that the combination capsule was bioequivalent. The most common adverse events were nausea, dizziness, vomiting, headache, and abdominal discomfort.

New FDA Safety Alerts:
None Identified

References:

1. Wang J, Yu J-T, Wang H-F, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatr*. 2015;86(1):101-109. doi:10.1136/jnnp-2014-308112.

2. Birks JS, Grimley Evans J. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*. 2015;4:CD001191. doi:10.1002/14651858.CD001191.pub3.

3. Schmidt R, Hofer E, Bouwman FH, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. *Eur J Neurol*. 2015;22(6):889-898. doi:10.1111/ene.12707.

4. Trzepacz PT, Saykin A, Yu P, et al. Subscale validation of the neuropsychiatric inventory questionnaire: comparison of Alzheimer's disease neuroimaging initiative and national Alzheimer's coordinating center cohorts. *Am J Geriatr Psychiatry*. 2013;21(7):607-622. doi:10.1016/j.jagp.2012.10.027.

5. Tan C-C, Yu J-T, Wang H-F, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. [Review]. *Journal of Alzheimer*. 2014;41(2):615-631. doi:10.3233/JAD-132690.

6. FDA Center for Drug Evaluation and Research. Application Number: 206439Orig1s000. Namzaric Summary Review. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

7. Namzaric Prescribing Information. Forest Pharmaceuticals, In. 12/2014.

8. Namzaric--a combination of 2 old drugs for Alzheimer's disease. *Med Lett Drugs Ther*. 2015;57(1473):105-106.

9. Boinpally R, Chen L, Zukin SR, McClure N, Hofbauer RK, Periclou A. A Novel Once-Daily Fixed-Dose Combination of Memantine Extended Release and Donepezil for the Treatment of Moderate to Severe Alzheimer's Disease: Two Phase I Studies in Healthy Volunteers. *Clin Drug Investig*. 2015;35(7):427-435. doi:10.1007/s40261-015-0296-4.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND NAME	GENERIC NAME	PDL
ORAL	CAP24H PEL	GALANTAMINE HBR	GALANTAMINE HBR	Y
ORAL	CAP24H PEL	RAZADYNE ER	GALANTAMINE HBR	Y
ORAL	SOLUTION	NAMENDA	MEMANTINE HCL	Y
ORAL	TAB DS PK	NAMENDA	MEMANTINE HCL	Y
ORAL	TABLET	ARICEPT	DONEPEZIL HCL	Y
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	Y
ORAL	TABLET	GALANTAMINE HBR	GALANTAMINE HBR	Y
ORAL	TABLET	NAMENDA	MEMANTINE HCL	Y
ORAL	TABLET	RAZADYNE	GALANTAMINE HBR	Y
TRANSDERM	PATCH TD24	EXELON	RIVASTIGMINE	Y
ORAL	CAP SPR 24	NAMENDA XR	MEMANTINE HCL	N
ORAL	CAP24 DSPK	NAMENDA XR	MEMANTINE HCL	N
ORAL	CAPSULE	EXELON	RIVASTIGMINE TARTRATE	N
ORAL	CAPSULE	RIVASTIGMINE	RIVASTIGMINE TARTRATE	N
ORAL	SOLUTION	GALANTAMINE HYDROBROMIDE	GALANTAMINE HBR	N
ORAL	TAB RAPDIS	DONEPEZIL HCL ODT	DONEPEZIL HCL	N
ORAL	TABLET	ARICEPT	DONEPEZIL HCL	N
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	N
ORAL	TABLET	DONEPEZIL HCL	DONEPEZIL HCL	

Appendix 2: New Clinical Trials

Thirty potentially relevant clinical trials were evaluated from the literature search. After further review, all trials were excluded due to irrelevant outcomes, comparisons, and study design.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 donepezil.mp 2519
2 galantamine.mp or Galantamine/ 1269
3 memantine.mp or Memantine/ 2159
4 rivastigmine.mp 1271
5 alzheimer's disease.mp or Alzheimer Disease/ 74868
6 1 or 2 or 3 or 4 5727
7 5 and 6 3083
Limit 7 to (English language and humans and yr="2014 – Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) 30

Appendix 4: Prior Authorization Criteria for **Donepezil 23 mg only**

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used appropriately for an OHP-funded condition.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at http://www.orpdl.org/drugs/

Note:

A complete list of PDL classes is available at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny for medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4.	**No**: Go to #5.

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
5. RPH only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *7/15 (RC), 9/10; 9/09; 5/09*
Implementation: *TBD; 1/1/11, 9/16/10*

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

New Drug Evaluation: sacubitril/valsartan tablet, oral

Date of Review: September 2015
Generic Name: sacubitril/valsartan
PDL Class: not applicable

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): Entresto™ (Novartis)
Dossier Received: yes

Research Questions:

1. What is the evidence for sacubitril/valsartan to reduce mortality and cardiovascular (CV) morbidities; and if available, how does the drug's efficacy compare to ACE-inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) when used to manage chronic heart failure with reduced ejection fraction (HFrEF)?
2. Based on the evidence available, does sacubitril/valsartan have a clear place in therapy for chronic HFrEF compared to ACE-Is and ARBs?
3. How well is sacubitril/valsartan tolerated in patients; and if available, how does the safety of sacubitril/valsartan compare to ACE-Is and ARBs when used to manage chronic HFrEF?
4. Are there subgroups of patients in which sacubitril/valsartan may be safer or more effective than ACE-Is or ARBs when used to manage chronic HFrEF?

Conclusions:

- 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.[1] 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 (ie, beta-blocker, diuretic(s), aldosterone antagonist).[1]
- 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).[1]
- 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).[1]
- 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).[1] The difference in KCCQ scores were statistically significant when assessed at 8 months (a difference of 1.61 points on a 100-point scale),[1] but a much larger difference is needed to be clinically meaningful.[2,3]
- 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).[1] 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).[1]
- 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 ACE-I-naïve patients.[1] Blacks were also underrepresented in this trial despite the high prevalence of HF and higher incidence of angioedema in this population.[4]

Recommendation:

- Restrict use of sacubitril/valsartan to populations where it has demonstrated efficacy. See **Appendix 2** for the proposed prior authorization criteria.

Background:

Cardiac remodeling observed in both infarcted and non-infarcted myocardium is recognized as a major factor in the development of impaired LV dysfunction and HFrEF.[5] Cardiac remodeling involves molecular and cellular changes to the cardiomyocytes and interstitium which results structural and functional modification of the heart.[5] Cardiac dilatation, interstitial fibrosis, and reduction in contractility and relaxation are all consequences of cardiac remodeling.[5] The goals of management of HFrEF (ie, systolic HF) are to prevent hospital admission and improve survival, and to relieve signs (eg, edema) and symptoms (eg, dyspnea).[6] The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[6,7] The most well-studied system in the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has shown to have a significant impact on the pathophysiology and progression of HF.[6,7] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[6,7] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a select beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralcorticoid (aldosterone) receptor antagonist (spironoloactone or eplerenone).[6,7] Both an ACE-I and a beta-blocker should be initiated as soon as HFrEF is diagnosed.[6,7]

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[6,7] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD.[7] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[6] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[6,7] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[7] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[8] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[6,7] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[7] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials that were designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see Table 1).[6,7]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[6]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-35 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg Qday • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation

* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

There are also other therapeutic options for management of HFrEF that do not inhibit RAAS or other components of neurohormonal activation. Hydralazine and isosorbide dinitrate has shown to decrease morbidity and mortality in self-identified African-Americans/Blacks with NYHA class III-IV and reduced EF.[7] Digoxin has no effect on survival, but it can have a modest effect on reducing hospitalizations regardless of the underlying rhythm or cause of HF (ischemic or non-ischemic cardiomyopathy).[7] In Europe, consideration for ivabradine (approved by European Medicines Agency in 2005 and U.S. Food and Drug Administration in 2015) is given to reduce HF hospitalization in patients in sinus rhythm with an EF of 35% or less, a HR of at least 70 beats-per-minute, and persistent symptoms (NYHA class II-IV) despite a recommended dose of a beta-blocker, an ACE-I/ARB and an aldosterone antagonist.[6]

Neprilysin inhibitors were first investigated as a therapeutic strategy in HF in the 1990s.[5] Neprilysin is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides and bradykinin.[1] Natriuretic peptides, which include atrial natriuretic peptide and B-type natriuretic peptide, are secreted by the heart in response to increased cardiac wall stress (it is also secreted by other organs in response to other stimuli).[9] Natriuretic peptides have potent natriuretic properties, also inhibits RAAS, and reduces sympathetic drive.[9] Inhibiting neprilysin increases the levels of these peptides and counters the neurohormonal activation associated with vasoconstriction, sodium retention and cardiac remodeling.[1] However, the combined use of an ACE-I and a neprilysin inhibitor (enalapril/omapatrilat) was associated with serious angioedema when studied in HF.[10] Subsequently, sacubitril, a prodrug converted into the neprilysin inhibitor LBQ657, was studied in combination with an ARB (valsartan) in patients with HFrEF in the PARADIGM-HF trial.[1] Evidence from this trial was used by the U.S. Food and Drug Administration (FDA) to grant approval for its use in July 2015.[11] The combination of sacubitril and valsartan (previously referred to as LCZ696) is indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic NYHA class II-IV HF with reduced EF.[12] Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). After ingestion, the drug delivers systemic exposure of sacubitril, a neprilysin inhibitor pro-drug, and valsartan.[12] Sacubitril is rapidly metabolized by esterases to the active neprilysin inhibitor LBQ657.[12] The twice daily maintenance dose of the sacubitril/valsartan 97/103 mg formulation yields plasma concentrations of valsartan equivalent to valsartan 160 mg twice daily.[13]

In HF patients with preserved EF (HFpEF), sacubitril/valsartan was compared to valsartan in a phase 2 trial evaluating reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline.[14] There was a superior reduction of NT-proBNP with sacubitril/valsartan compared to valsartan alone at 12 weeks; however, this difference in reduction was lost by 36 weeks.[14] Research is currently underway to determine how sacubitril/valsartan compares to valsartan alone when clinically relevant outcomes are assessed in patients with HFpEF (NCT01920711).[15] Other future therapeutic considerations may also include refractory hypertension – sacubitril/valsartan significantly improved systolic blood pressure (SBP) by -6.01 mmHg compared to valsartan 320 mg daily.[16]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including the Black Boxed Warning on fetal toxicity associated with drugs that act directly on the RAAS, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The 'Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure' (PARADIGM-HF, NCT01035255) trial was a randomized, double-blind, active-controlled, multi-centered trial that compared the long-term efficacy and safety of sacubitril/valsartan with enalapril in patients with chronic HFrEF (EF ≤35%). Table 4 provides details of the study methodology, results, biases, and applicability. The investigators used an innovative approach: instead of adding new therapy to standard of care, the investigators substituted a cornerstone of HF therapy, the ACE-I, for sacubitril/valsartan. The investigators used a careful, step-wise approach to their study to maximize safety. First, there was a screening period to assess patient eligibility based on multiple inclusion and exclusion criteria. The screening period was followed by a single-blind run-in period to determine if the eligible patients (n=10,521) were able to tolerate a target dose of enalapril 10 mg BID, which was followed by a 36-hour washout period and a second single-blind run-in period to determine if patients who tolerated the target dose of enalapril could also tolerate the target dose of sacubitril/valsartan 200 mg BID. Over 20% of eligible patients based on the inclusion and exclusion criteria were not eligible for randomization into the clinical trial – mostly because of intolerance to the target doses. Patients who could tolerate target doses of both drugs were randomized 1:1 to enalapril 10 mg BID (n=4,212) or sacubitril/valsartan 200 mg BID (n=4,187) for the clinical trial.

Baseline characteristics were similar between the groups. Overall, the population studied had stable, mildly symptomatic HFrEF on recommended HF therapy. Only about 5% of patients enrolled at sites in the United States.[17] Most patients were white males, with few females or racial and/or ethnic groups represented other than moderately sized number of Asian populations represented. The mean EF was 29% and most patients had NYHA class II HF, and about one-quarter had NYHA class III HF. Most patients concurrently received beta-blockers and diuretics. The median duration of follow-up was 27 months. Interestingly, the SBP was relatively equal between groups and baseline (121-122 mmHg) but mean SBP at 8 months was 3.2±0.4 mmHg lower in the sacubitril/valsartan group than in the enalapril group (p<0.001).

The primary end point included a composite of death from cardiovascular causes or first hospitalization for HF. Key secondary endpoints included all-cause mortality, change in the clinical summary score on the KCCQ, time to new onset atrial fibrillation, and time to the first decline in renal function. The KCCQ is a validated 23-item, self-administered instrument that quantifies physical function, symptoms, social function, and quality of life.[2,3,18] An overall summary score is derived and Scores are transformed to a range of 0-100, in which higher scores reflect better health status.[2,18]

Prior to the scheduled completion of the study, the trial was terminated early based on meeting the pre-specified boundary of overwhelming benefit for the primary end point (enalapril, 26.5% vs. sacubitril/valsartan, 21.8%; HR=0.80 (95% CI, 0.73-0.87; p<0.001). The absolute difference of 4.7% predicts that 22 patients would need to be treated for 27 months with sacubitril/valsartan instead of enalapril to prevent one hospitalization for HF or one death from CV causes. The effect of sacubitril/valsartan was fairly consistent across multiple subgroups except for those without prior use of an ACE-I, in which the effect of sacubitril/valsartan was unclear.

All-cause mortality was also significantly reduced with sacubitril/valsartan compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; p<0.001). The absolute difference of 2.8% demonstrates that 36 patients would need to be treated with sacubitril/valsartan for 27 months instead of enalapril to prevent one death. KCCQ scores improved by 1.61 points (scale, 0-100) with sacubitril/valsartan compared to enalapril. However, a variation of up to 4 points is frequently observed in stable HF patients[2] and a minimal 10-point improvement in the KCCQ is required to have important prognostic significance.[3] Thus, it is

doubtful patients in the PARADIGM-HF trial perceived better quality of life and health-status on sacubitril/valsartan compared to those on enalapril, but the difference was nonetheless statistically significant (p=0.001). The incidence of new-onset atrial fibrillation and protocol-defined decline in renal function (see evidence table) were similar between the 2 treatment groups.

Follow-up analyses of PARADIGM-HF trial data show patients who received sacubitril/valsartan also had slower deterioration of their clinical condition compared to those who received enalapril, which was evidenced by less intensification of drug therapy, emergency department visits and hospitalizations, and less use of advanced treatment modalities, such as inotropes, left ventricular assist devices or heart transplantation.[19]

The study had several strengths, such as its size, duration of follow-up, and the compelling effect sizes in the results. However, several limitations should also be noted. First, the order of the single-blinded run-in phases can compromise both internal validity and applicability of the study. Bias is introduced with the familiarization of treatment effect, especially in patients previously on an ACE-I. Alternatively, investigators un-blinded during the initial phases of the study may become familiar with how a patient responded to both treatments. If this occurs, blinding is compromised after randomization and treatment allocation. About 20% in each study arm still dropped out of the study prematurely, which can significantly impact the applicability of the study after consideration for the 20% of eligible patients who were not randomized into the trial because of intolerance to the drugs in the run-in phases. Second, it is not clear if the efficacy of sacubitril/valsartan can be attributed to the addition of the neprilysin inhibitor to a maximally dosed valsartan, or if it can be attributed to the maximally dosed valsartan alone. Both doses of valsartan and enalapril in this study are optimal,[20–22] but a comparison of sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain the benefits of the neprilyxin inhibitor when added to valsartan. An ACE-I is preferred to an ARB for management of HF based on superior mortality data; however, when valsartan has been directly compared to enalapril in different populations, various outcomes studied show that a daily 40 mg dose of enalapril may have been a more reasonable comparator.[23–26] Third, the study was spread out among 1043 sites in 47 countries.[1] With so many participating sites, there would have been an average of 8 patients enrolled at each site, which may have affected the ability to monitor quality and recognize discrepancies. Lastly, early termination of randomized controlled trials tend to exaggerate differences between comparator groups,[27] though the difference between the arms in the primary endpoint appeared to be consistent throughout the 27-month trial.[1]

Clinical Safety:
Overall, sacubitril/valsartan and enalapril were tolerated equally well and no major or unanticipated safety issues were identified in this Phase 3 trial.[1] The study drug was discontinued in 19.8% of patients on enalapril and 17.8% on sacubitril/valsartan.[1] Fewer patients who received sacubitril/valsartan discontinued their treatment because of an adverse event when compared to those who received enalapril (10.7% vs. 12.3%, respectively; p=0.03).[1] There were more patients who experienced angioedema with sacubitril/valsartan than with enalapril, but these events were relatively low overall (0.45% vs. 0.24%, respectively).[1] Symptomatic hypotension also occurred more frequently with sacubitril/valsartan (14.0% vs. 9.2%; p<0.001).[1] However, elevated serum creatinine ≥2.5 mg/dL (4.5% vs. 3.3%; p=0.007), elevated serum potassium >6.0 mEq/L (5.6% vs. 4.3%; p=0.007), and cough (14.3% vs. 11.3%; p<0.001) occurred more frequently with enalapril.[1] The common adverse reactions reported in the PARADIGM-HF trial are noted in Table 2.

Table 2. Adverse Reactions Reported in ≥5% of Patients Treated with Sacubitril/Valsartan in PARADIGM-HF.[12]

	Sacubitril/Valsartan (n=4,203)	Enalapril (n=4,229)
Hypotension	18%	12%
Hyperkalemia	12%	14%
Cough	9%	13%
Dizziness	6%	5%
Renal Failure/Acute Renal Failure	5%	5%

Patients on sacubitril/valsartan should be regularly monitored initially to assess for deteriorating renal function, hypotension and hyperkalemia. At a minimum, patients enrolled in the PARADIGM-HF trial were evaluated every 2 to 8 weeks for the first 4 months and then every 4 months thereafter.[1] Once the patient is stable on the target daily dose of 400 mg, patients may only need to be monitored at a frequency similar as recommended for patients on ACE-I or ARB therapy.

Look-alike / Sound-alike Error Risk Potential: The Institute for Safe Medication Practice (ISMP) has not updated their List of Confused Drug Names since approval of sacubitril/valsartan.[28]

Pharmacology and Pharmacokinetic Properties:

Table 3. Basic Pharmacology and Pharmacokinetic Properties of Sacubitril/Valsartan.[12]

Parameter	
Mechanism of Action	Inhibition of neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug sacubitril, and blockade of the angiotensin II type-1 receptor and inhibition of angiotensin II-dependent aldosterone release via valsartan.
Oral Bioavailability	Sacubitril: ≥60%. Note: the valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.
Distribution and Protein Binding	The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively. Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%).
Elimination	52% to 68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces.
Half-Life	Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively. Following twice-daily dosing of ENTRESTO, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days.
Metabolism	Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality (all-cause; secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptomatic relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality of life

Primary Study Endpoint:
1) Composite (death from cardiovascular causes or first hospitalization from heart failure)

Table 4. Comparative Evidence of Sacubitril/Valsartan.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Risk of Bias/Applicability
1. PARADIGM-HF [1,13,29,30] MC, R, DB, AC PG	1. Sacubitril 97 mg/ valsartan 103 mg BID (200 mg BID) (S/V) 2. Enalapril 10 mg BID (E) Study Phases: i. Screening period ii. Single-blind enalapril run-in of 10 mg BID x2 wks iii. Single-blind LCZ696 run-in titration to 200 mg BID x4-6 wks iv. Randomized double-blind treatment to enalapril or LCZ696 27 months	<u>Demographics</u>: -Age: 64 y -Male: 78% -White: 66% -Asian: 18% -Black: 5% -NYHA class II: 70% -NYHA class III: 24% -NYHA class IV: 0.7% -LVEF: 29% -Ischemic etiology 60% -Beta-blocker: 94% -Diuretic: 82% -Aldosterone antagonist 58% -ICD/CRT 15% <u>Inclusion Criteria</u>: -Age ≥18 y -NYHA class II-IV -LVEF ≤35% -Hospitalization for HF last 12 months -Stable dose* of ACE-I/ARB and beta-blocker ≥4 wks <u>Exclusion Criteria</u>: -SBP <100 mmHg -h/o angioedema -Decompensated HF -eGFR <30 mL/min -K+ >5.2 mEq/L -ACS, CVA, TIA, PCI, cardiac or carotid surgery ≤3 m -Coronary or carotid disease *likely* to require surgery ≤6 m -Valvular disease -LV assistance device -Severe pulm disease -Life expectancy <5 y	<u>mITT</u>: S/V: n=4187 E: n=4212 <u>Attrition</u>: S/V: 17.8% E: 19.8%	<u>Primary Endpoint</u>: CV Death or Hospitalization for HF: S/V: 914 (21.8%) E: 1117 (26.5%) HR=0.80 (95% CI, 0.73-0.87; p<0.001) <u>Secondary Endpoints</u>: All-cause mortality: S/V: 17.0% vs. E: 19.8%; HR=0.84 (95% CI, 0.76-0.93; p<0.001) Change in KCCQ Score at 8 months (scale, 0-100): S/V: -2.99±0.36 vs. E: -4.63±0.36; mean difference=1.61 points (95% CI, 0.63-2.65; p=0.001)	4.7%/22 2.8%/36 NA	<u>D/C due to AE:</u> S/V: 10.7% E: 12.3% p=0.03 New Onset AFib: S/V: 3.1% E: 3.1% p=0.83 <u>Symptomatic Hypotension</u>: S/V: 14.0% E: 9.2% p<0.001 <u>Hyperkalemia >6.0 mEq/L</u>: S/V: 4.3% E: 5.6% p=0.007 <u>Cough</u>: S/V: 11.3% E: 14.3% p<0.001 <u>Angioedema</u>: (all severities) S/V: 19 (0.45%) E: 10 (0.24%) p=0.18 Decline in renal function (50% decline in eGFR, >30 mL/min decline if baseline eGFR <60 mL/min, or ESRD): S/V: 2.2% E: 2.6% p=0.28	1.6%/62 NS 4.8%/20 1.3%/76 3.0%/33 NS NS	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) allocation concealed through randomization by central IVRS;[31] baseline characteristics of both groups well balanced. <u>Performance</u>: (mod) match placebo provided to both groups in double-blind phase;[31] however, order of single-blind run-in phases poses risk of un-blinding after allocation. <u>Detection</u>: (low) blinded adjudication of outcomes; <u>Attrition</u>: (low) attrition similar between groups; data censored at last contact; modified ITT analysis. **Applicability**: <u>Patient</u>: only patients who tolerated both E 10 mg BID and S/V 200 mg BID were eligible for randomization. Extended run-in phases followed by 36-hr wash-out periods limit inferences to OHP population. <u>Intervention</u>: maintenance dose of S/V designed to yield systemic exposure of valsartan equal to 320 mg/d, the dose achieved in Val-HeFT[20] and VALIANT[21]; mean dose achieved was 375 mg/day. <u>Comparator</u>: enalapril dose similar to SOLVD Treatment trial;[22] mean dose was 18.9 mg/day. Valsartan a better comparison? Valsartan 320 mg/d may be superior to enalapril 20 mg/d when directly compared for various CV outcomes.[23–26] <u>Outcomes</u>: clinically relevant outcomes; composite primary endpoint driven by both outcomes equally; all-cause mortality composed mostly of CV deaths; <u>Setting</u>: Clinic visits every 2-8 weeks x4 months, and every 4 months thereafter.

Abbreviations [alphabetical order]: AC = active-controlled; ACE-I = ACE Inhibitors; ACS = acute coronary syndrome; AE = adverse events; AFib = atrial fibrillation; ARB = angiotensin receptor blockers; ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; CRT = cardiac resynchronization therapy-defibrillator; CV = cardiovascular; CVA = stroke/transient ischemic attack; DB = double-blind; eGFR = estimated glomerular filtration rate (in mL/min/1.73 m^2); ESRD = end stage renal disease; h/o = history of; HR = hazard ratio; HTN = hypertension; ICD = implantable cardioverter-defibrillator; IVRS = interactive voice system response; K+ = potassium levels; KCCQ = Kansas City Cardiomyopathy Questionnaire (higher scores indicate better perceived health status and quality of life); LV = left ventricular; LVEF = left ventricular ejection fraction; m = months; MC = multi-centered; MI = myocardial infarction; mITT = modified intention to treat; n = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PG = parallel-group; R = randomized; SBP = systolic blood pressure; y = years.

*Minimum Required Pre-study Daily Doses of Common ACE-Is or ARBs.

Enalapril 10 mg	Candesartan 16 mg
Captopril 100 mg	Irbesartan 150 mg
Fosinopril 20 mg	Losartan 50 mg
Lisinopril 10 mg	Olmesartan 10 mg
Moexipril 7.5 mg	Telmisartan 40 mg
Quinapril 20 mg	Valsartan 160 mg
Ramipril 5 mg	

References:

1. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *New England Journal of Medicine*. 2014;371:993-1004. doi:10.1056/NEJMoa1409077.

2. Green C, Porter C, Bresnahan D, Spertus J. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35:1245-1255.

3. Kansas City Cardiomyopathy Questionnaire, KCCQ Interpretibility. Cardiovascular Outcomes, Inc. Available at http://cvoutcomes.org/pages/3217. Accessed July 23, 2015.

4. Bahrami H, Kronmal R, Bluemke D, et al. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med*. 2008;168:2138-2145. doi:10.1001/archinte.168.19.2138.

5. Lang C, Struthers A. Targeting the renin-angiotensin-aldosterone system in heart failure. *Nat Rev Drug Discov*. 2013;10:125-134. doi:10.1038/nrcardio.2012.196.

6. 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.

7. Yancy C, 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:e147-e239. doi:http://dx.doi.org/10.1016/j.jacc.2013.05.019.

8. van Veldhuisen D, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-2158. doi:10.1016/j.jacc.2009.02.046.

9. von Lueder T, Sangaralingham S, Wang B, et al. Renin–angiotensin blockade combined with natriuretic peptide system augmentation novel therapeutic concepts to combat heart failure. *Circ Heart Fail*. 2013;6:594-605. doi:10.1161/CIRCHEARTFAILURE.112.000289.

10. Kostis J, Packer M, Black H, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the omapatrilat cardiovascular treatment vs. enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111. doi:10.1016/j.amjhyper.2003.09.014.

11. ENTRESTO (sacubitril/valsartan) New Drug Application Approval Letter. Center for Drug Evaluation and Research, Food and Drug Administration. U.S. Department of Health and Human Services. Available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf. Accessed July 20, 2015.

12. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, July 2015.

13. McMurray J, Packer M, Desai A, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062-1073. doi:10.1093/eurjhf/hft052.

14. Solomon S, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395. doi:10.1016/ S0140-6736(12)61227-6.

15. Solomon S, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395. doi:10.1016/ S0140-6736(12)61227-6.

16. Ruilope L, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz M. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. 2010;375:1255-126. doi:10.1016/ S0140-6736(09)61966-8.

17. Sacubitril/Valsartan FDA Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000SumR.pdf. Accessed 21 August 2015.

18. Kansas City Cardiomyopathy Questionnaire, KCCQ Overview. Cardiovascular Outcomes, Inc. Available at http://cvoutcomes.org/pages/3214. Accessed August 12, 2015.

19. Packer M, McMurray J, Desai A, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131:54-61. doi:10.1161/CIRCULATIONAHA.114.013748.

20. Cohn J, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized tiral of the angiotensin-receptor blocker valsartan in chronic heart failure. *New England Journal of Medicine*. 2001;345:1667-1675.

21. Pfeffer M, McMurray J, Velazquez E, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *New England Journal of Medicine*. 2003;349:1893-1906.

22. The SOLVD Investigators. Effect on enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *New England Journal of Medicine*. 1991;325:293-302.

23. Fogari R, Mugellini A, Zoppi A, et al. Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. *Eur J Clin Pharmacol*. 2004;59:863-868. doi:10.1007/s00228-003-0717-9.

24. Holwerda N, Fogari R, Angeli P, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens*. 1996;14:1147-1151.

25. Schaefer F, Litwin M, Zachwieja J, et al. Efficacy and safety of valsartan compared to enalapril in hypertensive children: a 12-week, randomized, double-blind, parallel-group study. *J Hypertens*. 2011;29:2484-2490. doi:10.1097/HJH.0b013e32834c625c.

26. Willenheimer R, Helmers C, Pantev E, Rydberg E, Lofdahl P, Gordon A. Safety and efficacy of valsartan versus enalapril in heart failure patients. *Int J Cardiol*. 2002;85:261-270.

27. Bassler D, Briel M, Montori V, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA*. 303:1180-1187.

28. ISMP's List of Confused Drug Names, Updated 2015. Institute for Safe Medication Practices. Available at www.ismp.org/Tools/confuseddrugnames.pdf. Accessed July 6, 2015.

29. McMurray J, Packer M, Desai A, et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16:817-825. doi:10.1002/ejhf.115.

30. ENTRESTO (sacubitril and valsartan) [Formulary Submission Dossier]. East Hanover, NJ: Novartis Pharmaceuticals, July 2015.

31. Personal Communication. Mary Kemhus, PharmD, Regional Account Scientific Director. Novartis Pharmaceuticals Corporation. August 19, 2015.

Appendix 1: Highlights of Prescribing Information[12]

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

ENTRESTO™ (sacubitril and valsartan) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.
- **When pregnancy is detected, discontinue ENTRESTO as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

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

ENTRESTO is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. (1.1)

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. (1.1)

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

- The recommended starting dose of ENTRESTO is 49/51 mg (sacubitril/valsartan) twice-daily. Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient. (2.1)
- Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:
  - patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents (2.2)
  - patients with severe renal impairment (2.3)
  - patients with moderate hepatic impairment (2.4)

  Double the dose of ENTRESTO every 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient. (2.2, 2.3, 2.4)

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

- Film-coated tablets (sacubitril/valsartan): 24/26 mg; 49/51 mg; 97/103 mg (3)

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

- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACE inhibitor or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aliskiren in patients with diabetes. (4, 7.1)

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

- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

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

Adverse reactions occurring ≥5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Dual blockade of the renin-angiotensin system: Do not use with an ACEi, do not use with aliskiren in patients with diabetes, and avoid use with an ARB. (4, 7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- NSAIDs: May lead to increased risk of renal impairment. (7.3)
- Lithium: Increased risk of lithium toxicity. (7.4)

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

- Lactation: Breastfeeding or drug should be discontinued. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.4, 8.6)

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

Revised: 7/2015

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:

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

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on sacubitril/valsartan)?	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 for 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 for 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 for 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: *09/15 (AG)*
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

New Drug Evaluation: ivabradine tablet, oral

Date of Review: September 2015
Generic Name: ivabradine
PDL Class: not applicable

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): CORLANOR® (Amgen, Inc.)
Dossier Received: yes

Research Questions:

1. What is the current evidence for the efficacy of ivabradine to reduce to reduce mortality and cardiovascular (CV) morbidities; and if available, how does the drug's efficacy compare to other drugs used to manage chronic heart failure with reduced ejection fraction (HFrEF)?
2. Based on the evidence available, does ivabradine have a clear place in therapy for management of chronic HFrEF?
3. How well is ivabradine tolerated in patients; and if available, how does the safety of ivabradine compare to other drugs used to manage chronic HFrEF?
4. Are there subgroups of patients in which ivabradine may be safer or more effective than other drugs used to manage chronic HFrEF?

Conclusions:

- Evidence for use of ivabradine is based on one 23-month clinical trial (n=6,505) with low overall risk bias.[1] 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 32% in normal sinus rhythm with a minimum resting heart rate (HR) of 70 beats-per-minute (BPM).[1] Patients in the study remained on standard HF therapy, which typically included an ACE-inhibitor [ACE-I] or angiotensin-2 receptor blocker [ARB]), beta-blocker, diuretic(s), and an aldosterone antagonist.[1]
- There is low quality evidence, based on a secondary endpoint, that ivabradine 5-7.5 mg twice daily (BID) may reduce risk of hospitalizations for heart failure (HF) by 4.7% compared to placebo (15.9% vs. 20.6%, respectively; Hazard Ratio [HR]=0.74; 95% Confidence Interval [CI], 0.66-0.83; p<0.0001; number needed-to-treat [NNT] =22).[1] However, ivabradine does not appear to be any different from placebo in regards to ability to reduce all-cause or CV-related mortality in these patients.[1]
- Overall, studies that evaluated other populations provide moderate quality evidence that ivabradine does not reduce CV outcomes or mortality in patients with HFrEF in normal sinus rhythm when baseline resting HR is not considered,[2] or in CAD patients without HF.[3]
- There is moderate quality evidence ivabradine can cause asymptomatic and symptomatic bradycardia.[1–3] Negative chronotropic drugs such as non-dihydropyridine calcium channel blockers (i.e., diltiazem and verapamil), or amiodarone increases risk for adverse events with ivabradine.[4]
- There is moderate quality evidence ivabradine increases risk for development of atrial fibrillation.[1,3] Ivabradine should be avoided in patients with atrial fibrillation and should be discontinued if it develops after starting the drug.[4]

Recommendation:

- Restrict use of ivabradine to populations where it has demonstrated some efficacy. See **Appendix 2** for the proposed prior authorization criteria.

Background:

The goals of management of HFrEF (ie, systolic HF) are to prevent hospital admission and improve survival, and to relieve signs (eg, edema) and symptoms (eg, dyspnea).[5] The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[5,6] The most well-studied system in the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has shown to have a significant impact on the pathophysiology and progression of HF.[5,6] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[5,6] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a select beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralcorticoid (aldosterone) receptor antagonist (spironoloactone or eplerenone).[5,6]

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[5,6] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD.[6] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[5] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[5,6] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[6] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[7] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[5,6] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[6] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials that were designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see Table 1).[5,6]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[5]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-35 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg Qday • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation

* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

There are also other therapeutic options for management of HFrEF that do not inhibit RAAS or other components of neurohormonal activation. Hydralazine and isosorbide dinitrate has shown to decrease morbidity and mortality in self-identified African-Americans/Blacks with NYHA class III-IV and reduced EF.[6] Digoxin has no effect on survival, but it can have a modest effect on reducing hospitalizations regardless of the underlying rhythm or cause of HF (ischemic or non-ischemic cardiomyopathy).[6] Ivabradine inhibits I_f channels in the sinoatrial node of the heart, which acts as a pacemaker by slowing the heart rate; but unlike beta-blockers, ivabradine does not have an effect on myocardial contractility or intracardiac conduction.[4] In Europe, consideration for ivabradine is given to

reduce HF hospitalization in patients in normal sinus rhythm with HFrEF (EF ≤35%), a baseline resting HR of 70 BPM or more, and persistent symptoms (NYHA class II-IV) despite a recommended dose of a beta-blocker, an ACE-I/ARB and an aldosterone antagonist.[5] Ivabradine was recently approved by the U.S. Food and Drug Administration for a similar indication as that recommended in Europe.[4]

Previous evidence has shown increased HR, even at relatively low rates of 77-82 BPM, in patients with CAD is associated with higher higher CV mortality and CV complications.[8] In patients with HF with preserved EF (HFpEF), every increase in HR by 10 BPM was associated with a statistically significant 7% increased risk of all-cause mortality, and 8% increased risk of CV death or hospital admission for HF.[9] In patients with confirmed CAD and HFrEF, a baseline resting HR of 70 BPM or higher was associated with 34% higher risk for CV death, 53% increase in hospital admission for HF, and 46% increase in hospital admission for myocardial infarction (MI), which were statistically significant differences relative to a baseline resting HR lower than 70 BPM.[10] Patients with symptomatic HFrEF (NYHA Class II or higher) with high resting HR (≥87 BPM) were at a 3.5-fold higher risk for death from HF, and almost 2-fold higher risk for all-cause mortality and CV mortality than patients with a resting HR under 72 BPM.[11] However, decreasing HR may not necessarily improve CV risk. For example, sustained-release metoprolol succinate reduced mortality and hospitalizations independent of resting baseline HR, change in HR from baseline, or the HR achieved at the end of study follow-up.[12]

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

Clinical Efficacy:
The first large trial (median duration 19 months; n=10,917) of ivabradine was a fair-quality study called "morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left-ventricULar dysfunction" (i.e., "BEAUTIFUL").[2] The study was a multi-centered, double-blind, randomized, controlled trial (RCT) that compared ivabradine 5 mg twice daily (BID), titrated up to 7.5 mg BID if tolerated, to placebo in mostly males with NYHA Class II HF. Most patients enrolled into the study were on appropriate concurrent HF therapies, including ACE-Is or ARBs (90%), beta-blockers (84%), aspirin or other antithrombotic agent (94%), and lipid lowering therapy (i.e., statins) (90%). Patients enrolled into the study had a mean left-ventricular ejection fraction (LVEF) of 32% and had stable CAD, defined as previous MI at least 6 months prior to enrollment, previous interventional coronary revascularization at least 6 months prior to enrollment, or patients with evidence of at least 1 major coronary artery with at least 50% occlusion. In addition, patients had to be in normal sinus rhythm with a resting HR of at least 60 BPM. The mean age in the study was 65 years and 82% were males. The primary endpoint was a composite of CV death, hospital admission for MI, or hospital admission for new-onset or worsening HF. CV death was defined as sudden cardiac death, death from a vascular procedure, death from arrhythmia, death from stroke, death from any vascular event, or sudden death from an unknown cause. The primary endpoint occurred in 15.4% of patients receiving ivabradine (mean dose 6.18 mg BID) and 15.3% of patients receiving placebo (hazard ratio [HR] =1.00 (95% confidence interval [CI], 0.91 to 1.10; p=0.94). In addition, there was a no significant difference in all secondary outcomes measured, including all-cause mortality, cardiac death, CV death (defined above), coronary revascularization, hospital admission for HF, and hospital admission for MI. The protocol was amended to evaluate a subgroup of patients with a resting HR of at least 70 BPM as data became available that ivabradine may be more beneficial in these patients. The subgroup analysis found a significant reduction in 2 secondary endpoints: hospital admission for MI, admission to hospital for MI or unstable angina, or coronary revascularization. There was no statistically significant difference between ivabradine and placebo for all other study endpoints, including the composite primary endpoint. Bradycardia was the most commonly associated adverse event (13%) attributed to ivabradine.[2]

The second trial (median duration 22.9 months) of ivabradine was a fair-quality study that evaluated the drug in patients (n=6505) with stable, symptomatic chronic HF (NYHA Classes II and III) with systolic dysfunction (LVEF ≤35%) and was titled the "Systolic Heart failure treatment with the If inhibitor ivabradine

Trial" (i.e., "SHIFT").[1] It was a multi-centered, double-blind, RCT that compared ivabradine 5 mg BID, titrated up to 7.5 mg BID if tolerated, to placebo in mostly White male subjects. Most patients enrolled into the study were on appropriate concurrent heart failure therapies, including ACE-I/ARBs (91%), and beta-blockers (89%); however, only 26% of the patients enrolled in the study were on target beta-blocker doses and under half (49%) were receiving 50% or more of the targeted beta-blocker dose, per the European Society of Cardiology (ESC).[5] No data were provided on the proportion of patients receiving target doses of ACE-Is or ARBs. Patients enrolled into the study had a LVEF of 29% and 84% regularly received diuretics. Only 2% were classified with NYHA Class IV HF. The mean age in the study was 60 years and 76% were males, mostly of Eastern European descent (no U.S. sites). The primary endpoint was a composite of CV death or hospital admission for worsening HF. CV death was defined as any sudden death unless an unequivocal non-CV cause of death was established. At 28 days, HR in patients on ivabradine fell by a mean 15.4 BPM compared to pre-treatment, which was a net reduction of 10.9 BPM (95% CI, 10.4-11.4) relative to placebo. The primary endpoint occurred in 24.5% of patients receiving ivabradine (mean dose 6.5 mg BID) and 28.7% of patients receiving placebo (absolute difference of 4.2%; HR =0.82 (95% CI, 0.75 to 0.90; p<0.0001; NNT=26 for 1 year). These data were driven by a reduction in the number of hospital admissions for worsening HF (15.9% vs. 20.6%; HR=0.74, 95% CI 0.66-0.83; p<0.0001) and not CV death (13.9% vs. 15.0%; HR=0.91, 95% CI 0.80-1.03; p=0.128). A sub-group analysis found that patients with a baseline resting HR of less than 77 BPM had a significant reduction in the composite primary endpoint, but there was no difference between the groups in patients with HR of 77 BPM or higher. Other secondary outcomes that demonstrated statistically significant reductions with ivabradine use included death attributed to HF (3.5% vs. 4.6%; HR=0.74, 95% CI 0.58-0.94; p=0.014), hospital admissions due to any CV reason (30.1% vs. 34.4%; HR=0.85, 95% CI 0.78-0.92; p=0.0002), and all-cause hospitalizations (38.0% vs. 41.5%; HR=0.89, 95% CI 0.75-0.90; p=0.003). However, there was no statistically significant difference in all-cause mortality between those receiving ivabradine (15.5%) and those receiving placebo (16.9%). In addition, there was no statistically significant difference in the primary endpoint in patients who were on at least 50% of the target beta-blocker dose as recommended by the ESC – a pre-specified secondary endpoint. A sub-group analysis of the study found there to be a direct association between HR achieved at 28 days and subsequent cardiac outcomes.[11] Patients with HRs lower than 60 BPM at 28 days on treatment had fewer primary composite endpoint events in the study (17.4%, 95% CI 15.3-19.6) than did patients with higher HRs.[11] However, there were statistically significant baseline differences in some confounding factors: patients enrolled into the study with lower baseline resting HRs were younger, had lower rates of current smoking status, had a higher LVEF, and lower NYHA classification status than patients with much higher baseline HRs.[11] Notable adverse events included symptomatic and asymptomatic bradycardia, which occurred at a statistically significantly greater extent with ivabradine.[1] More patients on ivabradine also experienced atrial fibrillation (9.5% vs. 7.7%), which occurred significantly more often than in patients receiving placebo (number needed to harm = 55 patients).[1]

The third trial (median duration 27.8 months) of ivabradine was a good-quality study that evaluated the drug in patients (n=19,102) with stable CAD but without any evidence of clinical HF and was titled "Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease" (i.e., "SIGNIFY").[3] The study was a multi-centered (no U.S. sites), double-blind, RCT that compared ivabradine 7.5 mg BID, adjusted to 5 mg, 7.5 mg or 10 mg BID if tolerated, to placebo in mostly White males without HF. Eligible patients had stable CAD, were in normal sinus rhythm, and a LVEF greater than 40% with a resting HR of 70 BPM or greater. However, patients had to have either activity-limiting angina pectoris (Canadian Cardiovascular Scale [CCS] class II or higher), a history of myocardial ischemia in the past year or were hospitalized for a coronary event in the past year. Otherwise, if patients did not meet one of the previous 3 criteria, they had to meet at least 2 other criteria put them at risk for a cardiac event, such as dyslipidemia, diabetes mellitus, current smoker, age 70 years or older, or peripheral artery disease. Most patients enrolled into the study were receiving ACE-I/ARBs (82.8%), beta-blockers (83.1%), aspirin or other antithrombotic agent (91.6%), and lipid lowering therapy (i.e., statins) (92.2%). Patients enrolled into the study had a mean age of 65 years and 72.4% were males. About 73% had a previous MI, 68% had a history of coronary revascularization, and 63% had activity-limiting angina. The primary endpoint was a composite of nonfatal MI and multiple outcomes under the umbrella term "cardiovascular death". CV death was defined as sudden cardiac death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause), death from a vascular procedure, fatal stroke, or non-sudden death from an unknown cause. The primary endpoint occurred in 6.8% of patients receiving ivabradine (mean dose 8.0 mg BID) and 6.4% of patients receiving placebo (HR =1.08; 95% CI, 0.96 to 1.20; p=0.20). In addition, there was a non-statistically significant difference in all secondary outcomes measured, including all-cause

mortality, cardiac death, CV death (defined above), fatal/non-fatal MI, coronary revascularization, and hospital admission for HF. Overall, the addition of ivabradine did not reduce CV events in patients with stable CAD without HF.[3]

Based on the evidence provided from these 3 trials, the FDA granted approval for the use of ivabradine to reduce risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with a LVEF of 35% or less, who are in sinus rhythm with a resting HR of 70 BPM or more and either on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.[4] The approval was based on the efficacy demonstrated as a secondary endpoint in SHIFT, which showed a statistically significant 4.7% reduction in hospitalizations for worsening HF with ivabradine relative to placebo. Thus, 22 patients would need to be treated with ivabradine for nearly 2 years (22.9 months) to prevent 1 hospitalization for worsening HF. Based on the evidence available, patients that do not fit the criteria within the FDA approval will likely not benefit from ivabradine.

Clinical Safety:
A summary of the clinical safety of ivabradine will focus on the stable but symptomatic chronic HF population enrolled in SHIFT[1], which is the population for which the FDA has approved use of the drug. A summary of common adverse events associated with ivabradine is available in Table 2.

In SHIFT, symptomatic and asymptomatic bradycardia was more frequent in the ivabradine group than in patients taking placebo (both $p<0.001$).[1] The rate of bradycardia was 6.0% per patient-year in patients on ivabradine (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Bradycardia resulted in premature withdrawal from the study in 48 (1.5%) of patients on ivabradine and 10 (0.3%) of those on placebo.[1] Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, or amiodarone).[4] In addition, sinus arrest and heart block have occurred with use of ivabradine.[4] Therefore, patients on ivabradine should be monitored closely for signs and symptoms of bradycardia, especially early in therapy.

In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients on ivabradine and 3.9% per patient-year in patients treat with placebo. The manufacturer advises discontinuing ivabradine if atrial fibrillation develops.[4]

Table 2. Adverse Events with Rates ≥1% Higher with Ivabradine than Placebo Occurring in >1% of Patients Enrolled in SHIFT.[1,4]

Adverse Event	Ivabradine (n=3260)	Placebo (n=3278)
Bradycardia	10%	2.2%
Hypertension; Increased Blood Pressure	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes, Visual Brightness	2.8%	0.5%

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images. Phosphenes are typically triggered by sudden variations in light intensity.[4]

According to the SHIFT investigators, there were no relevant between-group differences in laboratory parameters (unpublished data).[1]

Animal studies have shown ivabradine to result in embryo-fetal toxicity and cardiac teratogenic effects. It can therefore be assumed ivabradine may cause fetal toxicity when administered to pregnant women and it is advised females on ivabradine use effective contraception.[4]

Look-alike / Sound-alike Error Risk Potential: The Institute for Safe Medication Practice (ISMP) has not updated their List of Confused Drug Names since approval of ivabradine.[13]

Pharmacology and Pharmacokinetic Properties:

Table 3. Basic Pharmacology and Pharmacokinetic Properties of Ivabradine.

Parameter	
Mechanism of Action	Specific inhibitor of the I_f current in the sinoatrial node, decreasing heart rate without affecting blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarization.[4]
Oral Bioavailability	40% due to extensive first-pass metabolism and elimination in the gut and liver.[4]
Distribution and Protein Binding	Volume of distribution at steady state is about 100 L; approximately 70% of the drug in plasma is bound to protein.[4]
Elimination	Total clearance is 24 L/h, with renal clearance of about 4.2 L/h (4% unchanged in urine).[4]
Half-Life	Effective half-life is about 6 hours.[4]
Metabolism	Extensively metabolized in the liver and intestines by CYP 3A4-mediated oxidation.[4] The major metabolite is a N-desmethylated derivative that is as potent as ivabradine and circulates at about 40% that of ivabradine.[4]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality (all-cause, secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptom-relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality-of-life

Primary Study Endpoints:
1) Composite (cardiovascular death*, hospital admission for MI, or hospital admission for HF)
2) Composite (cardiovascular death* or hospital admission for HF)
3) Composite (cardiovascular death* and nonfatal MI)

*Cardiovascular death was also a composite of several outcomes, which are defined individually in the Comparative Evidence Table.

Table 4. Comparative Evidence of Ivabradine.

Ref./ Study Design	Drug Regimens/ Median Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. BEAUTIFUL[2] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR ≥60 BPM (I) 2. Placebo (P) 19 months	Demographics: -Mean Age 64.6 y -82% Males -Mean HR 79.2 BPM -Mean LVEF 32% -NYHA I 14% -NYHA II 59% -NYHA III 27% -ACE-I/ARB 90% -Beta-blocker 84% Key Inclusion Criteria: -Age ≥55 y (or ≥18 years if have DM) -CAD (previous MI, previous coronary revascularization, or evidence ≥1 major coronary artery narrowed by ≥50%) -LVEF <40% -Normal sinus rhythm -Resting HR ≥60 BPM Key Exclusion Criteria: -MI or coronary revascularization previous 6 months -Stroke/TIA previous 3 months -Implanted pacemaker, cardioverter or defibrillator -Valvular disease -Sick sinus syndrome -Sinoatrial block -Congenital long QT -Complete AV block -Uncontrolled HTN -NYHA Class IV	ITT: I: n=5479 P: n=5438 Attrition: I: 28% P: 16%	Primary Endpoint: CV Death, Hospital Admission for MI, or Hospital Admission for HF: I: 15.4% vs. P: 15.3%; HR=1.00 (95% CI, 0.91-1.10; p=0.94) Secondary Endpoints: All-cause Mortality: I: 10.4% vs. P: 10.1%; HR=1.04 (95% CI, 0.92-1.16; p=0.55) Cardiac Death (death from MI, HF or cardiac surgery): I: 2.5% vs. P: 2.8%; HR=0.89 (95% CI, 0.71-1.12; p=0.33) CV Death (cardiac death, or death from vascular procedure, arrhythmia, stroke, other vascular event, or sudden death of unknown cause): I: 8.6% vs. P: 8.0%; HR=1.07 (95% CI, 0.94-1.22; p=0.32) Coronary Revascularization: I: 2.8% vs. P: 3.4%; HR=0.83 (95% CI, 0.67-1.02; p=0.078) Hospital Admission for HF: I: 7.8% vs. P: 7.9%; HR=0.99 (95% CI, 0.86-1.13; p=0.85) Hospital Admission for MI: I: 3.6% vs. P: 4.2%; HR=0.87 (95% CI, 0.72-1.06; p=0.16)	 NS NS NS NS NS NS NS	Any Serious AE: I: 23% P: 23% P=NS Discontinuation due to AE: I: NR P: NR Bradycardia: I: 705 (13%) P: 79 (2%) P=NR Cardiac disorders: I: 18% P: 15% P<0.001	 NS NR 11%/NR 3%/33	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographic characteristics evenly matched. Performance: (mod) allocated by interactive web-response system to ensure allocation remained concealed; blinding not described. Detection: (mod) 2 major protocol amendments; power assumptions described; censoring rules appropriate; ITT analysis performed; assessors blinded. Attrition: (mod) high attrition, w/ 12% higher attrition w/ ivabradine but controlled w/ ITT. **Applicability**: Patient: patients w/ mild symptomatic HF; mostly male; unknown racial makeup; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.). Intervention: mean dose of 6.18 mg BID; 40% remained on 7.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; clinically relevant individual outcomes; AEs only described by body system except for bradycardia. Setting: outpatient visits at 2 weeks, 1, 3 and 6 months; and every 6 months thereafter. **Analysis**: The drug sponsor used a subgroup analysis that found patients w/ HR ≥70 BPM may benefit from the following outcomes w/ ivabradine: hospital admission for MI, or hospital admission for coronary revascularization. The analysis was used to test the hypothesis in the SHIFT trial.

2. SHIFT[1] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR >60 BPM; dose reduced by 2.5 mg if HR <50 BPM or symptomatic (I) 2. Placebo (P) 22.9 months	Demographics: -Mean Age 60.4 y -Male 76% -HR 79.9 BPM -LVEF 29% -NYHA II 48.7% -NYHA III 49.5% -NYHA IV 1.7% -Ischemic etiology 68% -Non-ischemic etiology 32% -Hypertension 67% -ACE-I/ARB 91% -Beta-blocker 89% -Diuretics 84% -Aldosterone antagonists 60% Key Inclusion Criteria: -Age ≥18 y -Stable, symptomatic HF ≥4 weeks -LVEF ≤35% -Normal sinus rhythm -Resting HR ≥70 BPM -Optimal and stable background HF therapy x ≥4 weeks -Previous hospitalization for HF in last 12 months Key Exclusion Criteria: -Recent MI <2 months -CVA/TIA <4 weeks -Ventricular or atrioventricular pacing operative ≥40% of day -Atrial fib/flutter -Symptomatic hypotension -HF from congenital disease or severe valvular disease -diltiazem/verapamil -Class I antiarrhythmic	mITT: I: n=3241 P: n=3264 Attrition: I: 21% P: 19%	Primary Endpoint: CV Death or Hospital Admission for HF: I: 24.5% vs. P: 28.7%; HR=0.82 (95% CI, 0.75-0.90; p<0.0001) Secondary Endpoints: CV Death or Hospital Admission for HF in Patients on ≥50% Target Beta-blocker Dose per the ESC*: I vs. P data NR; HR=0.90 (95% CI, 0.77-1.04; p=0.155) All-cause Mortality: I: 15.5% vs. P: 16.9%; HR=0.90 (95% CI, 0.80-1.02; p=0.092) Death from HF: I: 3.5% vs. P: 4.6%; HR=0.74 (95% CI, 0.58-0.94; p=0.014) CV Mortality: I: 13.9% vs. P: 15.0%; HR=0.91 (95% CI, 0.80-1.03; p=0.128) Hospital Admission for HF: I: 15.9% vs. P: 20.6%; HR=0.74 (95% CI, 0.66-0.83; p<0.0001) Hospital Admission for any CV reason: I: 30.1% vs. P: 34.4%; HR=0.85 (95% CI, 0.78-0.92; p=0.0002) All-cause Hospitalization: I: 38.0% vs. P: 41.5%; HR=0.89 (95% CI, 0.75-0.90; p=0.003)	4.2%/24 NS 1.4%/NS 1.1%/91 1.1%/NS 4.7%/22 4.3%/24 3.5%/29	Serious AEs: I: 1450 (45%) P: 1553 (48%) p=0.025 Discontinuation due to AE: I: 467 (14%) P: 416 (13%) p=0.051 Symptomatic Bradycardia: I: 150 (4.6%) P: 32 (1.3%) p<0.0001 Asymptomatic Bradycardia: I: 184 (5.7%) P: 48 (1.5%) p<0.0001 Atrial Fibrillation: I: 306 (9.5%) P: 251 (7.7%) p=0.012 Phosphenes (transient enhanced brightness in a restricted area of the visual field): I: 89 (2.8%) P: 17 (0.5%) p<0.0001 Blurred Vision: I: 17 (1%) P: 7 (<1%) p=0.042	NA NS 3.3%/30 4.2%/23 1.8%/55 2.3%/43 0.3%/333	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization with well-balanced demographics. Performance: (low) allocated by interactive web-response system to ensure allocation remained concealed; placebo identical in appearance, ensuring blinding maintained. Detection: (mod) power assumptions described; modified ITT analysis performed after 2 centers' data removed due to misconduct; imputation of missing data unclear; censoring rules unclear. Attrition: (low) 2% more patients on ivabradine (n=682) withdrew vs. placebo (n=605) (HR=1.14; 95% CI, 1.02-1.27; p=0.017). **Applicability**: Patient: majority White males w/ Class II or III NYHA HF; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.), similar doses between groups; only 26% in each grp at target dose of beta-blocker. Intervention: mean dose 6.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary endpoint driven by decreased hospitalizations for HF; primary endpoint not significantly reduced in patients w/ baseline HR <77 BPM; primary endpoint also favors age <65 years; ivabradine resulted in a net HR reduction of 8.1 (95% CI, 8.5-9.7) BPM vs. placebo by end of study; all deaths categorized as CV deaths unless unequivocal non-CV cause established. Setting: no USA sites, mostly Eastern Europe (66%); outpatient clinic visits every 4 months. **Analysis**: Results of the trial were considered by the FDA to grant approval of the drug with specific criteria for use.

3. SIGNIFY[3] MC, R, DB, PC PG	1. Ivabradine 7.5 mg BID (5 mg BID if age ≥75 y). Dose adjusted to 5, 7.5 or 10 mg BID per HR (goal 55-60 BPM) and bradycardia symptoms (I) 2. Placebo (P) 27.8 months	Demographics: -Mean Age 65 y -72.4% Males -Mean HR 77.2 BPM -Mean LVEF 56.4% -73.3% previous MI -67.8% previous coronary revascularization -63.1% w/ activity-limiting angina (CCS class ≥II) Key Inclusion Criteria: -Age ≥55 y -Stable CAD w/o HF -LVEF >40% -Normal sinus rhythm -Resting HR ≥70 BPM And either: -≥1 major adverse prognostic factor: • angina pectoris (CCS class ≥2) • myocardial ischemia past 1 y • hospitalization for coronary event past 1 y -Or 2 minor adverse prognostic factors: • HDL <40 mg/dL or LDL >160 mg/dL (on meds) • T1DM or T2DM • PAD • Current smoking • Age ≥70 y Key Exclusion Criteria: -NYHA class II or higher -MI, coronary revascularization, stroke/TIA w/i 3 months	ITT: I: n=9550 P: n=9552 Attrition: I: 20.6% P: 14.5%	Primary Endpoint: Death from CV cause or nonfatal MI: I: 6.8% vs. P: 6.4%; HR=1.08 (95% CI, 0.96-1.20; p=0.20) Secondary Endpoints: All-cause mortality: I: 5.1% vs. P: 4.8%; HR=1.06 (95% CI, 0.94-1.21; p=0.35) Coronary Death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause): I: 2.8% vs. P: 2.6%; HR=1.06 (95% CI, 0.89-1.26; p=0.52) CV Death (coronary death; death from CV procedure; fatal stroke; non-sudden death of unknown cause): I: 3.4% vs. P: 3.2%; HR=1.10 (0.94-1.28; p=0.25) MI (fatal/non-fatal): I: 4.1% vs. P: 3.9%; HR=1.06 (95% CI, 0.92-1.22; p=0.43) Coronary Revascularization: I: 5.9% vs. P: 5.9%; HR=1.00 (95% CI, 0.89-1.12; p=0.98) Hospital Admission for HF: I: 2.3% vs. P:1.9%; HR=1.20 (95% CI, 0.99-1.46; p=0.07)	0.4%/NS 0.3%/NS NA/NS NA/NS NA/NS 0%/NS NA/NS	Serious AEs: I: 37.6% P: 35.4% p=0.001 Discontinuation due to AE: I: 13.2% P: 7.4% P<0.001 Symptomatic Bradycardia: I: 7.9% P: 1.2% p<0.001 Asymptomatic Bradycardia: I: 11.0% P: 1.3% p<0.001 Discontinuation due to Asymptomatic Bradycardia: I: 272 (2.8%) P: 17 (0.2%) p<0.001 Discontinuation due to Symptomatic Bradycardia: I: 194 (2.0%) P: 33 (0.3%) p<0.001 Atrial Fibrillation: I: 5.3% P: 3.8% p<0.001 Phosphenes: I: 5.4% P: 0.5% p<0.001	2.2%/45 5.8%/17 6.7%/14 9.7%/10 2.6%/38 1.7%/58 1.5%/66 4.9%/20	**Quality Rating**: GOOD **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographics well-balanced between groups. Performance: (low) allocated by interactive voice/web-response system to ensure allocation remained concealed; matching placebo, ensuring blinding maintained. Detection: (mod) power assumptions described; true ITT analysis performed; data assessors remained blinded during study; censoring rules unclear. Attrition: (low) attrition high for ivabradine, w/ 6.1% more ivabradine patients who withdrew from study vs. placebo. **Applicability**: Patient: population studied different from previous trials (no HF); majority White males w/moderate angina but stable CAD; notable concurrent meds were beta-blockers (83.1%), ACE-I/ARB (82.8%), statins (92.2%), ASA (91.6%), diltiazem/verapamil (4.4%). Intervention: mean dose 8.2 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; ivabradine resulted in HR of 60.7 BPM at 3 months vs. 70.6 BPM w/ placebo; difference in HR maintained to end of study. Setting: no USA sites; outpatients visits at 1,2,3 and 6 months and every 6 months thereafter. **Analysis**: Well performed study confirmed lack of efficacy of ivabradine in CAD patients with preserved EF.

Abbreviations [alphabetical order]: ACE-I = ACE Inhibitors; AE = adverse events; ARB = angiotensin receptor blockers; ARR = absolute risk reduction; ASA = aspirin; AV = atrioventricular; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society scale I-IV; CI = confidence interval; CV = cardiovascular; DB = double-blind; DM = diabetes mellitus; DF = ejection fraction; ESC = European Society of Cardiology; HDL = high-density lipoprotein cholesterol; HR = heart rate or hazard ratio; HTN = hypertension; ITT = intention to treat; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MC = multi-centered; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; NYHA = New York Heart Association; PAD = peripheral artery disease; PC = placebo-controlled; PG = parallel-group; R = randomized; T1DM; type-1 diabetes mellitus; T2DM = type-2 diabetes mellitus; TIA = transient ischemic attack.

*Target doses: carvedilol: 25-50 mg BID; metoprolol succinate: 200 mg Qday; bisoprolol 10 mg Qday; nebivolol 10 mg Qday.[5]

References:

1. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885. doi:10.1016/S0140-6736(10)61198-1.

2. Fox K, Ford I, Steg P, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807-816. doi:10.1016/S0140-6736(08)61170-8.

3. Fox K, Ford I, Steg P, Tardif J, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. *New England Journal of Medicine*. 2014;371:1091-1099. doi:10.1056/NEJMoa1406430.

4. Corlanor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc., April 2015.

5. 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.

6. Yancy C, 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:e147-e239. doi:http://dx.doi.org/10.1016/j.jacc.2013.05.019.

7. van Veldhuisen D, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-2158. doi:10.1016/j.jacc.2009.02.046.

8. Diaz A, Bourassa M, Guertin M, Tardif J. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J*. 2005;26:967-674. doi:10.1093/eurheartj/ehi190.

9. Pocock S, Wang D, Pfeffer M, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27:65-75. doi:10.1093/eurheartj/ehi555.

10. Fox K, Ford I, Steg P, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008;372:817-821. doi:10.1016/S0140-6736(08)61171-X.

11. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886-894. doi:10.1016/S0140- 6736(10)61259-7.

12. Gullestad L, Wikstrand J, Deedwania P, et al. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the metoprolol controlled release/extended release randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol*. 2005;45:252-259. doi:10.1016/j.jacc.2004.10.032.

13. ISMP's List of Confused Drug Names, Updated 2015. Institute for Safe Medication Practices. Available at www.ismp.org/Tools/confuseddrugnames.pdf. Accessed July 6, 2015.

Appendix 1: Highlights of Prescribing Information[4]

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

CORLANOR (ivabradine) tablets, for oral use
Initial U.S. Approval: 2015

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

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use. (1)

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

- Starting dose is 5 mg twice daily. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. (2)
- In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily. (2)

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

Tablets: 5 mg, 7.5 mg (3)

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

- Acute decompensated heart failure (4)
- Blood pressure less than 90/50 mmHg (4)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present (4)
- Resting heart rate less than 60 bpm prior to treatment (4)
- Severe hepatic impairment (4)
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) (4)
- In combination with strong cytochrome CYP3A4 inhibitors (4)

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

- Fetal toxicity: Females should use effective contraception. (5.1)
- Monitor patients for atrial fibrillation. (5.2)
- Monitor heart rate decreases and bradycardia symptoms during treatment. (5.3)
- Not recommended in patients with 2nd degree AV block. (5.3)

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

Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-772-6436 (1-800-77-AMGEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- CYP3A4 inhibitors increase Corlanor plasma concentrations and CYP3A4 inducers decrease Corlanor plasma concentrations. (7.1)
- Negative chronotropes: Increased risk of bradycardia, monitor heart rate. (7.2)
- Pacemakers: Not recommended for use with demand pacemakers set to rates ≥ 60 beats per minute. (7.3)

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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2015

Ivabradine (Corlanor®)

Goals:

- Restrict use of ivabradine to populations in which the drug has demonstrated efficacy.
- Encourage use of ACE-inhibitors or angiotensin II receptor blockers (ARBs) with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.
- Encourage use of with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ivabradine (Corlanor®)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on ivabradine)?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have current documentation of 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 for medical appropriateness
4. Is the patient in normal sinus rhythm with a resting heart rate of 70 beats per minute or greater (≥70 BPM)?	Yes: Go to #5	No: Pass to RPh. Deny for 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 these 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: Go to #6	No: Pass to RPh. Deny for medical appropriateness
6. Is the patient currently on a maximally tolerated dose of an ACE-inhibitor or an ARB; and if not, is there a documented intolerance or contraindication to both ACE-inhibitors and ARBs?	Yes: Approve for up to 6 months	No: Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Is the patient in normal sinus rhythm with no documented history of atrial fibrillation since ivabradine was initiated?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

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. *Eur J Heart Fail*. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *9/15 (AG)*
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 with New Drug Evaluation: Influenza Antiviral Agents

Date of Review: September 2015
Generic Name: peramivir injection

Date of Last Review: January 2012
Brand Name (Manufactuer): Rapivab™ (BioCryst Pharmaceuticals)
Dossier Received: no

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

Purpose for Class Update:
Rapivab (peramivir) was approved by the United States (U.S.) Food and Drug Administration (FDA) to treat uncomplicated influenza in adults.

Research Questions:
1. What is the comparative efficacy/effectiveness between antiviral agents to treat and prevent influenza?
2. What are the comparative harms between antiviral agents?
3. Are there any populations in which a specific antiviral agent for influenza is more effective or associated with greater harms than other agents?

Conclusions:
- There is insufficient comparative evidence between neuraminidase inhibitors to assess relative safety and efficacy between these drugs.
- There is moderate quality evidence that influenza symptoms improve sooner with neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) compared to placebo in previously healthy adults if the drug is started within 48 hours of onset of symptoms.[1–5] Time to alleviation of symptoms were reduced by 14 to 21 hours (about a 10% reduction) depending on the drug.[1–5] However, the clinical significance of such a modest effect is not well defined.
- In previously healthy children, there is moderate quality evidence that oseltamivir can reduce the time to alleviation of influenza symptoms by about 1 day relative to placebo; however, oseltamivir does not appear to have any effect in children with asthma.[2,3] There is moderate quality evidence that treatment with zanamivir is ineffective in children.[1,3] There is insufficient evidence for peramivir in this population.[5]
- There is low quality evidence that treatment with oseltamivir and zanamivir do not reduce complications from influenza in children or adults.[1–3] There is insufficient evidence to determine if peramivir can reduce complications from influenza.
- There is low quality evidence that treatment with oseltamivir does not reduce hospitalizations.[2,3] There is insufficient evidence to determine if treatment with zanamivir or peramivir can improve rates of hospitalizations.[1,3,5]

- There is moderate quality evidence that prophylactic use of oseltamivir or zanamivir in previously healthy adults and children can reduce risk of developing influenza symptoms by 2 to 4% compared to placebo. These drugs do not reduce complications of influenza if it develops.[1–4]
- There is moderate quality evidence that the prophylactic use of oseltamivir does not reduce hospitalizations.[2,3] There is insufficient evidence to determine if prophylactic use of zanamivir can reduce hospitalizations.[1,3] Peramivir for prophylaxis of influenza is not recommended.
- There is insufficient evidence to support the use of amantadine and rimantadine for the prevention or treatment of influenza A. Lack of knowledge about the safety of amantadine, inactivity against influenza B virus, and complete resistance to influenza A virus preclude use of these drugs for influenza.[6,7]
- The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, and psychiatric effects in adults and vomiting in children.[1–3] Zanamivir and peramivir were well tolerated in clinical trials.[1,3,5]

Recommendations:
- Remove amantadine and rimantadine from the Oregon Health Plan (OHP) Preferred Drug List (PDL) due to lack of efficacy for influenza and other conditions (eg, Parkinson's disease), and possible increased harms.
- Designate peramivir non-preferred at this time due to limited evidence.
- No other changes to the PDL are recommended at this time. Review comparative drug costs in the executive session.
- Approve modified prior authorization (PA) criteria but restrict the PA to neuraminidase inhibitors only (see **Appendix 4**).

Previous Conclusions:
- Vaccination is the primary method of preventing influenza infection.
- Amantadine or rimantadine are not recommended for the treatment or prophylaxis of influenza A due to high prevalence of resistance.
- Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders.

Previous Recommendations:
- Recommend taking into account current public health recommendations for appropriate populations, duration and dosing schedules.

Background:
Influenza is a respiratory infection caused by influenza viruses A and B, the primary viruses that result in influenza epidemics in humans.[8] Influenza can be described as uncomplicated or complicated influenza, and can also become a progressive disease.[8] Persons with uncomplicated influenza may present with influenza-like symptoms (e.g., fever, cough, sore throat, muscle pain, malaise, etc.) but without shortness of breath (SOB). Though it can be a self-limited disease, there can be serious complications. Persons with complicated influenza may present with sinusitis, otitis media, or pneumonia (SOB, tachypnea, hypoxia and/or radiologic signs), which can also be associated with altered mental status, severe dehydration, secondary complications (e.g., multiorgan failure, septic shock), or exacerbation of an underlying chronic disease.[8]

The current report of influenza activity in the U.S. can be found online at CDC Weekly FluView.[9] During the 2014-15 influenza season, 83.5% of circulating influenza viruses were influenza A (nearly all subtyped were H3N2) and 16.5% were influenza B.[10] Hospitalizations for influenza were double the incidence seen in the 2013-14 season with 65.5 hospitalizations per 100,000 persons.[10] Deaths from pneumonia or influenza were at or above epidemic level for 8 consecutive weeks.[10]

The annual influenza vaccine is the primary method to prevent influenza.[11] The vaccination is recommended for all persons 6 months of age and older who do not have contraindications.[11] No vaccine is preferred over any other in adults for whom multiple versions are appropriate, including trivalent or quadrivalent inactivated influenza vaccines, live attenuated influenza vaccines, or recombinant influenza vaccines.[11] Five influenza antiviral medications are also available in the U.S. However, only 3 are recommended for use: oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®) are recommended for acute treatment of influenza or prevention of influenza in susceptible individuals (eg, severe immune deficiency); injectable peramivir (Rapivab™), approved in December 2014, is recommended for the treatment of acute uncomplicated influenza in adults.[7,12] Each of these drugs are known as neuraminidase inhibitors and have activity against both influenza A and B.[7] Amantadine and rimantadine are antiviral drugs known as adamantanes, which are not active against influenza B, but are also not recommended for treatment of prevention of currently circulating influenza A viruses.[7] Since the 2005-06 season, resistance to amantadine and rimantadine have been widespread.[8] In the 2014-15 season, circulating viruses remained highly resistant (>99%) to amantadine and rimantadine.[10]

Oseltamivir, zanamivir and peramivir are approved by the U.S. Food and Drug Administration treatment of acute, uncomplicated influenza in patients who have had symptoms for up to 48 hours.[13–15] Treatment effects in controlled clinical trials showed improvement in time to alleviation of a constellation of symptoms rated as “none” or “mild” including: nasal congestion, sore throat, headache, aches, or chills.[5] Oseltamivir received FDA approval for patients as young as 14 days, while zanamivir is limited to patients aged 7 years and older and peramivir is limited to adult use only.[13,14] Oseltamivir and zanamivir are also FDA-approved for prophylaxis of influenza.[13,14] Oseltamivir is approved in patients 1 year and older and zanamivir is approved in patients 5 years and older.[13,14] Neuraminidase inhibitors may reduce symptoms duration by about 1 day in adults and by 0.5-3 days in children.[8] Oseltamivir is the most studied drug and does not appear to reduce likelihood of hospitalization or pneumonia in adults and adolescents with influenza-like illness; however, oseltamivir may reduce complications and hospitalization in children with influenza and chronic medical conditions.[8] At the time these drugs were last reviewed in January 2012, there was no evidence these drugs reduced mortality.

Amantadine has been used as an antiparkinsonian agent in the past but there is insufficient evidence of efficacy for its use.[8] Besides high rates of resistance, use of amantadine and rimantadine are limited by high rates of adverse events, particularly central nervous system adverse events.[8]

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:

Zanamivir

A Cochrane systematic review with meta-analysis of zanamivir for influenza in adults and children was conducted.[1,3] Eligible studies were published or unpublished and limited to randomized, placebo-controlled trials testing the effects of zanamivir for prophylaxis, post-exposure prophylaxis, and treatment of influenza in previously healthy adults and children.[1,3] Trial registries and several electronic databases were searched, in addition to regulatory archives and correspondences with the manufacturer.[1,3] The effects of zanamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalizations and adverse events in the intention-to-treat (ITT) population were analyzed.[1,3] Twenty-eight studies were identified that met explicit inclusion criteria: 6 compared zanamivir with usual care in the prevention of influenza A and B among populations exposed to a local epidemic, 2 studies for the prevention of transmission of influenza among households, and 20 trials for the treatment of influenza A and B.[1,3] All trials identified were sponsored by the manufacturer.[1,3] Quality of the studies varied and posed large threats that introduce biases: only 1 study showed adequate randomization technique; adequate blinding of participants and personnel was reported in only 2 studies, and 24 studies showed adequate blinding of outcome assessors.[1,3]

For treatment of influenza, zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% Confidence Interval [CI], 0.39 to 0.81 days; $p<0.001$; $I^2=9\%$), which translated to an average 14.4-hour time reduction, or a 10% reduction in the mean duration of symptoms from 6.6 days to 6.0 days.[1,3] However, the treatment effect of zanamivir in children was not significant (mean difference -1.08 days; 95% CI, -2.32 to 0.15 days).[1,3] In subgroup analysis, there was no significant difference in treatment effects by infection status for time to first alleviation of symptoms in adults.[1,3] The treatment effect was an improvement by 0.67 days in patients with confirmed influenza (95% CI, 0.35 to 0.99 days) compared to 0.52 days (0.18 to 0.86 days) in patients without confirmed influenza.[1,3] Zanamivir treatment reduced the risk of bronchitis in adults (Relative Risk [RR]=0.75; 95% CI, 0.61 to 0.91: $I^2=3\%$; NNT=56), but there were no significant reduction found for serious complications of influenza, nor in incidence of otitis media (RR=0.81; 95% CI, 0.54 to 1.20; $I^2=0\%$) and sinusitis (RR=1.12; 95% CI, 0.84 to 1.48; $I^2=30\%$).[1,3] No data were reported on the effect of zanamivir treatment on rates of hospitalizations.[1,3] No studies specifically defined pneumonia, but self-reported, investigator-mediated verified and unverified pneumonia was not reduced with zanamivir (RR=0.90; 95% CI, 0.58 to 1.40; $I^2=0\%$).[1,3]

For prevention of influenza, zanamivir reduced the risk of symptomatic influenza by 2% versus placebo (RR=0.39; 95% CI, 0.22 to 0.70; $I^2=45\%$; Number Needed-to-Treat [NNT]=51), as well as in post-exposure prophylaxis of households by 14.84% (RR=0.33; 95% CI, 0.18 to 0.58; $I^2=40\%$; NNT=7).[1,3] No data were reported on the effect of zanamivir prophylaxis on prevention of hospitalizations.[1,3] Zanamivir prophylaxis had no effect on reduction of complications from influenza in adults or children.[1,3]

Studies reported zanamivir was well tolerated with no evidence of increased risk of adverse events.[1,3]

Oseltamivir

A systematic review with meta-analysis[2,3] of oseltamivir for influenza in adults and children was also conducted by the same Cochrane Collaboration group that conducted the review of zanamivir[1,3]. The same methodology applied to the previous systematic review was also applied to this review.[1–3] Studies of previously healthy adults and children and patients with a chronic illnesses (e.g., asthma, diabetes, etc.) were included; however, patients with immunosuppression were excluded from the analysis.[2,3] About 48% (11/23) of studies adequately reported random sequence generation, and 65% showed adequate allocation concealment.[2,3] Forty-eight percent showed adequate blinding of outcome assessors.[2,3] There was high risk of bias for included outcomes as a result of missing

data, selective reporting, potentially active placebo, lack of outcome definitions, suboptimal measurement, and incomplete reporting in the study reports.[2,3] There were inadequate measures in place to protect 11 studies from performance bias due to non-identical placebo products, which may have included active substances. In addition, attrition bias was high across the studies.[2,3]

In treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.7 hours (95% CI, 8.4 to 25.1 hours; p<0.001).[2,3] This difference represents a 10% reduction in time to first alleviation of symptoms from 7 days to 6.3 days in the oseltamivir group versus the placebo group.[2,3] In previously healthy children, oseltamivir reduced the time to first alleviation of symptoms by 29 hours (95% CI, 12 to 27 hours; p=0.001), but there was no significant effect for children with asthma (p=0.53).[2,3] Because of strong selection bias in treatment trials, an analysis was not performed by influenza-infected status.[2,3] In treatment of adults, there was a non-significant difference of 0.15% in rate of hospitalization between oseltamivir and placebo groups (RR=0.92; 95% CI, 0.57 to 1.50; I^2=0%; p=0.84).[2,3] Oseltamivir treatment also did not affect hospitalizations in children.[2,3] Oseltamivir had no significant treatment effect in adults or adults or children for sinusitis, bronchitis, otitis media, or any serious complications.[2,3] Oseltamivir reduced unverified pneumonia by 1% versus placebo when used as treatment in adults (95% CI, 0.22 to 1.49%; NNT=100).[2,3] There was no significant difference in studies that used more detailed definitions of pneumonia (e.g., radiologically confirmed pneumonia).[2,3]

In prophylaxis trials, oseltamivir reduced symptomatic influenza in subjects by 3.05% versus placebo (95% CI, 1.83 to 3.88; NNT=33) and in households by 13.6% (95% CI, 9.52 to 15.47%; NNT=7).[2,3] In these trials, oseltamivir did not reduce incidence of pneumonia in children or adults versus placebo.[2,3] In addition, prophylaxis with oseltamivir did not reduce rates of hospitalizations in adults or children.[2,3]

Treatment of oseltamivir was associated with increased risk of nausea in adults (RR=1.57; 95% CI, 1.14 to 2.51) and children (RR=1.70; 95% CI, 1.23 to 2.35).[2,3] Other adverse effects that occurred significantly more with oseltamivir use in adults were headache and vomiting.[2,3] In addition, oseltamivir appeared to be associated with increased risk of 1.06% for psychiatric adverse events (including depression, confusion, hallucinations, and psychosis) versus placebo in prophylaxis trials (RR=1.80; 95% CI, 1.05 to 2.08; Number Needed to Harm =94). this observation was not found at treatment doses.[2,3]

<u>Neuraminidase Inhibitors Oseltamivir and Zanamivir</u>

A systematic review of high-quality reviews of neuraminidase inhibitors (oseltamivir, zanamivir) using the Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Database of Abstracts of Reviews of Effects, and Medline (January 2006 to July 2012) was also conducted.[4] Nine systematic reviews were identified and were based on randomized controlled trials restricted to ITT results and assessed review (AMSTAR) and study quality (GRADE).[4] In healthy adults given oseltamivir as prophylaxis, risk of developing influenza symptoms by reduced by an absolute risk reduction (ARR) of 3.6% compared to placebo (95% CI, 2.0 to 4.3%) (GRADE moderate).[4] Prophylaxis with zanamivir reduced risk of developing influenza symptoms by an ARR of 4.4% (95% CI, 2.3 to 5.1%) versus placebo (GRADE moderate).[4] Similar efficacy was also observed for post-exposure prophylaxis in adults who received oseltamivir.[4] In children, only post-exposure prophylaxis studies were performed, which found and ARR of 12.1% (95% CI, 3.0 to 16.1%) with oseltamivir.[4] In at-risk adults and adolescents, prophylaxis with zanamivir reduced risk of influenza (ARR 4.0%; 95% CI, 1.6 to 4.4%) (GRADE moderate); however, no effect in elderly patients was observed.[4] Similar to the Cochrane analyses previously noted,[1–3] treatment with oseltamivir or zanamivir in adults and children alleviated symptoms of influenza less than 1 day sooner than with placebo (GRADE moderate).[4] No evidence was available on the treatment benefits of neuraminidase inhibitors in elderly and at-risk groups and their effects on hospitalization and mortality.[4] In oseltamivir trials, nausea, vomiting and diarrhea were significant adverse effects.[4] Zanamivir was well tolerated.[4]

Amantadine and Rimantidine

A Cochrane review did not find sufficient evidence for the use of amantadine and rimantadine for the prevention or treatment of influenza A in children and the elderly.[6] The lack of knowledge about the safety of amantadine and the limited benefit of rimantadine were of particular concern to the reviewers.[6]

New Guidelines:

The CDC antiviral recommendations were last published in January 2015.[7,12] The CDC recognizes clinical trials and observational data that show early antiviral treatment can shorten the duration of fever and symptoms, and may reduce the risk of complications from influenza. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.[7] Oral oseltamivir (Tamilfu®), inhaled zanamivir (Relenza®) and intravenous peramivir (Rapivab™) are the antiviral medications recommended by the CDC for treatment against influenza A and B for the 2014-15 season. **Table 1** lists the antiviral drugs recommended by the CDC, which may not reflect official labeling of the drugs.

Table 1. Centers for Disease Control and Prevention (CDC) Recommendations for Antiviral Use in Influenza (2014-2015 Season).[7]

Antiviral Agent	Use	Recommended	NOT Recommended	Dose
Oseltamivir #	Treatment	Any age	N/A	75 mg BID** x5 days
	Chemo-prophylaxis	Age ≥3 months	N/A	75 mg once daily** x7 days
Zanamivir *	Treatment	Age ≥7 years	Patients with underlying respiratory disease (e.g., asthma, COPD)	10 mg BID x5 days
	Chemo-prophylaxis	Age ≥5 years		10 mg once daily x7 days
Peramivir ^	Treatment	Age ≥18 years	N/A	One dose
	Chemo-prophylaxis	N/A	N/A	N/A

Abbreviations: COPD = chronic obstructive pulmonary disease; N/A = not applicable.

Oseltamivir is the preferred treatment of pregnant women.

* Relenza is contraindicated in patients with history of allergy to milk protein.

^ Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

**See current prescribing information for dosing in patients ≤40 kg or in patients with renal impairment.

Briefly, any of the following patients with suspected or confirmed influenza should be treated as early as possible, without laboratory confirmation of influenza, after illness onset with a neuraminidase inhibitor[7]:

1. All hospitalized patients
2. Severe, complicated or progressive illness (e.g., prolonged progressive symptoms or pneumonia complications)
3. High risk for influenza complications
    - Children <2 years of age
    - Adults ≥65 years of age
    - Chronic pulmonary, cardiovascular, renal, hepatic, hematologic, and neurologic/neurodevelopment conditions
    - Immunosuppression
    - Pregnancy or immediate post-partum
    - Persons ≤18 years on long-term aspirin
    - American Indians/Alaska Natives

- Morbidly obese (body mass index ≥40)
- Residents of nursing homes and other chronic care facilities

A history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms of influenza.[7] Antiviral treatment can also be considered in previously healthy, symptomatic outpatients not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.[7]

The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis due to risk of emergence of antiviral resistant viruses.[7] Antiviral medications for chemoprophylaxis are 70-90% effective in preventing influenza and may be useful adjuncts to the vaccine.[7] The CDC suggests patients with severe immune deficiencies or at high risk for complications of influenza who cannot receive the influenza vaccine, or during the first 2 weeks following vaccination, may be appropriate for chemoprophylaxis with antiviral agents.[7]

New Safety Alerts:
None identified.

New Formulations or Indications:
No new formulations or indications were identified. However, a new neuraminidase inhibitor was identified. Rapivab (peramivir) for injection was approved in December 2014 for treatment of influenza.[15]

Randomized Controlled Trials:
Two hundred fifty-five potentially relevant clinical trials or systematic reviews were evaluated from the literature search (see **Appendix 2**). After further review, none of the trials were randomized, head-to-head trials that compared one antiviral drug to another, and were therefore excluded.

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

Clinical Efficacy:
Peramivir is the third drug in the neuraminidase class and is recommended for use in adult patients with acute uncomplicated illness based primarily on data from the 4 placebo-controlled Phase 2 or 3 trials in adults with acute uncomplicated influenza (studies 621, 211, 212 and 311).[5] The analysis of safety was based chiefly on data from Study 621,[16] with supplemental data from the other studies.[5] Study 621 was a 3-arm randomized, multi-centered, blinded trial conducted in Japan that evaluated a single intravenous (IV) dose of peramivir 300 mg, peramivir 600 mg, or placebo administered over 30 minutes in previously healthy patients 20 to 64 years of age (n=297) with acute uncomplicated influenza that had developed within the previous 48 hours.[5] Patients were eligible if they had fever greater than 38 ^{o}C, a positive rapid antigen test for influenza virus, with at least 2 symptoms (cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue, or headache) of moderate severity.[5] All enrolled patients were allowed to take medication for fever during the study.[5] The primary endpoint was time to alleviation of symptoms (TTAS), defined as the number of hours from initiation of study drug until the start of the 24-hour period in which all 7 symptoms of influenza (cough, sore throat, nasal congestion, headache, fever, myalgia and fatigue) were either absent or present at a level no greater than

"mild" for at least 21.5 hours.[5] The group assigned to 600 mg of peramivir demonstrated significant improvement.[5] In the group assigned to peramivir 600 mg (n=98), alleviation of symptoms occurred a median of 21 hours sooner than those receiving placebo.[5] The median time to recover to normal temperature in the 600 mg group was approximately 12 hours sooner compared to placebo.[5] In the 600 mg peramivir group, 55% were male; 34% were smokers; and 99% were infected with influenza A virus (1% were infected with influenza B virus).[5] Pooled analysis of all the placebo-controlled trials in acute uncomplicated influenza are described in **Table 2**, which shows the duration of influenza symptoms was shortest in patients treated with peramivir 300 mg and 600 mg.[5]

Table 2. Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza.[5]

	Paramivir 150 mg	Paramivir 300 mg	Paramivir 600 mg	Paramivir Overall	Placebo
N (number censored)	100 (17)	255 (33)	256 (22)	611 (72)	399 (41)
Median TTAS in hours (95% CI)	120.7 (96.1 to 148.1)	81.7 (68.1 to 102.0)	79.4 (68.1 to 91.6)	87.6 (78.3 to 96.1)	107.3 (95.7 to 115.2)

Abbreviations: CI = confidence interval; N = number of patients; TTAS = time to alleviation of symptoms.

Clinical Safety:

Across controlled clinical trials in adults with uncomplicated influenza, a total of 1,399 patients were exposed to at least 1 dose of peramivir.[5] Among the 664 patients who received peramivir 600 mg, the most commonly observed adverse reaction was diarrhea (8% vs. 7% with placebo).[5] No serious adverse events were reported in the trials.[5] One death due to meningitis occurred in the clinical trials and was deemed unlikely to be related to the study drug.[5] Clinically significant laboratory abnormalities that occurred more frequently with peramivir 600 mg than placebo are listed in **Table 3**.[5]

Table 3. Laboratory Abnormalities Occurring in ≥2% of Patients Treated with Peramivir 600 mg.[5]

Laboratory Parameter	Peramivir 600 mg	Placebo
Alanine Aminotransferase (>2.5 x ULN)	3%	2%
Serum Glucose (>160 mg/dL)	5%	3%
Creatine Phosphokinase (≥ 6.0 x ULN)	4%	2%
Neutrophils (<1.000 $x10^9$/L)	8%	6%

Abbreviations: dL = deciliters; L = liters; ULN = upper limit of normal range.

References:

1. Heneghan C, Onakpoya I, Thompson M, Spencer E, Jones M, Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2547. doi:10.1136/bmj.g2547.

2. Jefferson T, Jones M, Doshi P, Spencer E, Onakpoya I, Heneghan C. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2545. doi:10.1136/bmj.g2545.

3. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews*. 2014;(Issue 4. Art. No.: CD008965). doi:10.1002/14651858.CD008965.pub4.

4. Michiels B, Van Puyenbroeck K, Verhoeven V, Vermeire E, Coenen S. The Value of Neuraminidase Inhibitors for the Prevention and Treatment of Seasonal Influenza: A Systematic Review of Systematic Reviews. *PLoS ONE*. 2013;8(4):e60348. doi:10.1371/journal.pone.0060348.

5. Center for Drug Evaluation and Research. U.S. Food and Drug Administration. Peramivir Summary Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206426Orig1s000SumR.pdf. Accessed June 2, 2015.

6. Alves Galvao M, Rocha Crispino Santos M, Alves da Cunha A. Amantadine and rimantadine for influenza A in children and elderly. *Cochrane Database of Systematic Reviews*. 2014;(Issue 11. Art. No.: CD002745). doi:10.1002/14651858.CD002745.pub4.

7. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf. Accessed June 2, 2015.

8. DynaMed [internet database]. Ipswich, MA: EBSCO Information Services. Updated periodically. Registration and login required.

9. Situation Update: Summary of Weekly FluView. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/flu/weekly/summary.htm. Accessed July 27, 2015.

10. Influenza Activity - United States, 2014-15 Season and Composition of the 2015-16 Influenza Vaccine; June 5, 2015. Morbidity and Mortality Weekly Report (MMWR), Centers for Disease Control and Prevention. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6421a5.htm. Accessed July 27, 2015.

11. Key Facts About Seasonal Flu Vaccine. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/flu/protect/keyfacts.htm. Accessed July 27, 2015.

12. CDC Health Update Regarding Treatment of Patients with Influenza with Antiviral Medications - January 2015. Health Alert Network, Centers for Disease Control and Prevention. Available at http://emergency.cdc.gov/han/han00375.asp. Accessed July 24, 2015.

13. TAMIFLU (oseltamivir phosphate) [prescribing information]. South San Francisco, CA: Genentech, Inc., November 2014.

14. RELENZA (zanamivir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, October 2013.

15. RAPIVAB (peramivir injection) [prescribing information]. Durham, NC: BioCryst Pharmaceuticals, Inc., December 2014.

16. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrobial Agents and Chemotherapy*. 2010;54:4568-4574. doi:10.1128/AAC.00474-10.

Appendix 1: Current Status on Preferred Drug List

Generic Name	Brand Name	Form	PDL Status	Current Drug Use Criteria
AMANTADINE HCL	AMANTADINE	CAPSULE	Y	
AMANTADINE HCL	AMANTADINE	SOLUTION	Y	
AMANTADINE HCL	AMANTADINE	TABLET	Y	
OSELTAMIVIR PHOSPHATE	TAMIFLU	CAPSULE	Y	Quantity Limit
OSELTAMIVIR PHOSPHATE	TAMIFLU	SUSP RECON	Y	Quantity Limit
RIMANTADINE HCL	RIMANTADINE HCL	TABLET	Y	
RIMANTADINE HCL	FLUMADINE	TABLET	Y	
ZANAMIVIR	RELENZA	BLST W/DEV	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2015
1 exp Amantadine/ 2973
2 exp Rimantadine/ 259
3 exp Oseltamivir/ 2154
4 exp Zanamivir/ 816
5 peramivir.mp. 210
6 1 or 2 or 3 or 4 or 5 5501
7 limit 6 to (yr="2012 -Current" and (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 pragmatic clinical trial or randomized controlled trial or systematic reviews)) 255

Appendix 3: Highlights of Prescribing Information

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

RAPIVAB™ (peramivir injection), for intravenous use
Initial U.S. Approval: [2014]

----------INDICATIONS AND USAGE----------
RAPIVAB is an influenza virus neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. (1)

Limitations of Use:
- Efficacy based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1)
- Efficacy could not be established in patients with serious influenza requiring hospitalization. (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer as a single dose within 2 days of onset of influenza symptoms (2.1)
- Recommended dose is 600 mg, administered by intravenous infusion for a minimum of 15 minutes (2.1)
- Renal Impairment:: Recommended dose for patients with creatinine clearance 30-49 mL/min is 200 mg and the recommended dose for patients with creatinine clearance 10-29 mL/min is 100 mg (2.2)
- Hemodialysis: Administer after dialysis. (2.2)
- RAPIVAB must be diluted prior to administration (2.3)
- See the Full Prescribing Information for drug compatibility information (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 200 mg in 20 mL (10 mg/mL) in a single-use vial (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
- Serious skin/hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have occurred with RAPIVAB. (5.1)
- Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reaction (incidence >2%) is diarrhea (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-844-273-2327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Live attenuated influenza vaccine (LAIV), intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB, unless medically indicated (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Use if benefit outweighs risk.(8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

Neuraminidase Inhibitors

Goal:

- Restrict use of extended prophylactic influenza antiviral therapy to high risk populations recognized by the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA).

Length of Authorization:

- Up to 30 days

Requires PA:

- Non-preferred neuraminidase inhibitors
- Oseltamivir therapy for greater than 5 days

Covered Alternatives:

Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded diagnosis?	Yes: Go to #3	No: Pass to RPH. Deny; not funded by the OHP
3. Is the antiviral agent to be used to treat a current influenza infection (ICD9 487.x; 488.xx)?	Yes: Go to #4	No: Go to #5
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.	No: Approve for length of therapy or 5 days, whichever is less.

Approval Criteria		
5. Is the antiviral prescribed oseltamivir or zanamivir?	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness.
6. Does the patient have any of the following CDC[1] and IDSA[2] criteria that may place them at increased risk for complications requiring chemoprophylaxis? • Persons at high risk of influenza complications during the first 2 weeks following vaccination after exposure to an infectious person (6 weeks in children not previously vaccinated and require 2 doses of vaccine) • Persons with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person • Persons at high risk for complications from influenza who cannot receive influenza vaccine after exposure to an infectious person • Residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution. • Pregnancy and women up to 2 weeks postpartum who have been in close contact with someone suspected or confirmed of having influenza	Yes: Approve for duration of prophylaxis or 30 days, whichever is less. Current recommended duration of prophylaxis: 7 days (after last known exposure; minimum 2 weeks to control outbreaks in institutional settings and hospitals, and continue up to 1 week after last known exposure. .	No: Pass to RPh. Deny for medical appropriateness.

References:
1. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf. Accessed June 2, 2015.
2. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2009; 48:1003-32.

P&T/DUR Review: *9/15 (AG); 1/12; 9/10*
Implementation: *1/11*

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

Drug Use Evaluation: modafinil and armodafinil

Research Questions:

- What is the overall Oregon Health Plan (OHP) utilization trend of modafinil and armodafinil from 2014 to present?
- What was the impact on utilization of the dose and age limits implemented in September 2014?
- What diagnoses are most commonly associated with OHP patients with modafinil and armodafinil drug claims?
- What is the evidence for efficacy and safety of modafinil and armodafinil for the most prevalent diagnoses and are they funded by OHP?

Conclusions:

- The number of OHP patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015 and 14% per 1000 members per month. The attention deficit hyperactivity disorder (ADHD) drug class ranked 3rd by net cost in quarter 1 of 2015 and modafinil ranked 26th.[1]
- The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) of patients newly started on modafinil or armodafinil and that exceeded recommended doses dramatically decreased after the prior authorization policy was implemented. The number of pediatric patients were very low initially (n=2) and increased slightly (n=4) after the age limit was implemented. The net cost of modafinil and armodafinil was $560,000 in quarter 3 of 2014[2] but dropped to $300,000 in quarter 1 of 2015.[1]
- The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had only a non-funded diagnosis of interest but, there was no diagnosis of interest associated with 23.5% of patients.
- There is moderate level evidence modafinil and armodafinil statistically improves sleep latency in patients with narcolepsy or with continuous positive airway pressure (CPAP) treated obstructive sleep apnea as measured by the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. The clinical relevance of the seemingly modest mean differences is debatable.[3,4,5] No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.[6] Treatment guidelines indicate obstructive sleep apnea be first treated with CPAP or mandibular advancement devices.[5]
- There is insufficient evidence for armodafinil for any off-label use evaluated here.
- There is low level and inconsistent evidence of short-term benefit of modafinil for fatigue associated with multiple sclerosis,[7,8,9] cancer[9,10] and anti-psychotic use.[11] Despite the low level evidence, consensus based guidelines recommend its use for both multiple sclerosis- and cancer-related fatigue.[12] There is insufficient evidence of modafinil efficacy for fatigue associated with other conditions.
- There is low level evidence from small, heterogeneous and poorly controlled trials that modafinil used as augmentation treatment improves short-term depression scores.[13,14,15] There is low evidence of inconsistent benefit for residual fatigue in patients responsive to antidepressants or mood stabilizers.[16]
- There is insufficient and inconsistent evidence of modafinil for adult ADHD.[17,18] The data are more robust, but still low level for pediatrics.
- There are reports of potential use for cognition enhancement with little supporting evidence.[19,20,21]

Recommendations:

- Implement a prior authorization for patients initiated on modafinil or armodafinil (no claims evidence within 102 days) and without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57) See Proposed PA criteria **Appendix 4**

Background:

Modafinil[22] and armodafinil[23] are both approved by the United States Food and Drug Administration (FDA) for treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder. They are also used extensively off-label with varying levels of evidence (**Appendix 1**). The OHP currently funds treatment of obstructive sleep apnea and narcolepsy but does not fund treatment of shift work disorder.[24] A prior authorization (PA) of excessive doses (>250 mg of armodafinil or > 200mg of modafinil) and use in patients younger than 18 was implemented in September of 2014.[25] The net cost of modafinil and armodafinil was $560,000 in quarter 3 of 2014[2] but dropped to $300,000 in quarter 1 of 2015.[1] The ADHD class ranked 3rd by net cost in quarter 1 of 2015 and modafinil ranked 26th.[1]

Modafinil and armodafinil (the R enantiomer of modafinil) produce alterations in mood, perception, thinking and feelings that are typical of central nervous system stimulants but differ from the sympathomimetic amines in pharmacological profile.[26,27] Modafinil and armodafinil stimulate discrete brain regions rather than broad brain activation.[26,27] They also do not bind to norepinephrine, serotonin, dopamine, gamma-aminobutyric acid, adenosine, histamine 3, melatonin, or benzodiazepine receptors, nor do they inhibit monoamine oxidase-B or phosphodiesterases II through V.[26,27] The mechanism of action is still unknown.[26,27] Modafinil and armodafinil appear to be well tolerated, with the main adverse effects being headache and nausea.[26,27]

Narcolepsy is characterized primarily by excessive daytime sleepiness with involuntary episodes of falling asleep and frequently includes episodes of cataplexy.[28] It can also include sleep paralysis, hallucinations at sleep initiation or awakening or disturbed nighttime sleep.[28] The prevalence is estimated to be 25 per 100,000 in white populations.[29] The majority of cases have no discernable secondary cause and are first diagnosed from age 15 to 35 years old.[28] It is a life-long illness that can affect all aspects of life quality.[29] Scheduled sleep periods (daytime napping plus regular bedtime) is recommended and may reduce symptom severity.[28] Modafinil is recommended first-line for daytime sleepiness[29] based upon a 9 week randomized trial (n=271) comparing modafinil 400 mg versus 200 mg versus placebo. Sleep latency was evaluated using the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.[3] At baseline the mean Multiple Sleep Latency Test score in minutes was 2.7, 3.0 and 2.2 respectively, and at 9 weeks was 5.1 ($p < 0.001$), 4.9 ($p = 0.03$) and 3.5.[3] The Maintenance of Wakefulness Test was 5.9, 6.1 and 6 minutes at baseline and increased to 7.8 ($p < 0.001$), 8.2 ($p < 0.001$) and 5.5 minutes at 9 weeks.[3] Armodafinil was studied in 196 patients aged 18-65 years who were randomized to armodafinil 150 mg versus armodafinil 250 mg versus placebo once daily for 12 weeks. Change in mean Maintenance of Wakefulness Test at 12 weeks was +1.3 minutes, +2.6 minutes and -1.9 minutes ($p < 0.01$).[4] The clinical relevance of the statistical, but seemingly modest differences on objective sleep measures by modafinil and armodafinil is debatable. No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.[6] Methylphenidate has been recommended second line treatment for excessive daytime sleepiness based upon lower levels of evidence for efficacy.[29]

Obstructive sleep apnea is a sleep disorder where the upper airway is obstructed causing repeated complete or partial apnea and resulting in frequent awakenings and poor sleep.[30] One cohort study of 1149 adults from Cleveland, estimates the 5-year incidence to be 10% - 16%.[5] Risk factors include obesity and older age.[5] Complications of untreated obstructive sleep apnea include cardiovascular disease and increased risk of motor vehicle accidents.[5] The Maintenance of Wakefulness Test does not reliably predict safer drivers.[5] Treatment recommendations include weight reduction for overweight patients, correction of positional apnea issues, CPAP and mandibular advancement devices to reduce the apneic episodes and improve sleep quality.[5] There is moderate level evidence that modafinil and armodafinil may reduce residual daytime sleepiness in CPAP treated patients.[5] The studies are limited by subjective measures and the unknown clinical relevance of statistical difference over placebo.

The goals of this drug use evaluation are to describe overall utilization trends, assess the effectiveness of the age and dose restrictions implemented in September 2014 and document the diagnoses associated with patients who use modafinil and armodafinil to inform drug policy.

Methods:

All patients with OHP fee-for-service (FFS) paid drug claims for modafinil (HSN = 010865) or armodafinil (HSN = 034868) from January 1, 2014 through March 30, 2015 were included in the trend analysis. Only patients newly initiated on either drug during quarter 1 of 2014 (Pre-Policy) and quarter 1 of 2015 (Post-Policy) were included in the diagnostic and dose analyses. Newly started patients were identified if they had no prior claim in the 100 days prior to the first drug claim and the first claim was labeled the index event. Patients not initiated during either quarter were excluded. Part D patients identified with drug benefit packages BMM or BMD were excluded. No eligibility length restrictions were applied.

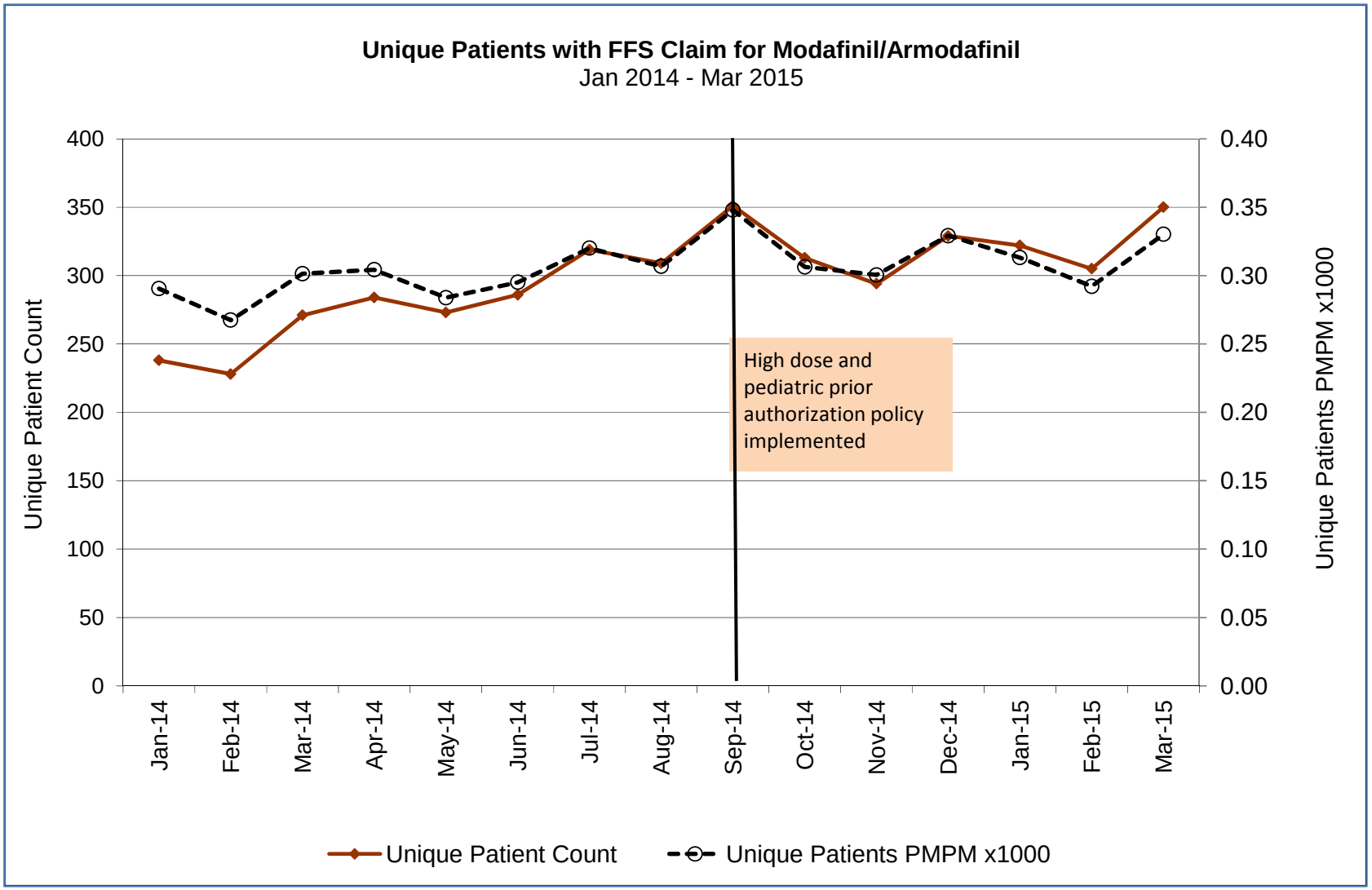
Off-label diagnoses (**Appendix 1**) were identified from Micromedex™ and American Hospital Formulary Service™ and included if there was mid-level evidence of benefit in either reference. Patients were categorized into the diagnostic groups in **Appendix 1** if a diagnosis code occurred on either FFS or encounter medical claim within 5 years prior to and including the date of index event. Patients that exceeded the recommended maximum dose (**Appendix 2**), as calculated using "Dispensed Quantity" divided by "Days Supply", for any claim during in quarter of 2014 and 2015 were identified.

A Medline™ literature search for systematic reviews or meta-analyses assessing modafinil or armodafinil efficacy or effectiveness for the most prevalent off-label diagnoses (depression, fatigue associated with multiple sclerosis or cancer and attention deficit hyperactivity disorder) was conducted. The Medline™ search strategies used for this review are 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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed™, 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.

Results:

Figure 1 indicates the number of unique patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015. When controlled for enrollment, the increase rate drops to 14% per 1000 members per month.

Figure 1 - Unique Patient Count with Drug Claim for Modafinil or Armodafinil



After exclusion of Medicare patients, a total of 811 unique patients were identified (348 in the Pre-PA Group and 463 in the Post-PA Group). After limiting to patients newly initiated, the Pre-PA group was 133 and the Post-PA Group was 135. There were 7 patients that met the criteria for both groups. Table 1 displays the demographics of patients initiated on either modafinil or armodafinil before and after the dose and pediatric limit policy was implemented September 2014. The absolute number and rate of pediatric patients actually increased slightly from 2 (1.5%) prior to the PA to 4 (3.0%) after the PA. However, the lowest age increased from 14 to 15 years. In general, the Post-PA group is somewhat younger and more patients are enrolled in coordinating care organizations.

Table 1: New Modafinil and Armodafinil Patient Demographics

	Pre-PA		Post-PA	
	133	%	**135**	%
Mean age (range)	43.3	(14-63)	41.4	(15-65)
<19	2	1.5%	4	3.0%
19-30	16	12.0%	28	20.7%
>30	115	86.5%	103	76.3%
Female	87	65.4%	88	65.2%
White	105	78.9%	113	83.7%
FFS (at index claim)	25	18.8%	12	8.9%

Table 2 displays the number of patients initiated on modafinil or armodafinil who exceeded the maximum recommended dose per day. The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) dramatically decreased after the prior authorization policy was implemented.

Table 2: Patients Exceeding Maximum Dose Per Day

	Pre-Policy		Post-Policy	
	133	%	**135**	%
Modafinil 200mg daily	27	20.3%	5	3.7%
Armodafinil 250mg daily	4	3.0%	1	0.7%
Total	31	23.3%	6	4.4%

Table 3 displays the selected diagnoses associated with patients on modafinil and armodafinil and puts them in mutually exclusive groups in priority order. The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had a non-funded diagnosis of interest but there was no diagnosis of interest associated with 23.5% of patients.

Table 3: Associated Diagnoses of All New Patients Combined
Mutually-exclusive groups in priority of 1, 2, 3, 4

	n=	268	
FDA Funded Indications (Group 1)		**123**	**45.9%**
Narcolepsy		51	19.0%
Organic sleep apnea (except high altitude)		96	35.8%
Funded Off-Label Indications (Group 2)		**71**	**26.5%**
Attention deficit hyperactivity disorder		19	7.1%
Depression (unipolar or bipolar)		51	19.0%
Steinert myotonic dystrophy syndrome		0	0.0%
Cancer		2	0.7%
Multiple sclerosis		15	5.6%
Non-Funded Indications (Group 3)		**11**	**4.1%**
Narcolepsy in conditions classified elsewhere		0	0.0%
Organic sleep disorders except organic sleep apneas		1	0.4%
Shift work sleep disorder		6	2.2%
Hypersomnia, unspecified		8	3.0%
No Diagnosis of Interest (Group 4)		**63**	**23.5%**

A summary of the Medline literature search results, including abstracts is in **Appendix 3**. There were 10 reviews including modafinil or armodafinil for fatigue (2 excluded as not systematic reviews,[31,32] 2 were unavailable[33,34] 1 excluded for irrelevant intervention[35]), 5 reviews for depression (1 excluded for irrelevant outcomes assessed[36] and 1 excluded for irrelevant intervention[37]), 4 reviews for ADHD (2 excluded for intervention irrelevance[38,39]). There were 4 reviews for cognition enhancement[19,20,21,40] and 2 general reviews documenting off-label uses.[41,42] The remaining reviews and those identified from the gray literature sources are discussed below.

FATIGUE

Cancer (0.7%) and multiple sclerosis (5.6%) was associated new modafinil and armodafinil users. The evidence of efficacy for fatigue related to these conditions and to drug-related sedation is limited and inconsistent.

Multiple Sclerosis Fatigue

The most recent systematic review included studies that evaluated modafinil treatment versus placebo for fatigue and excessive daytime sleepiness associated with neurological disorders.[7] Eight randomized controlled trials (RCTs) were included: 3 for multiple sclerosis, 2 for Parkinson's Disease, 2 for traumatic brain injury and 1 for post-polio syndrome.[7] The meta-analyses of the 3 multiple sclerosis studies (n=800, 5-8 weeks duration) used the Fatigue Severity Scale and the Modified Fatigue Impact Scale and failed to prove a beneficial effect.[7] The efficacy of modafinil on excessive daytime sleepiness in patients with multiple sclerosis was investigated in two of the studies (n=600, 5-8 weeks duration) and was not confirmed in the pooled studies.[7] The authors conclude that the majority of studies are small and the evidence is insufficient to recommend modafinil for routine treatment for fatigue or excessive daytime sleepiness associated with multiple sclerosis and the other diagnoses that were reviewed.[7]

Six trials (3 open-label, n= 100; 1 single-blind, n=72; and 2 double-blind RCTs n=136) were included in another systematic review of modafinil for treatment of multiple sclerosis-related fatigue.[8] Six different, self-reported symptom scales were used to measure outcomes.[8] Lower doses had positive results in the open-label trials and higher doses did not.[8] Only one of the RCTs found a reduction on the Fatigue Severity Scale at 8 weeks, the other did not.[8] The evidence was conflicting.

7

Cancer Fatigue

The Cochrane Collaborative produced a review of pharmacological treatment for fatigue associated with palliative care.[9] There were 45 studies included (n=4696) involving 18 different drugs.[9] There was a very high degree of statistical and clinical heterogeneity in the trials.[9] Studies of modafinil for multiple sclerosis-related fatigue were also included.[9] There was weak and inconclusive evidence for the efficacy of modafinil in multiple sclerosis.[9] Modafinil was evaluated for cancer-related fatigue in 2 studies (n=704) with mixed results.[9] The first found an interaction with baseline fatigue; those with severe fatigue benefited and those with mild or moderate fatigue did not.[9] The second study found that both modafinil and placebo produced a clinically significant improvement and there was no difference between them.[9] The meta-analysis showed an estimated superior effect for methylphenidate in cancer-related fatigue as measured by the Brief Fatigue Inventory instrument (standardized mean difference 0.49, 95% confidence interval (CI) 0.15 to 0.83).[9]

Four trials (2 open-label, 1 RCT with open-label extension, 1 RCT published in abstract only) were included in another systematic review of modafinil for the treatment of cancer-related fatigue.[10] The open-label trials involved 133 breast cancer patients treated for 1 month.[10] The open-label extension trial was in patients with cerebral tumors and the RCT involved 888 patients with unknown cancers.[10] The studies all used different self-reported scales or lacked detail.[10] Published results were statistically significant but of unknown clinical relevance.[10]

Drug-related Fatigue

A systematic review of modafinil for adjunctive treatment of antipsychotic-related sedation evaluated the evidence from 6 trials (2 RCTs, 3 randomized cross-over trials and 1 open-label).[11] The results were inconsistent with only 1 study finding a significant beneficial effect of treating antipsychotic-induced fatigue. The authors concluded the available trials were too limited by small samples, contradictory results and differences in cognitive testing to draw conclusions.

DEPRESSION

Depression (either unipolar or bipolar) was associated with 19.0% of new modafinil or armodafinil users. Stimulants are used for adjunctive treatment for patients non-responsive to antidepressants or mood stabilizers and also to treat lingering fatigue symptoms in responsive patients. There is low level evidence of short-term improvement of depression scores when added to antidepressants or mood stabilizers. There is insufficient evidence of benefit for residual fatigue symptoms.

Acute Bipolar Depression

A recent systematic review of all treatments for acute bipolar depression limited study designs to randomized, double-blind and placebo controlled trials with clearly defined outcomes identified 2 studies; 1 of modafinil (n=87, 6 weeks) and 1 of armodafinil (n=257, 8 weeks).[13] Both studies were reported to significantly reduce the Inventory of Depressive Symptomatology score when added to a mood stabilizer. Over half of the participants were also on an antidepressant. Few study details were presented and no author conclusions were drawn from this information.

Unipolar or Bipolar Depression Augmentation

Another systematic review,[14] criticized by Database of Abstracts of Reviews of Effects[43] as potentially unreliable due to the small, heterogeneous and unclear quality of the evidence base, identified 6 RCTs (n=910) evaluating modafinil: 4 for major depressive disorder (n=568) and 2 for bipolar depression (n=342).[14] Study durations ranged from 6-8 weeks and outcomes were measured using a variety of depression scales.[14] Selective serotonin reuptake inhibitors were the primary treatment in the major depression studies. Lithium was the primary treatment one bipolar study and mood stabilizer with or without antidepressant was used in the other. The results were pooled using the percentage reduction in the various depression scores. The point estimate for the pooled studies was -0.3543 95% CI -0.6071 to -0.1016 p=0.006, I^2 = 67.39%.[14] The authors concluded modafinil is an effective augmentation strategy for acute depressive episodes.[14]

Cochrane published a review of stimulants for depression that was last updated in 2008.[15] It included 5 drugs (dexamphetamine, methylphenidate, methyl-amphetamine, pemoline and modafinil). Most trials were short-term, up to 6 weeks. Modafinil was evaluated separately due to its unique pharmacology and 3 trials (n=642) were included. The results obtained using fixed effects models suggest that for people with depression, treatment with oral stimulants in comparison with a placebo in the short term (up to 4 weeks) statistically reduces symptoms. The effect was not replicated in the meta-analysis of trials that used modafinil. The authors could draw few clinically relevant conclusions due to the small sample sizes and heterogeneity.

Residual fatigue after depression treatment

A systematic review included studies where modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales.[16] One retrospective, 5 open-label and 2 RCTs were included. Modafinil improved residual fatigue scores in the open-label trials but the results were not confirmed in the RCTs. The open-label trials were limited by small numbers or lack of control. Outcome measures were also inconsistent.

ADHD

ADHD was associated with 7.1% of new of new modafinil or armodafinil users. There are inconsistent results and little evidence to support this use in adults and low level evidence in children.

Adult ADHD comorbid with mood disorders

The Canadian Network for Mood and Anxiety Treatments task force published a systematic review[44] and treatment recommendations for adult patients with comorbid mood disorders (depression or bipolar disease) with ADHD. This review is comprehensive in nature and includes epidemiology, clinical presentation, neurobiology, and treatment recommendations. Mean comorbidity rates for ADHD and bipolar disease were reported at 12.8%; for ADHD and major depression was reported as 7.8%. These are 3 and 2 times more prevalent than in the general population for adults (i.e. 3%-4%). Modafinil was not assessed in comorbid individuals but there were 2 placebo-controlled studies conducted in adult ADHD patients that demonstrated short-term efficacy. The 2 studies were not described but, they are the same as described in the following review below. Modafinil is recommended second-line after bupropion for adult ADHD comorbid with bipolar disease. This recommendation is made with the caution that there is a potential to destabilize mood during the long-term as there is no data beyond 6 weeks. Modafinil was not recommended for ADHD comorbid with major depression.

Adult ADHD

An earlier systematic review of modafinil for ADHD included 4 RCTs.[17] Two were placebo controlled and conducted in children (n= 272) for 6-9 weeks, 1 was a single dose placebo-controlled crossover trial in 20 adults and the last was a phase 3 crossover trial comparing modafinil to dextro-amphetamine in 22 adults for 6 weeks. All used different outcome scales and all showed significant improvements. The populations met ADHD diagnostic criteria but were not required to fail other therapies. Patients were excluded if they had comorbid developmental or psychiatric diagnoses. The authors conclude that modafinil may be viable for some patients for whom the standard ADHD treatment are ineffective or not tolerated but that additional long-term studies are needed.

The Canadian Agency for Drugs and Technologies in Health reviewed non-stimulant therapies (including modafinil) for treatment of adult ADHD.[18] Two studies were included, one of which is the 6 week placebo crossover trial described above. The other was a 9-week, placebo RCT. The authors conclude that the efficacy of modafinil in reducing ADHD symptoms is not statistically significantly different than dextro-amphetamine and superiority over placebo was not consistent across the trials.

COGNITION ENHANCEMENT

There were 3 systematic reviews[19,20,21] exploring the evidence of modafinil for enhanced cognition. All focused on healthy adults. Each found the evidence gaps to be large and generally conclude that expectations likely exceed the actual drug effect.

References:

1. Internal Report. OHP FFS Q1-2015 Market Share Report (no 340b). April 2015.
2. Internal Report. OHP FFS Q3-2014 Market Share Report (no 340b). October 2014.
3. Group UM in NMS. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*. 2000;54(5):1166-1175. doi:10.1212/WNL.54.5.1166.
4. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22(4):761-774. doi:10.1185/030079906X100050.
5. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*. 2003;289(17):2230-2237. doi:10.1001/jama.289.17.2230.
6. Freedman N. Quantifying sleepiness. In: *UpToDate [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. http://www-uptodate-com.liboff.ohsu.edu/contents/quantifying-sleepiness?source=see_link#H10. Accessed June 22, 2015.
7. Sheng P, Hou L, Wang X, et al. Efficacy of Modafinil on Fatigue and Excessive Daytime Sleepiness Associated with Neurological Disorders: A Systematic Review and Meta-Analysis. Paul F, ed. *PLoS ONE*. 2013;8(12):e81802. doi:10.1371/journal.pone.0081802.
8. Brown JN, Howard CA, Kemp DW. Modafinil for the Treatment of Multiple Sclerosis–Related Fatigue. *Ann Pharmacother*. 2010;44(6):1098-1103. doi:10.1345/aph.1M705.
9. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. [Review]. *Cochrane Database Syst Rev*. 2010. doi:10.1002/14651858.CD006788.pub2.
10. Cooper MR, Bird HM, Steinberg M. Efficacy and Safety of Modafinil in the Treatment of Cancer-Related Fatigue. *Ann Pharmacother*. 2009;43(4):721-725. doi:10.1345/aph.1L532.
11. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer J-P. Modafinil as an Adjunctive Treatment of Sedation, Negative Symptoms, and Cognition in Schizophrenia: A Critical Review. *J Clin Psychiatry*. 2009;70(1):104-112. doi:10.4088/JCP.07r03982.
12. Modafinil. In: *AHFS DI (Adult and Pediatric) In Lexicomp Online [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/essential_ashp/410736. Accessed June 5, 2015.
13. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr*. 2013;18(04):199-208. doi:10.1017/S1092852913000102.
14. Goss AJ, Kaser M, Costafreda SG, Sahakian BJ, Fu CHY. Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2013;74(11):1101-1107. doi:10.4088/JCP.13r08560.
15. Candy M, Jones L, Williams R, Tookman A, King M. Psychostimulants for depression. [Review] [126 refs]. *Cochrane Database Syst Rev*. 2008. doi:10.1002/14651858.CD006722.pub2.
16. Lam JY, Freeman MK, Cates ME. Modafinil Augmentation for Residual Symptoms of Fatigue in Patients with a Partial Response to Antidepressants. *Ann Pharmacother*. 2007;41(6):1005-1012. doi:10.1345/aph.1H526.
17. Lindsay SE, Gudelsky GA, Heaton PC. Use of Modafinil for the Treatment of Attention Deficit/Hyperactivity Disorder. *Ann Pharmacother*. 2006;40(10):1829-1833. doi:10.1345/aph.1H024.
18. Tricyclic Antidepressants, Clonidine, Venlafaxine, and Modafinil for the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: A Review of the Clinical Evidence. *Can Agency Drugs Technol Health*. March 2013. https://www.cadth.ca/tricyclic-antidepressants-clonidine-venlafaxine-and-modafinil-treatment-attention. Accessed June 24, 2015.
19. Bagot KS, Kaminer Y. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. [Review]. *Addiction*. 2014;109(4):547-557.
20. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. [Review]. *Pharmacol Res*. 2010;62(3):187-206. doi:10.1016/j.phrs.2010.04.002.
21. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. *Aviat Space Environ Med*. 2012;83(7):685-690.
22. PROVIGIL® (modafinil) Label. January 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf. Accessed June 5, 2015.
23. NUVIGIL® (armodafinil) Label. April 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021875s021lbledt.pdf. Accessed June 5, 2015.
24. Health Evidence Review Commission Prioritized List of health services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed June 5, 2015.
25. Oregon Health Authority. Oregon Medicaid Pharmaceutical Services Program Information - Oregon Medicaid PA Criteria, April 2015. *Or Health Auth Med Assist Program*. April 2015. http://www.oregon.gov/oha/healthplan/tools/Oregon%20Medicaid%20PA%20Criteria,%20April%202015.pdf. Accessed June 9, 2015.

26. Modafinil. In: *Micromedex Solutions [database online]*. 2015 ed. United States: Truven Health Analytics Inc.; 2015. http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/97423E/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/C193F5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Modafinil&UserSearchTerm=Modafinil&SearchFilter=filterNone&navitem=searchGlobal#. Accessed June 5, 2015.
27. Armodafinil. In: *Micromedex Solutions [on-Line Database]*. Vol 2015th ed. United States: Truven Health Analytics Inc.; 2015. http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/26CA27/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/3510F5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=armodafinil#. Accessed June 5, 2015.
28. Narcolepsy. In: *DynaMed [database online]*. 2015 ed. United States: EBSCO Information Services; 2014. http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=2&sid=e978e5d9-cacb-48f7-98d0-689ee54715e4%40sessionmgr113&hid=106&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=116132. Accessed June 13, 2015.
29. Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. *Eur J Neurol*. 2006;13(10):1035-1048. doi:10.1111/j.1468-1331.2006.01473.x.
30. Obstructive sleep apnea (OSA): DynaMed. In: *DynaMed [database online]*. 2015 ed. United States: EBSCO Information Services; 2015. http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=4&sid=a9393e86-988b-46d0-8ed3-1c8dd4438436%40sessionmgr115&hid=101&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=115600. Accessed June 22, 2015.
31. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst*. 2013;105(19):1432-1440. doi:10.1093/jnci/djt242.
32. Harris J-D. Fatigue in chronically ill patients. [Review] [63 refs]. *Curr Opin Support Palliat Care*. 2008;2(3):180-186. doi:10.1097/SPC.0b013e32830baed0.
33. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. [Review] [75 refs]. *Oncologist*. 2007:43-51.
34. Kirshbaum M. Pharmacologic treatments for fatigue associated with palliative care. [Review]. *J Oncol Nurs*. 2011;15(4):438-439. doi:10.1188/11.CJON.438-439.
35. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. [Review]. *AIDS*. 2010;24(10):1387-1405. doi:10.1097/QAD.0b013e328339d004.
36. Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. [Review]. *Neuropharmacology*. January 2013:168-184. doi:10.1016/j.neuropharm.2012.07.011.
37. Moulton CD, Hopkins C w. p., Bevan-Jones WR. Systematic review of pharmacological treatments for depressive symptoms in Huntington's disease. *Mov Disord*. 2014;29(12):1556-1561. doi:10.1002/mds.25980.
38. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. [Review]. *Cochrane Database Syst Rev*. 2011. doi:10.1002/14651858.CD007813.pub2.
39. Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry*. 2011;69(12):1192-1203. doi:10.1016/j.biopsych.2010.08.019.
40. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. [Review]. *Pharmacol Rev*. 2014;66(1):193-221. doi:10.1124/pr.112.007054.
41. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. *J Med Internet Res*. 2011;13(1). doi:10.2196/jmir.1643.
42. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. [Review] [146 refs]. *J Clin Psychiatry*. 2006;67(4):554-566.
43. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]: Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials. http://www-ncbi-nlm-nih-gov.liboff.ohsu.edu/pubmedhealth/PMH0061792/. Accessed June 22, 2015.
44. Bond DJ, Hadjipavlou G, Lam RW, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. *Ann Clin Psychiatry*. 2012;24(1):23-37.
45. Aromodafinil. In: *AHFS DI (Adult and Pediatric) In Lexicomp Online [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/complete_ashp/3011443. Accessed June 5, 2015.

Appendix 1 – Diagnoses of Interest[27,26,45,12]

Diagnoses	OHP Funded codes
Funded*[24] *FDA Indications (Group 1)	
Narcolepsy	347.00-347.01
Organic sleep apnea (except high altitude)	327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57
Funded*[24] *Off-Label Indications (Group 2)	
Attention deficit hyperactivity disorder: *AHFS Level C* *MM Level B (Adult), A (Pediatric)*	314.00-314.9
Depression, Unipolar or bipolar; Adjunct: *MM Level B (Adult)*	296.20-296.22, 296.25-296.26, 296.90-296.99, 298.0, 311, 625.4
Steinert myotonic dystrophy syndrome: *MM Level B (Adult)*	359.21
Fatigue in adult cancer survivors: *AHFS Level G*	140.xx - 209.xx
Multiple sclerosis-related fatigue: *AHFS Levels B & G* *MM Level B*	340.xx
Non-Funded*[24] *Indications (Group 3)	
Narcolepsy in conditions classified elsewhere	347.10 -347.11
Organic sleep disorders except organic sleep apneas	327.00, 327.01, 327.02, 327.09-327.13, 327.14, 327.15, 327.19, 327.22
Shift work sleep disorder	327.30-327.8
Hypersomnia, unspecified *Adverse reaction to drug - Somnolence:* *MM Level B* *Sleep deprivation:* *MM Level B (Adult)*	780.54
No Diagnosis of Interest (Group 4)	

Micromedex (MM) Evidence Levels:
Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

AHFS Evidence Levels:
A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (e.g., results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Appendix 2 – Maximum daily dose for drugs of interest

HSN	GSN	Brand	Generic	Strength	Maximum Units per Day
010865	025848	PROVIGIL	MODAFINIL	100 mg	2
010865	041478	PROVIGIL	MODAFINIL	200 mg	1
034868	062819	NUVIGIL	ARMODAFINIL	150 mg	1
034868	062820	NUVIGIL	ARMODAFINIL	50 mg	5
034868	062821	NUVIGIL	ARMODAFINIL	250 mg	1
034868	072017	NUVIGIL	ARMODAFINIL	200 mg	1

Appendix 3 – Medline literature search details

Ovid Technologies, Inc. Email Service----------Search for: limit 10 to (meta analysis or systematic reviews)Results: 27

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 2 2015> Search Strategy:
---

1 modafinil.mp. (1256)
2 armodafinil.mp. (99)
3 1 or 2 (1281)
4 exp Depression/ (82108)
5 exp Fatigue/ (21739)
6 exp Cognition/ (116136)
7 exp Attention Deficit Disorder with Hyperactivity/ (21441)
8 4 or 5 or 6 or 7 (234593)
9 3 and 8 (317)
10 limit 9 to (english language and humans) (284)
11 limit 10 to (meta analysis or systematic reviews) (25)

****

1. Moulton CD, Hopkins CW, Bevan-Jones WR. Systematic review of pharmacological treatments for depressive symptoms in Huntington's disease. Mov Disord. 2014;29(12):1556-61. doi:10.1002/mds.25980
AB BACKGROUND: Depressive symptoms are common in Huntington's disease (HD), profoundly affect quality of life, and predict suicidal ideation. However, no recent review of antidepressant treatment in HD has been published. METHODS: We performed a PRISMA systematic review of HD studies, which used a recognized antidepressant and measured change in depressive symptoms using a validated psychiatric scale. Controlled trials, uncontrolled trials, observational studies, and case series were included. RESULTS: Eleven studies were included, totalling 190 patients. One study examined venlafaxine, one fluoxetine, one citalopram, one atomoxetine, one modafinil, one lithium, and five antipsychotics. No studies were of adequate duration, size, or outcome, and no controlled trial in a depressed population produced a positive result. CONCLUSIONS: Inadequate evidence exists to guide antidepressant treatment in HD. Further research is needed to assess antidepressant efficacy and to examine whether treatment of depression represents a modifiable target for the high suicide rate in HD.

EXCLUDED; INTERVENTION

2. Bagot KS, Kaminer Y. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. Addiction. 2014;109(4):547-57. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24749160. Accessed June 23, 2015.

AB BACKGROUND AND AIMS: Increasing prescription stimulant abuse among youth without diagnoses of attention deficit hyperactivity disorder (ADHD) is of concern. The most frequently cited motive for abuse is improved academic achievement via neurocognitive enhancement. Our aim in reviewing the literature was to identify neurocognitive effects of prescription stimulants in non-ADHD youth. METHODS: A systematic review

was conducted for youth aged 12-25 years using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Fourteen papers were included. RESULTS: Modafinil appears to improve reaction time (P < 0.04), logical reasoning (P < 0.05) and problem-solving. Methylphenidate appears to improve performance in novel tasks and attention-based tasks (P < 0.05), and reduces planning latency in more complex tasks (P < 0.05). Amphetamine has been shown to improve consolidation of information (0.02 > P < 0.05), leading to improved recall. Across all three types of prescription stimulants, research shows improved attention with lack of consensus on whether these improvements are limited to simple versus complex tasks in varying youth populations. CONCLUSIONS: The heterogeneity of the non-attention deficit hyperactivity disorder youth population, the variation in cognitive task characteristics and lack of replication of studies makes assessing the potential global neurocognitive benefits of stimulants among non-attention deficit hyperactivity disorder youth difficult; however, some youth may derive benefit in specific cognitive domains.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

3. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. Pharmacol Rev. 2014;66(1):193-221. doi:10.1124/pr.112.007054

AB Psychostimulants such as cocaine have been used as performance enhancers throughout recorded history. Although psychostimulants are commonly prescribed to improve attention and cognition, a great deal of literature has described their ability to induce cognitive deficits, as well as addiction. How can a single drug class be known to produce both cognitive enhancement and impairment? Properties of the particular stimulant drug itself and individual differences between users have both been suggested to dictate the outcome of stimulant use. A more parsimonious alternative, which we endorse, is that dose is the critical determining factor in cognitive effects of stimulant drugs. Herein, we review several popular stimulants (cocaine, amphetamine, methylphenidate, modafinil, and caffeine), outlining their history of use, mechanism of action, and use and abuse today. One common graphic depiction of the cognitive effects of psychostimulants is an inverted U-shaped dose-effect curve. Moderate arousal is beneficial to cognition, whereas too much activation leads to cognitive impairment. In parallel to this schematic, we propose a continuum of psychostimulant activation that covers the transition from one drug effect to another as stimulant intake is increased. Low doses of stimulants effect increased arousal, attention, and cognitive enhancement; moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse. This continuum helps account for the seemingly disparate effects of stimulant drugs, with the same drug being associated with cognitive enhancement and impairment.

EXCLUDED: DIAGNOSIS NOT OF INTEREST; NARRATIVE REVIEW

4. Sheng P, Hou L, Wang X, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. PLoS ONE. 2013;8(12):e81802. doi:10.1371/journal.pone.0081802

AB BACKGROUND: Modafinil is a novel wake-promoting agent approved by the FDA ameliorating excessive daytime sleepiness (EDS) in three disorders: narcolepsy, shift work sleep disorder and obstructive sleep apnea. Existing trials of modafinil for fatigue and EDS associated with neurological disorders provided inconsistent results. This meta-analysis was aimed to assess drug safety and effects of modafinil on fatigue and EDS associated with neurological disorders. METHODS: A comprehensive literature review was conducted in order to identify published studies assessing the effects of modafinil on fatigue and EDS associated with neurological disorders. Primary outcomes included fatigue and EDS. Secondary outcomes included depression and adverse effects. FINDINGS: Ten randomized controlled trials were identified including 4 studies of Parkinson's disease (PD), 3 of multiple sclerosis (MS), 2 of traumatic brain injury (TBI) and 1 of post-polio syndrome (PPS). A total of 535 patients were enrolled. Our results suggested a therapeutic effect of modafinil on fatigue in TBI (MD -0.82 95% CI -1.54 - -0.11 p=0.02, I(2)=0%), while a beneficial effect of modafinil on fatigue was not confirmed in the pooled studies of PD or MS. Treatment results demonstrated a clear beneficial effect of modafinil on EDS in patients with PD (MD -2.45 95% CI -4.00 - -0.91 p=0.002 I(2)=14%), but not with MS and TBI. No difference was seen between modafinil and placebo treatments in patients with PPS. Modafinil seemed to have no therapeutic effect on depression. Adverse events were similar between modafinil and placebo groups except that more patients were found with insomnia and nausea in modafinil group. CONCLUSIONS: Existing trials of modafinil for fatigue and EDS associated with PD, MS, TBI and PPS provided inconsistent results. The majority of the studies had small sample sizes. Modafinil is not yet sufficient to be recommended for these medical conditions until solid data are available.

INCLUDED

5. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. J Natl Cancer Inst. 2013;105(19):1432-40. doi:10.1093/jnci/djt242

AB Over the past decades, some scientific progress has been made in understanding and treating cancer-related fatigue (CRF). However, three major problems have limited further progress: lack of agreement about measurement, inadequate understanding of the underlying biology, and problems in the conduct of clinical trials for CRF. This commentary reports the recommendations of a National Cancer Institute Clinical Trials Planning Meeting and an ongoing National Cancer Institute working group to address these problems so that high-priority research and clinical trials can be conducted to advance the science of CRF and its treatment. Recommendations to address measurement issues included revising the current case definition to reflect more rigorous criteria, adopting the Patient Reported Outcomes Measurement Information System fatigue scales as standard measures of CRF, and linking legacy measures to the scales. With regard to the biology of CRF, the group identified the need for longitudinal research to examine biobehavioral mechanisms underlying CRF and testing mechanistic hypotheses within the context of intervention research. To address clinical trial issues, recommendations included using only placebo-controlled trial designs. setting eligibility to minimize sample heterogeneity or enable subgroup analysis, establishing a CRF severity threshold for participation in clinical trials, conducting dissemination trials of efficacious interventions (such as exercise), and combining

nonpharmacologic and pharmacologic interventions to exploit the potential synergy between these approaches. Accomplishing these goals has the potential to advance the science of CRF and improve the clinical management of this troubling symptom.

EXCLUDED: DESIGN (COMMENTARY)

6. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. CNS Spectr. 2013;18(4):199-208. doi:10.1017/S1092852913000102

AB In this article, we examined evidence for the acute treatment of depression in bipolar I disorder, focusing on double-blind, placebo-controlled studies with a definite primary outcome measure and published in peer review journals. Quetiapine and olanzapine/fluoxetine are currently approved by the FDA for the treatment of bipolar depression, and a number of additional agents (including other atypical antipsychotics, mood stabilizers, antidepressants, and novel compounds) have been studied with varying degrees of efficacy. The medication with the most evidence for efficacy in bipolar depression is quetiapine, with five studies showing positive efficacy compared to placebo. In contrast, five studies of lamotrigine were negative, although meta-analyses of the pooled have found some treatment effects. Two studies of olanzapine and olanzapine/fluoxetine and three small studies of divalproex showed significant efficacy in treating bipolar depression. Two studies of aripiprazole found no differences compared to placebo. Early research on lithium in bipolar depression had significant methodological flaws, and only one study of lithium met our primary search criteria. To better understand the role of antidepressants, we also examined studies of antidepressants as adjunctive treatment of bipolar depression in participants taking mood stabilizers or atypical antipsychotics. These studies reported mixed results for a variety of antidepressants, but the majority found no differences compared to placebo. Other studies of adjunctive treatment were also discussed. There has been one positive adjunctive study each of lamotrigine, omega-3 fatty acids, modafinil, and armodafinil, while there was one negative trial each of omega-3 fatty acids, ziprasidone, and levetiracetam.

INCLUDED

7. Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. Neuropharmacology. 2013;64:168-84. doi:10.1016/j.neuropharm.2012.07.011

AB Modafinil is a central nervous system wake promoting agent used for the treatment of excessive daytime sleeping. Its vigilance promoting properties and low abuse potential has intrigued the scientific community and has led to use it as a cognitive enhancer, before its neural functions were understood. Here, we review the effects of modafinil in human cognition and emotion and its specific actions on symptoms in patients with schizophrenia and whether these are consistently effective throughout the literature. We also performed a systematic review on the effects of modafinil on neurotransmitter signalling in different areas of the brain in order to better understand the neuromechanisms of its cognitive and emotional enhancing properties. A review of its effects in schizophrenia suggests that modafinil facilitates cognitive functions, with pro-mnemonic effects and problem solving improvements. Emotional processing also appears to be enhanced by the drug, although to date there are only a limited number of studies. The systematic review on the neurochemical modulation of the modafinil suggests that its mnemonic enhancing properties might be the result of glutamatergic and dopaminergic increased neuronal activation in the hippocampus and in the prefrontal cortex respectively. Other neurotransmitters were also activated by modafinil in various limbic brain areas, suggesting that the drug acts on these brain regions to influence emotional responses. These reviews seek to delineate the neuronal mechanisms by which modafinil affects cognitive and emotional function. This article is part of a Special Issue entitled 'Cognitive Enhancers'.

EXCLUDED – OUTCOMES NOT OF INTEREST

8. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med. 2012;83(7):685-90. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22779312. Accessed June 23, 2015.

AB INTRODUCTION: Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning, some of which may ultimately be considered for such use in military operations. Some drugs with potential for cognition enhancement have already been studied for use in military operations specific to their primary effect in sleep regulation (i.e., dextroamphetamine, modafinil, caffeine). There is considerable information available on many of these drugs. However, considerations for military appropriateness must be based on proficient research (e.g., randomly controlled trial design). METHODS: A meta-analysis was conducted to summarize the current state of knowledge of these potentially cognition-enhancing drugs. The analysis only included studies which met inclusion criteria relevant to military research. RESULTS: The results of the literature review reveal a gap in research of the enhancement properties of the drugs of interest. The results yielded three studies (all of which studied modafinil) that met the criteria. The meta-analysis of these three studies revealed a relatively weak pooled effect of modafinil on some aspects of cognitive performance in normal, rested adults. DISCUSSION: While the results of this study support the efficacy of modafinil, the main finding is the large literature gap evaluating the short- and long-term effects of these drugs in healthy adults.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

9. Bond DJ, Hadjipavlou G, Lam RW, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry. 2012;24(1):23-37. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22303520. Accessed June 23, 2015.

AB BACKGROUND: Patients with bipolar disorder (BD) and major depressive disorder (MDD) experience adult attention-deficit/hyperactivity disorder (ADHD) at rates substantially greater than the general population. Nonetheless, ADHD frequently goes untreated in this population. METHODS: We reviewed the literature regarding the management of adult ADHD in patients with mood disorders. Because a limited number of studies have been conducted in adults, our treatment recommendations also are partly informed by research in children and adolescents with BD+ADHD or MDD+ADHD, adults with ADHD, and our clinical experience. RESULTS: In individuals with mood disorders, ADHD is best diagnosed when typical symptoms persist during periods of sustained euthymia. Individuals with BD+ADHD, particularly those with bipolar I disorder (BD I), are at risk for mood destabilization with many ADHD treatments, and should be prescribed mood-stabilizing medications before initiating ADHD therapies. Bupropion is a reasonable first-line treatment for BD+ADHD, while mixed amphetamine salts and methylphenidate also may be considered in patients determined to be at low risk for manic switch. Modafinil and cognitive-behavioral therapy (CBT) are second-line choices. In patients with MDD+ADHD and moderate to severe depression, MDD should be the treatment priority, whereas in mildly depressed or euthymic patients the order may be reversed. First-line treatments for MDD+ADHD include bupropion, an antidepressant plus a long-acting stimulant, or an antidepressant plus CBT. Desipramine, nortriptyline, and venlafaxine are second-line options. CONCLUSIONS: Clinicians should be vigilant in screening for comorbid ADHD in mood disorder patients. ADHD symptoms can respond to appropriately chosen treatments.

INCLUDED

10. Kirshbaum M. Pharmacologic treatments for fatigue associated with palliative care. Clin J Oncol Nurs. 2011;15(4):438-9. doi:10.1188/11.CJON.438-439

EXCLUDED: UNAVAILABLE AT OHSU

11. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. Cochrane Database Syst Rev. 2011;(6):CD007813. doi:10.1002/14651858.CD007813.pub2

AB BACKGROUND: Attention Deficit Hyperactivity Disorder (ADHD) is a childhood onset disorder that can persist into adulthood. Amphetamines are used to treat adult ADHD, but uncertainties persist about their efficacy and safety. OBJECTIVES: To examine the efficacy and safety of amphetamines for adults with ADHD, as well as the influence of dose, drug type and release formulation type. SEARCH STRATEGY: We searched CENTRAL, PubMed, EMBASE, CINAHL, PsycINFO, clinicaltrials.gov, UK Clinical Trials Gateway and references obtained from articles and experts in the field. We conducted the electronic searches on 25 February 2010. SELECTION CRITERIA: Randomized controlled trials comparing the efficacy of amphetamine derivatives against placebo or an active intervention. DATA COLLECTION AND ANALYSIS: Two authors extracted data from each included study. We used the standardized mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed the trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias. MAIN RESULTS: We included seven studies, which enrolled 1091 participants. All studies were placebo-controlled and three included an active comparator: guanfacine, modafinil and paroxetine. Most studies had short-term follow-up, with a mean study length of 8.1 weeks. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57) but did not improve retention in treatment overall and were associated with increased dropout due to adverse events (RR 3.03; 95% CI 1.52 to 6.05). The three amphetamine derivatives investigated (dextroamphetamine, lisdexamphetamine and mixed amphetamine salts (MAS)) were all efficacious for reducing ADHD symptoms, but MAS also increased retention in treatment. Different doses did not appear associated with differences in efficacy. We investigated immediate and sustained drug release formulations but found no difference between them on any outcome. When amphetamines were compared to other drug interventions, no differences were found. We did not find any study to be at low risk of bias overall, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment. AUTHORS' CONCLUSIONS: Amphetamines improved short-term ADHD symptom severity. MAS also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings. Furthermore, the possibility that the results of the included studies were biased was high, which could have led to an overestimation of amphetamine efficacy.

EXCLUDED: INTERVENTION

12. Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. Biol Psychiatry. 2011;69(12):1192-203. doi:10.1016/j.biopsych.2010.08.019

AB Attention-deficit/hyperactivity disorder (ADHD) is a prevalent condition associated with cognitive dysfunction. The Cambridge Neuropsychological Test Automated Battery is a computerized set of tests that has been widely used in ADHD and in translation/back-translation. Following a survey of translational research relevant to ADHD in experimental animals, a comprehensive literature review was conducted of studies that had used core Cambridge Neuropsychological Test Automated Battery tests 1) to evaluate cognitive dysfunction in ADHD and 2) to evaluate effects of salient drugs in patients and in volunteers. Meta-analysis was conducted where four or more independent datasets were available. Meta-analysis revealed medium-large decrements in ADHD for response inhibition ($d = .790$, $p < .001$), working memory ($d = .883$, $p < .001$), executive planning ($d = .491$, $p < .001$), and a small decrement in attentional set shifting ($d = .160$, $p = .040$). Qualitative review of the literature showed some consistent patterns. In ADHD, methylphenidate improved working memory, modafinil

improved planning, and methylphenidate, modafinil, and atomoxetine improved inhibition. Meta-analysis of modafinil healthy volunteer studies showed no effects on sustained attention or set shifting. Results were paralleled by findings in experimental animals on comparable tests, enabling further analysis of drug mechanisms. Substantial cognitive deficits are present in ADHD, which can be remediated somewhat with current medications and which can readily be modeled in experimental animals using back-translational methodology. The findings suggest overlapping but also distinct early cognitive effects of ADHD medications and have important implications for understanding the pathophysiology of ADHD and for future trials.

EXCLUDED: OUTCOMES NOT OF INTEREST

13. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res. 2011;13(1):e6. doi:10.2196/jmir.1643

AB BACKGROUND: Evaluating a new use for an existing drug can be expensive and time consuming. Providers and patients must all too often rely upon their own individual-level experience to inform clinical practice, which generates only anecdotal and unstructured data. While academic-led clinical trials are occasionally conducted to test off-label uses of drugs with expired patents, this is relatively rare. In this work, we explored how a patient-centered online research platform could supplement traditional trials to create a richer understanding of medical products postmarket by efficiently aggregating structured patient-reported data. PatientsLikeMe is a tool for patients, researchers, and caregivers (currently 82,000 members across 11 condition-based communities) that helps users make treatment decisions, manage symptoms, and improve outcomes. Members enter demographic information, longitudinal treatment, symptoms, outcome data, and treatment evaluations. These are reflected back as longitudinal health profiles and aggregated reports. Over the last 3 years, patients have entered treatment histories and evaluations on thousands of medical products. These data may aid in evaluating the effectiveness and safety of some treatments more efficiently and over a longer period of time course than is feasible through traditional trials. OBJECTIVE: The objective of our study was to examine the illustrative cases of amitriptyline and modafinil - drugs commonly used off-label. METHODS: We analyzed patient-reported treatment histories and drug evaluations for each drug, examining prevalence, treatment purpose, and evaluations of effectiveness, side effects, and burden. RESULTS: There were 1948 treatment histories for modafinil and 1394 treatment reports for amitriptyline reported across five PatientsLikeMe communities (multiple sclerosis, Parkinson's disease, mood conditions, fibromyalgia/chronic fatigue syndrome, and amyotrophic lateral sclerosis). In these reports, the majority of members reported taking the drug for off-label uses. Only 34 of the 1755 (1%) reporting purpose used modafinil for an approved purpose (narcolepsy or sleep apnea). Only 104 out of 1197 members (9%) reported taking amitriptyline for its approved indication, depression. Members taking amitriptyline for off-label purposes rated the drug as more effective than those who were taking it for its approved indication. While dry mouth is a commonly reported side effect of amitriptyline for most patients, 88 of 220 (40%) of people with amyotrophic lateral sclerosis on the drug reported taking advantage of this side effect to treat their symptom of excess saliva. CONCLUSIONS: Patient-reported outcomes, like those entered within PatientsLikeMe, offer a unique real-time approach to understand utilization and performance of treatments across many conditions. These patient-reported data can provide a new source of evidence about secondary uses and potentially identify targets for treatments to be studied systematically in traditional efficacy trials.

EXCLUDED: NOT RELEVANT

14. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2010;(11):CD006788. doi:10.1002/14651858.CD006788.pub2

AB BACKGROUND: In healthy individuals, fatigue is a protective response to physical or mental stress, often relieved by rest. By contrast, in palliative care patients fatigue can be severely debilitating, thereby impacting daily activity and quality of life, often with rest not counteracting fatigue. Fatigue frequently occurs in patients with advanced disease and modalities treating cancer often contribute or cause fatigue. Further complicating issues are its multidimensionality, subjective nature, and lack of a consensus definition of fatigue. Pathophysiology is not fully understood and evidence-based treatment approaches are needed. OBJECTIVES: The objective was to determine efficacy of pharmacological treatments on non-specific fatigue in palliative care. The focus was on patients at an advanced stage of disease, including cancer and other chronic diseases associated with fatigue, aiming to relieve fatigue. Studies aiming at curative treatment (e.g. surgical intervention for early breast cancer) were not included. SEARCH STRATEGY: We searched EMBASE; Psych Lit, CENTRAL and MEDLINE to June 2009. SELECTION CRITERIA: We considered randomised controlled trials (RCTs) concerning adult palliative care with focus on pharmacological treatment of fatigue. The primary outcome had to be non-specific fatigue (or related terms such as asthenia). DATA COLLECTION AND ANALYSIS: Results were screened and included if they met the selection criteria. If two or more studies were identified that investigated a specific drug in a population with the same disease, meta-analysis was conducted. In addition, comparison of type of drug investigated in a specific population as well as comparison of frequent adverse effects of fatigue treatment was done by creating overview tables. MAIN RESULTS: More than 2000 publications were screened, and 22 met inclusion criteria. In total, data from 11 drugs and 1632 participants were analysed. Studies investigating amantadine, pemoline, and modafinil in participants with Multiple Sclerosis (MS)-associated fatigue and methylphenidate in patients suffering from advanced cancer and fatigue could be used for meta-analysis. Amantadine in MS and methylphenidate in cancer patients showed a superior effect. Most studies had low participant numbers and were heterogenous. AUTHORS' CONCLUSIONS: Based on limited evidence, we cannot recommend a specific drug for treatment of fatigue in palliative care patients. Surprisingly, corticosteroids have not been a research focus for fatigue treatment, although these drugs are frequently used. Recent fatigue research seems to focus on modafinil, which may be beneficial although there is no evidence currently. Amantadine and methylphenidate should be further examined. Consensus regarding fatigue assessment in advanced disease is needed.

INCLUDED

15. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. Pharmacol Res. 2010;62(3):187-206. doi:10.1016/j.phrs.2010.04.002

AB The term neuroenhancement refers to improvement in the cognitive, emotional and motivational functions of healthy individuals through, inter alia, the use of drugs. Of known interventions, psychopharmacology provides readily available options, such as methylphenidate and modafinil. Both drugs are presumed to be in widespread use as cognitive enhancers for non-medical reasons. Based on a systematic review and meta-analysis we show that expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomised controlled trials. Only studies with sufficient extractable data were included in the statistical analyses. For methylphenidate an improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered. Modafinil on the other hand, was found to improve attention for well-rested individuals, while maintaining wakefulness, memory and executive functions to a significantly higher degree in sleep deprived individuals than did a placebo. However, repeated doses of modafinil were unable to prevent deterioration of cognitive performance over a longer period of sleep deprivation though maintaining wakefulness and possibly even inducing overconfidence in a person's own cognitive performance.

EXCLUDED: HEALTHY INDIVIDUALS

16. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. AIDS. 2010;24(10):1387-405. doi:10.1097/QAD.0b013e328339d004

AB OBJECTIVE: To assess predictors and reported treatment strategies of HIV-related fatigue in the combined antiretroviral (cART) era. METHOD: Five databases were searched and reference lists of pertinent articles were checked. Studies published since 1996 on predictors or therapy of HIV-related fatigue measured by a validated instrument were selected. RESULTS: A total of 42 studies met the inclusion criteria. The reported HIV-related fatigue prevalence in the selected studies varied from 33 to 88%. The strongest predictors for sociodemographic variables were unemployment and inadequate income. Concerning HIV-associated factors, the use of cART was the strongest predictor. Comorbidity and sleeping difficulties were important factors when assessing physiological influences. Laboratory parameters were not predictive of fatigue. The strongest and most uniform associations were observed between fatigue and psychological factors such as depression and anxiety. Reported therapeutic interventions for HIV-related fatigue include testosterone, psycho-stimulants (dextroamphetamine, methylphenidate hydrochloride, pemoline, modafinil), dehydroepiandrosterone, fluoxetine and cognitive behavioural or relaxation therapy. CONCLUSION: HIV-related fatigue has a high prevalence and is strongly associated with psychological factors such as depression and anxiety. A validated instrument should be used to measure intensity and consequences of fatigue in HIV-infected individuals. In the case of fatigue, clinicians should not only search for physical mechanisms, but should question depression and anxiety in detail. There is a need for intervention studies comparing the effect of medication (antidepressants, anxiolytics) and behavioural interventions (cognitive-behavioural therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy. Treatment of HIV-related fatigue is important in the care for HIV-infected patients and requires a multidisciplinary approach.

EXCLUDED: INTERVENTION

17. Brown JN, Howard CA, Kemp DW. Modafinil for the treatment of multiple sclerosis-related fatigue. Ann Pharmacother. 2010;44(6):1098-103. doi:10.1345/aph.1M705

AB OBJECTIVE: To review the efficacy and safety of off-label use of modafinil in the treatment of multiple sclerosis (MS)-related fatigue. DATA SOURCES: Literature was accessed via MEDLINE (1966-January 2010) and International Pharmaceutical Abstracts (1960-2010), using the medical subject heading terms modafinil, multiple sclerosis, and fatigue. STUDY SELECTION AND DATA EXTRACTION: All English-language, peer reviewed publications were analyzed for relevance. Studies appropriate to the objective were evaluated, including 3 open-label trials, 1 single-blind trial, and 2 randomized placebo-controlled trials. DATA SYNTHESIS: Fatigue symptoms, assessed by a variety of self-reported symptom scales, improved in each of the uncontrolled studies reviewed when participants with MS received modafinil 200 mg or less daily for up to 12 weeks. These benefits were not maintained, however, in one uncontrolled study when modafinil was increased to 400 mg daily. Of the 2 randomized, controlled trials, 1 study found that modafinil 200 mg once daily resulted in a reduction in fatigue symptoms measured by the Fatigue Severity Scale at 8 weeks. The other study found no difference in the reduction of fatigue symptoms, measured by the Modified Fatigue Impact Scale at 5 weeks, between the placebo group and patients who received modafinil 100-200 mg twice daily. The most common adverse reactions associated with modafinil use in all studies included gastrointestinal and central nervous system effects. CONCLUSIONS: Based on the available data, use of modafinil for the treatment of MS-related fatigue has demonstrated benefit in all uncontrolled studies but has conflicting results from 2 controlled studies. Modafinil is a reasonable therapeutic option in this patient population, although larger, long-term, randomized controlled studies are necessary to further elucidate the appropriate dose of modafinil, its effects on MS-related fatigue, and adverse effects associated with its use. [References: 26]

INCLUDED

18. Cooper MR, Bird HM, Steinberg M. Efficacy and safety of modafinil in the treatment of cancer-related fatigue. Ann Pharmacother. 2009;43(4):721-5. doi:10.1345/aph.1L532

AB OBJECTIVE: To review the efficacy and safety of modafinil in the treatment of cancer-related fatigue (CRF). DATA SOUCES: Literature was accessed via MEDLINE (1950-week 3, November 2008), International Pharmaceutical Abstracts, and Google Scholar using the terms modafinil, cancer, and fatigue. Reference citations from articles identified were reviewed. STUDY SELECTION AND DATA EXTRACTION: All English-language publications identified were analyzed for significance. Studies relevant to the objective were used, including 2 prospective open-label studies, one randomized double-blind, dose-controlled trial with an open-label extension, and one Phase 3 randomized, placebo-controlled, double-blind trial. DATA SYNTHESIS: Fatigue is a nearly universal adverse effect of cancer and its treatment that is unrelated to physical exertion, is not relieved by sleep or rest, and negatively affects quality of life. Modafinil is a central nervous system stimulant with minimal toxicity and a low propensity for abuse. Clinical data demonstrate that modafinil significantly reduces fatigue in patients who have received cancer treatment or are currently undergoing chemotherapy. Additional benefits include improvement in cognitive function, mood, general activity, walking ability, normal work ability, relations with other people, and enjoyment of life. Limitations of the available data include open-label design in 3 of the 4 studies; the absence of numerical results of fatigue assessments in the abstract of 1 trial, preventing the determination of clinical significance; and the full inclusion/exclusion criteria, which were not included in the published abstracts. These limitations leave readers without a clear picture of the study populations. Finally, different patient populations at different points in treatment with varying durations of therapy were used, which makes extrapolation of data to the general population challenging. CONCLUSIONS: Further randomized placebo-controlled trials are necessary to amass evidence for the effective and safe use of modafinil for CRF; however, if traditional therapies have failed or are intolerable, modafinil can be considered a treatment option. [References: 19]

INCLUDED

19. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer JP. Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry. 2009;70(1):104-12. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=19026265. Accessed June 23, 2015.

AB OBJECTIVE: Given recent reports about the off-label use of modafinil as an adjuvant for the treatment of antipsychotic-associated sedation in schizophrenia patients and the recent interest in its putative cognitive-enhancing effects in this population, we present a systematic review of available data on trials of modafinil as an adjuvant in the treatment of cognitive deficits, negative symptoms, and antipsychotic-induced fatigue, and its tolerability. DATA SOURCES: PubMed was searched for trials published in English up to January 2008 evaluating modafinil's effects on fatigue, negative symptoms, and cognition in schizophrenia with combinations of the following terms: schizophrenia, modafinil, cognition, negative symptoms, and fatigue. STUDY SELECTION: Six trials were identified: 2 randomized, prospective, double-blind placebo-controlled trials; 3 randomized, prospective, double-blind placebo-controlled crossover trials; and 1 open-label pilot study. Case series and case reports were excluded in the data analysis, except to identify potential adverse reactions to modafinil. DATA EXTRACTION: Studies were examined for number of subjects, trial duration, design, dosing, and outcomes with respect to sedation, negative symptoms, cognitive function, and tolerability. RESULTS: One of 4 reviewed studies found a significant effect of modafinil as an alerting agent for antipsychotic-induced fatigue and sedation. Neither of 2 reviewed studies found modafinil to improve negative symptoms of schizophrenia. Three of 6 reviewed studies showed that modafinil may improve short-term memory, attention, and the ability to shift mental sets. Two neuroimaging studies identified functional correlates in areas associated with working memory functions. The main adverse effect was found to be a small risk of psychosis exacerbation, which was seen in 5 of 83 patients (6.0%) in the active treatment groups as compared to 2 of 70 patients (2.9%) in the placebo groups. CONCLUSIONS: While the available data suggest that modafinil is generally well tolerated and may have some efficacy in the treatment of antipsychotic-induced sedation and cognitive domains, the small sample sizes, contradictory results, and methodological differences between trials, especially with respect to cognitive testing, make it difficult to draw firm conclusions about the overall effectiveness of modafinil as an adjunct in the treatment of schizophrenia. Well-powered, prospective, randomized placebo-controlled trials using the MATRICS battery concomitantly with functional outcome measures are necessary to elucidate modafinil's efficacy and effectiveness as an adjunctive treatment for sedation, negative symptoms, and cognitive deficits in schizophrenia. Hence, before prescribing modafinil to a schizophrenia patient, the possible risks and benefits of each particular case should be evaluated.Copyright 2009 Physicians Postgraduate Press, Inc. [References: 56]

19

INCLUDED.

20. Harris JD. Fatigue in chronically ill patients. Curr. opin. support. palliat. care. 2008;2(3):180-6. doi:10.1097/SPC.0b013e32830baed0

AB PURPOSE OF REVIEW: Fatigue is the most common symptom among palliative patients, often considered more distressing than pain, nausea or vomiting. This article reviews the current literature and puts forward up to date treatment recommendations. RECENT FINDINGS: Methylphenidate showed a small but significant improvement versus placebo in a recently published systematic review. Donepezil did not show a significant benefit versus placebo in a double blind, placebo-controlled study. Hypogonadism is a frequent condition that can cause fatigue in patients with advanced cancer and other chronic illnesses and androgen replacement therapy warrants further investigation. Among antidepressants, bupropion has shown encouraging results. The role of hematopoietic agents for advanced cancer patients receiving palliative care is minimal as anemia is less of a contributing factor in this setting. Cytokine receptor antagonists play an important theoretical role but further studies are needed before they could be recommended. L-Carnitine has shown encouraging results. SUMMARY: Methylphenidate is still considered the first choice of treatment among pharmacological therapies. Modafinil shows promise, but insufficient studies have been conducted in this setting. Bupropion may have benefits in treating depression and fatigue. Among complementary therapies, L-carnitine has the most potential. Further studies are needed before cytokine receptor antagonists and androgen replacement therapy can be recommended. [References: 63]

EXCLUDED: UNAVAILABLE AT OHSU

21. Candy M, Jones L, Williams R, Tookman A, King M. Psychostimulants for depression. Cochrane Database Syst Rev. 2008;(2):CD006722. doi:10.1002/14651858.CD006722.pub2

AB BACKGROUND: Depression is common, disabling, costly and under-treated. There are problems in the current first-line drug treatment, antidepressants, for moderate or severe depression. There is a body of research that has evaluated the effect of psychostimulants (PS) in the treatment of depression. This has not been reviewed systematically. OBJECTIVES: To determine the effectiveness of PS in the treatment of depression and to assess adverse events associated with PS. SEARCH STRATEGY: Databases CCDANCTR-Studies and CCDANCTR-References were searched on 21/6/2006. Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycInfo, AMED, CINAHL, Dissertation Abstracts and the National Health Service Research Register were searched. SELECTION CRITERIA: Randomised controlled trials (RCTs) assessing the effectiveness of PS were included. The trial population comprised adults of either sex with a diagnosis of depression. DATA COLLECTION AND ANALYSIS: Two review authors extracted the data independently and assessed trial quality. Meta-analysis was considered for trials with comparable key characteristics. The primary outcome was depression symptoms, based on a continuous outcome, using the standardised mean difference (SMD), or a dichotomous measure of clinical response, using odds ratios (OR), with 95% confidence intervals (CI). MAIN RESULTS: Twenty-four RCTs were identified. The overall quality of the trials was low. Five drugs were evaluated; dexamphetamine, methylphenidate, methylamphetamine, pemoline and modafinil. Modafinil was evaluated separately as its pharmacology is different to that of the other PS. PS were administered as a monotherapy, adjunct therapy, in oral or intravenous preparation and in comparison with a placebo or an active therapy. Most effects were measured in the short term (up to four weeks). Thirteen trials had some usable data for meta-analyses. Three trials (62 participants) demonstrated that oral PS, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.40, -0.33, with non-significant heterogeneity. A similar effect was found for fatigue. In the short term PS were acceptable and well tolerated. Tolerance and dependence were under evaluated. No statistically significant difference in depression symptoms was found between modafinil and placebo. AUTHORS' CONCLUSIONS: There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear. Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and, furthermore, to explore which PS may be more beneficial and in which clinical situations they are optimal. [References: 126]

INCLUDED

22. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. Oncologist. 2007;12 Suppl 1:43-51. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17573455. Accessed June 23, 2015.

AB Fatigue is the most commonly reported symptom in patients with cancer, with a prevalence of over 60% reported in the majority of studies. This paper systematically reviews pharmacologic agents in the treatment of cancer-related fatigue (CRF). We conducted a literature review of clinical trials that assessed pharmacologic agents for the treatment of CRF. These agents include hematopoietics (for anemia), corticosteroids, and psychostimulants. Other therapeutic agents that are less well studied for CRF but are currently the focus of clinical trials include l-carnitine, modafinil, bupropion, and selective serotonin reuptake inhibitors such as paroxetine. Disclosure of potential conflicts of interest is found at the end of this article. [References: 75]

EXCLUDED: UNAVAILABLE AT OHSU

23. Lam JY, Freeman MK, Cates ME. Modafinil augmentation for residual symptoms of fatigue in patients with a partial response to antidepressants. Ann Pharmacother. 2007;41(6):1005-12. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17519297. Accessed June 23, 2015.

AB OBJECTIVE: To evaluate the literature discussing the use of modafinil in the treatment of residual symptoms of fatigue in patients with depression. DATA SOURCES: PubMed (1966-March 2007) and International Pharmaceutical Abstracts (1970-March 2007) were searched using the key words modafinil and depression. A manual search of the reference section of the articles retrieved was conducted to identify articles not indexed in either of these sources. STUDY SELECTION AND DATA EXTRACTION: All articles published in English were evaluated. Studies were included if modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales. DATA SYNTHESIS: One retrospective study, 5 open-label trials, and 2 randomized controlled clinical trials met the inclusion criteria for assessment of residual symptoms of fatigue as assessed by commonly used fatigue subscales after modafinil administration. Although improvement with fatigue has occurred with modafinil therapy, literature regarding the topic is limited by the lack of well-controlled clinical trials. Modafinil does appear to improve residual fatigue with depression as evidenced by open-label trials; however, the efficacy of this agent has not been duplicated in randomized controlled trials. The open-label trials that have been conducted often had no comparator and a small number of patients. In addition, outcome measures used in the studies were not consistent between trials. Modafinil appears to be well tolerated, with the main adverse effects being headache and nausea. CONCLUSIONS: Open-label trials indicate that modafinil may be effective in ameliorating fatigue associated with depression; however, this effect has not been reproduced in randomized, double-blind, placebo-controlled clinical trials. Therefore, the use of modafinil for the treatment of residual fatigue is not recommended due to the lack of reproducible data of its efficacy. Long-term, adequately powered clinical trials should be conducted to determine its place in therapy. [References: 24]

INCLUDED

24. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006;40(10):1829-33. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16954326. Accessed June 23, 2015.

AB OBJECTIVE: To review the evidence for the use of modafinil in the treatment of attention deficit/hyperactivity disorder (ADHD). DATA SOURCES: A MEDLINE search (January 1990-May 2006) was conducted using MeSH terms ADHD and modafinil. The search was limited to English-language articles on clinical trials in humans. The Cochrane Database was also searched. STUDY SELECTION AND DATA EXTRACTION: The literature search yielded 4 randomized clinical trials. DATA SYNTHESIS: The use of modafinil in the treatment of ADHD is associated with significant improvements in primary outcome measures used to assess the status of patients diagnosed with ADHD. Several aspects of cognitive function in ADHD patients also appear to improve following modafinil treatment. Modafinil shows a favorable adverse effect profile. Insomnia and headache were the most common adverse effects, seen in approximately 20% of treated individuals. However, it has not been demonstrated that the beneficial effects of modafinil are maintained with chronic administration. CONCLUSIONS: Modafinil may be a viable option for some patients in the treatment of ADHD, perhaps those for whom standard ADHD therapies have not been successful or tolerated. There remains a need for additional large, long-term studies using flexible titration methods to optimize the dose of modafinil to establish safety and efficacy, as well as head-to-head comparisons between modafinil and both long- and short-acting stimulants to determine the role of modafinil in the treatment of ADHD. [References: 13]

INCLUDED

25. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. J Clin Psychiatry. 2006;67(4):554-66. Cited in: Ovid MEDLINE(R) at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16669720. Accessed June 23, 2015.

AB BACKGROUND: Modafinil is a novel wake-promoting agent that has U.S. Food and Drug Administration approval for narcolepsy and shift work sleep disorder and as adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Modafinil has a novel mechanism and is theorized to work in a localized manner, utilizing hypocretin, histamine, epinephrine, gamma-aminobutyric acid, and glutamate. It is a well-tolerated medication with low propensity for abuse and is frequently used for off-label indications. The objective of this study was to systematically review the available evidence supporting the clinical use of modafinil. DATA SOURCES: The search term modafinil OR Provigil was searched on PubMed. Selected articles were mined for further potential sources of data. Abstracts from major scientific conferences were reviewed. Lastly, the manufacturer of modafinil in the United States was asked to provide all publications, abstracts, and unpublished data regarding studies of modafinil. DATA SYNTHESIS: There have been 33 double-blind, placebo-controlled trials of modafinil. Additionally, numerous smaller studies have been performed, and case reports of modafinil's use abound in the literature. CONCLUSIONS: Modafinil is a promising drug with a large potential for many uses in psychiatry and general medicine. Treating daytime sleepiness is complex, and determining the precise nature of the sleep disorder is vital. Modafinil may be an effective agent in many sleep conditions. To date, the strongest evidence among off-label uses exists for the use of modafinil in attention-deficit disorder, postanesthetic sedation, and cocaine dependence and withdrawal and as an adjunct to antidepressants for depression. [References: 146]

EXCLUDED: OUTCOMES

Modafinil / Armodafinil

Goal(s):

- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit OR doses above those in Table 2.

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57)

Covered Alternatives:

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

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)
Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Depression augmentation (unipolar or bipolar)	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
CA-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
MS-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Drug-related fatigue	Not FDA approved; insufficient evidence	Not FDA approved;

Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome)	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
ADHD	Not FDA approved; Insufficient evidence	Not FDA approved; insufficient evidence
Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum Daily Dose
armodafinil	18 years	250 mg
modafinil	18 years	200 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a funded diagnosis? Non-funded diagnoses: - Shift work disorder (ICD9: 327.30-327.8) - Unspecified hypersomnia (ICD9: 780.54)	Yes: Go to #3	No: Pass to RPh; Deny, not funded by OHP
3. Will prescriber consider a preferred alternative?	Yes: Inform prescriber of options (eg, preferred methylphenidate or other CNS stimulant)	No: Go to #4
4. Is the request for continuation of current therapy?	Yes: Pass to RPh; Go to #12	No: Go to #5

Approval Criteria		
5. Is the prescribed daily dose higher than recommended in Table 2?	Yes: Pass to RPh; Deny for medical appropriateness.	No: Go to #6
6. Is diagnosis narcolepsy or obstructive sleep apnea (ICD9: 347.00-347.01; 327.20-327.21; 327.23-327.29; 780.51; 780.53; 780.57) AND Is the drug prescribed by, or in consultation with, a sleep specialist or neurologist?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #7
7. Is the request for armodafinil?	Yes: Pass to RPh; Deny for medical appropriateness. There is insufficient evidence for any off-label use.	No: Go to #8
8. Is the diagnosis unipolar or bipolar depression?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #9
9. Is the diagnosis MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	Yes: Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #10
10. Is the diagnosis ADHD?	Yes: Pass to RPh; Deny for medical appropriateness. There is insufficient evidence for benefit for ADHD. See available options at www.orpdl.org/drugs/	No: Go to #11

24

Approval Criteria
11. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness or fatigue as a result of other conditions is currently insufficient and should be denied for “medical appropriateness”. • Evidence to support cognition enhancement is insufficient and should be denied for “medical appropriateness”. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.
12. Continuation of therapy requires submission of documented evidence of clinical benefit and tolerability (faxed copy or equivalent). The same clinical measure (eg, Epworth score, Brief Fatigue Inventory, or other validated measure) used to diagnose fatigue or depression is recommended to document clinical benefit. • Approve up to 12 months with chart documentation of positive response. • Deny for “medical appropriateness” in absence of documented benefit.

25

P&T / DUR Review: *07/15 (kk)*
Implementation: *TBD*

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

Drug Use Evaluation: Tetracycline Antibiotics

Research Questions:

1. What are the most common durations of therapy, measured by both treatment duration and unique pharmacy claims, of tetracycline antibiotics?
2. What is the prevalence of members receiving short- (14 days or less), medium- (15-89 days) and long- (90 days or longer) term treatment with tetracyclines?
3. What is the prevalence and associated costs of members receiving tetracycline treatment of unfunded conditions?

Conclusions:

- 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 tetracyclines was identified, 86% of members received only short-term treatment.

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 are indicated for a variety of infections, including sexually transmitted diseases, respiratory tract infections, urinary tract infections, soft tissue infections, acne vulgaris, rosacea, as well as a variety of less common such as anthrax.[1–6] Therapy exceeding 21 days is rarely indicated for conditions other than acne and rosacea, with the most common durations for therapy limited to a 14 day course. Rosacea and most mild forms of acne fall below the current Oregon Health Plan (OHP) funded line on the Prioritized List of Health services.[7] The only funded form of acne is acne conglobata in the presence of recurrent abscesses or communicating sinuses.

Methods:

The study included patients with a paid (FFS) pharmacy claim for a qualifying tetracycline antibotic between January 1, 2014 and June 30, 2014. A complete list of qualifying appears in Table A1 of Appendix A. An Index Event (IE) was defined as the first paid FFS claim qualifying claims during the study period. All claims for tetracycline antibiotics for 6 months after the IE were included. Patients with dual Medicare and Medicaid coverage were excluded. Patients enrolled in a Coordinated Care Organization (CCO) within 6 months after the IE were excluded. Patients with more than a 25% gap in eligibility within 6 months after the IE were excluded.

Table 1 - Demographics

	#	%
Total	591	100.0%
Age		
0-11	3	0.5%
12-17	69	11.7%
18-30	218	36.9%
31-50	191	32.3%
51-64	108	18.3%
Over 65	2	0.3%
Gender		
F	380	64.3%
M	211	35.7%

ICD9 codes for the most likely indications for tetracyclines are included in table A2 of Appendix A. Diagnoses associated with medical claims ranging from 30 days before the IE to 7 days after the IE were used to identify likely indications for acute treatment. Diagnoses of chronic conditions (e.g. acne, rosacea) were included for all diagnoses from July 1, 2013 to December 31, 2014. This broad strategy was used in recognition that patients with stable, chronic conditions may not be seen more than once per year. Patients were categorized as having at least one funded condition (funded), at least one medical claim with a qualifying, unfunded diagnosis (unfunded), or no claims for qualifying diagnoses (no diagnosis available). Patients were also categorized based on the total number of days covered by a tetracycline antibiotic: short (14 days or less), medium (15-89) and long (90 days or longer).

Results:

Initial screening identified 927 members with qualifying tetracycline claims. Of these 10 were excluded due to dual Medicare/Medicaid coverage, 22 members were excluded due to gaps in eligibility, and 304 were excluded based on enrollment in a CCO. The basic demographics of the remaining 591 members appear in Table 1. A minority of members (n=236,40%) had a least one medical claim identified for a condition that would be an expected indication for a tetracycline antibiotic (Table 2). Of these, 165 had claims only for unfunded conditions. A small proportion (15%) of members received long term therapy (Table 3). A single member with claims for funded conditions received long term tetracycline therapy, while 86% of members with funded conditions received short term therapy (Table 3).

Table 2 – Prevalence of Diagnosis Information for Tetracycline Antibiotics

	Members		Amount Paid	
Diagnosis Funding Status	#	%	$	%
Funded	71	12.0%	$ 4,620	7.0%
No Diagnosis Available	355	60.1%	$ 32,636	49.7%
Unfunded	165	27.9%	$ 28,439	43.3%
Total	591	100.0%	$ 65,696	100.0%

Table 3 – Funded Status and Duration of Tetracycline Therapy

Duration of Therapy	Funded		Unfunded		No Diagnosis Available		Total Unique Members	
	#	%	#	%	#	%	#	%
Short	61	86%	62	38%	212	60%	335	57%
Medium	9	13%	65	39%	93	26%	167	28%
Long	1	1%	38	23%	50	14%	89	15%
Grand Total	71	100%	165	100%	355	100%	591	100%

Members receiving three or fewer prescriptions had an average duration of therapy of 24 days or less (Table 4). With one exception, the average prescription length for members with more than 3 claims had an average prescription duration of 27 days or more.

Table 4 – Total Claims Per Member and Average Day Supply per Claim

Total Claims	Members		Average Days Supply
	#	%	
1	409	69.2%	13
2	77	13.0%	20
3	36	6.1%	24
4	13	2.2%	28
5	20	3.4%	27
6	20	3.4%	29
7	15	2.5%	28
8	1	0.2%	10

Limitations:

The intended indications for long term therapy are unclear from the available claims data. Only 45% of members on long term therapy had diagnosis data available. In all but one case, the conditions were unfunded. Members receiving between 4 and 7 prescriptions have durations of therapy consistent with chronic therapy (average 27-29 days). Based on the literature, the most common indications for chronic tetracycline use are unfunded dermatologic conditions (e.g. Acne, Rosacea, see Table A2). The precision and specificity of time periods used to identify potential diagnosis information have not been validated, raising the possibility of incorrect characterizations of the conditions being treated. Time related effects, such as seasonal variations in community acquired pneumonia and recent increases in the rates of sexually transmitted diseases were not considered.

References:

1. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep Cent Dis Control*. 2010;59(RR-12):1-110.

2. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61(31):590-594.

3. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2011;53(7):e25-e76. doi:10.1093/cid/cir531.

4. 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.

5. 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.

6. Kayabas U, Karahocagil MK, Ozkurt Z, et al. Naturally Occurring Cutaneous Anthrax: Antibiotic Treatment and Outcome. *Chemotherapy*. 2012;58(1):34-43.

7. Oregon Health Policy and Research Current Prioritized List of Health Services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed June 1, 2015.

Appendix A

Table A1 – Study Eligible Tetracyclines

GSN	Generic Name	Drug Form
009213	DEMECLOCYCLINE HCL	TABLET
009214	DEMECLOCYCLINE HCL	TABLET
009217	DOXYCYCLINE CALCIUM	SYRUP
009218	DOXYCYCLINE HYCLATE	CAPSULE
009219	DOXYCYCLINE HYCLATE	CAPSULE
043362	DOXYCYCLINE HYCLATE	CAPSULE
049446	DOXYCYCLINE HYCLATE	CAPSULE DR
009220	DOXYCYCLINE HYCLATE	CAPSULE DR
009223	DOXYCYCLINE HYCLATE	TABLET
048077	DOXYCYCLINE HYCLATE	TABLET
072633	DOXYCYCLINE HYCLATE	TABLET
072634	DOXYCYCLINE HYCLATE	TABLET
059573	DOXYCYCLINE HYCLATE	TABLET DR
059574	DOXYCYCLINE HYCLATE	TABLET DR
064119	DOXYCYCLINE HYCLATE	TABLET DR
070917	DOXYCYCLINE HYCLATE	TABLET DR
060942	DOXYCYCLINE MONOHYDRATE	CAP IR DR
062496	DOXYCYCLINE MONOHYDRATE	CAPSULE
063058	DOXYCYCLINE MONOHYDRATE	CAPSULE
015943	DOXYCYCLINE MONOHYDRATE	CAPSULE
016815	DOXYCYCLINE MONOHYDRATE	CAPSULE
009225	DOXYCYCLINE MONOHYDRATE	SUSP RECON
027050	DOXYCYCLINE MONOHYDRATE	TABLET
036747	DOXYCYCLINE MONOHYDRATE	TABLET
051756	DOXYCYCLINE MONOHYDRATE	TABLET
059845	DOXYCYCLINE MONOHYDRATE	TABLET
042778	MINOCYCLINE HCL	CAPSULE
009226	MINOCYCLINE HCL	CAPSULE
009227	MINOCYCLINE HCL	CAPSULE
009229	MINOCYCLINE HCL	ORAL SUSP
060730	MINOCYCLINE HCL	TAB ER 24H
060731	MINOCYCLINE HCL	TAB ER 24H
060732	MINOCYCLINE HCL	TAB ER 24H
065433	MINOCYCLINE HCL	TAB ER 24H
065434	MINOCYCLINE HCL	TAB ER 24H
066683	MINOCYCLINE HCL	TAB ER 24H
066684	MINOCYCLINE HCL	TAB ER 24H
066685	MINOCYCLINE HCL	TAB ER 24H
009230	MINOCYCLINE HCL	TABLET
009231	MINOCYCLINE HCL	TABLET
052057	MINOCYCLINE HCL	TABLET
009189	TETRACYCLINE HCL	CAPSULE
009190	TETRACYCLINE HCL	CAPSULE
009195	TETRACYCLINE HCL	ORAL SUSP
009196	TETRACYCLINE HCL	TABLET
009197	TETRACYCLINE HCL	TABLET

Table A2 – Diagnosis Codes

ICD9	Description	Line	Chronic
020	Plague	N/A	0
0200	Bubonic plague	210	0
0201	Cellulocutaneous plague	210	0
0202	Septicemic plague	210	0
0203	Primary pneumonic plague	210	0
0204	Secondary pneumonic plague	210	0
0205	Pneumonic plague, unspecified	210	0
0208	Other specified types of plague	210	0
0209	Plague, unspecified	210	0
022	Anthrax	N/A	0
0220	Cutaneous anthrax	210	0
0221	Pulmonary anthrax	210	0
0222	Gastrointestinal anthrax	210	0
0223	Anthrax septicemia	210	0
0228	Other specified manifestations of anthrax	210	0
0229	Anthrax, unspecified	210	0
077	Oth diseases conjunctiva due viruses&chlamydiae	N/A	0
0779	Unspec dz conjunctiva due viruses&chlamydiae	N/A	0
07798	Unspecified diseases of conjunctiva due to chlamydiae	171	0
07799	Unspecified diseases of conjunctiva due to viruses	641	0
078	Other diseases due to viruses and chlamydiae	N/A	0
0788	Other specified diseases due viruses&chlamydiae	N/A	0
07888	Other specified diseases due to chlamydiae	623	0
08881	Lyme Disease	271	0
090	Congenital syphilis	N/A	0
0900	Early congenital syphilis, symptomatic	16	0
0901	Early congenital syphilis, latent	16	0
0902	Early congenital syphilis, unspecified	16	0
0903	Syphilitic interstitial keratitis	16	0
0904	Juvenile neurosyphilis	N/A	0
09041	Congenital syphilitic encephalitis	16	0
09042	Congenital syphilitic meningitis	16	0
09049	Other juvenile neurosyphilis	16	0
0905	Other late congenital syphilis, symptomatic	16	0
0906	Late congenital syphilis, latent	16	0
0907	Late congenital syphilis, unspecified	16	0
0909	Congenital syphilis, unspecified	16	0
091	Early syphilis, symptomatic	N/A	0
0910	Genital syphilis (primary)	42	0
0911	Primary anal syphilis	42	0
0912	Other primary syphilis	42	0
0913	Secondary syphilis of skin or mucous membranes	42	0
0914	Adenopathy due to secondary syphilis	42	0
0915	Early syphilis uveitis due to secondary syphilis	N/A	0
09150	Syphilitic uveitis, unspecified	42	0
09151	Syphilitic chorioretinitis (secondary)	42	0
09152	Syphilitic iridocyclitis (secondary)	42	0
0916	Early syphilis sec syphilis of viscera and bone	N/A	0
09161	Secondary syphilitic periostitis	42	0
09162	Secondary syphilitic hepatitis	42	0
09169	Secondary syphilis of other viscera	42	0
0917	Secondary syphilis, relapse	42	0
0918	Early syphilis other forms of secondary syphilis	N/A	0
09181	Acute syphilitic meningitis (secondary)	42	0
09182	Syphilitic alopecia	42	0
09189	Other forms of secondary syphilis	42	0
0919	Unspecified secondary syphilis	42	0
092	Early syphilis, latent	N/A	0
0920	Early syphilis, latent, serological relapse after treatment	42	0
0929	Early syphilis, latent, unspecified	42	0
093	Cardiovascular syphilis	N/A	0
0930	Aneurysm of aorta, specified as syphilitic	42	0
0931	Syphilitic aortitis	42	0
0932	Syphilitic endocarditis	N/A	0
0938	Other specified cardiovascular syphilis	N/A	0
09389	Other specified cardiovascular syphilis	42	0
0939	Cardiovascular syphilis, unspecified	42	0
094	Neurosyphilis	N/A	0
0943	Asymptomatic neurosyphilis	386	0
0948	Other specified neurosyphilis	N/A	0
095	Other forms of late syphilis with symptoms	N/A	0
0950	Syphilitic episcleritis	386	0
0951	Syphilis of lung	386	0
0952	Syphilitic peritonitis	386	0
0953	Syphilis of liver	386	0
0954	Syphilis of kidney	386	0
0955	Syphilis of bone	386	0
0956	Syphilis of muscle	386	0
0957	Syphilis of synovium, tendon, and bursa	386	0
0958	Other specified forms of late symptomatic syphilis	386	0
0959	Late symptomatic syphilis, unspecified	386	0
096	Late syphilis, latent	386	0
097	Other and unspecified syphilis	N/A	0
0970	Late syphilis, unspecified	386	0
0971	Latent syphilis, unspecified	386	0
0979	Syphilis, unspecified	386	0
098	Gonococcal infections	N/A	0
0980	Gonococcal infection (acute) of lower genitourinary tract	56	0
0981	Gonococcal infection upper genitourinary tract	N/A	0
09810	Gonococcal infection (acute) of upper genitourinary tract, site unspecified	56	0
09811	Gonococcal cystitis (acute)	56	0
09812	Gonococcal prostatitis (acute)	56	0
09813	Gonococcal epididymo-orchitis (acute)	56	0
09814	Gonococcal seminal vesiculitis (acute)	56	0
09815	Gonococcal cervicitis (acute)	56	0
09816	Gonococcal endometritis (acute)	56	0
09817	Gonococcal salpingitis, specified as acute	56	0
09819	Other gonococcal infection (acute) of upper genitourinary tract	56	0
0982	Gonococcal infection, chronic, of lower genitourinary tract	56	0
0983	Gonococcal infections chronic upper gu tract	N/A	0
09830	Chronic gonococcal infection of upper genitourinary tract, site unspecified	56	0
09831	Gonococcal cystitis, chronic	56	0
09832	Gonococcal prostatitis, chronic	56	0
09833	Gonococcal epididymo-orchitis, chronic	56	0
09834	Gonococcal seminal vesiculitis, chronic	56	0
09835	Gonococcal cervicitis, chronic	56	0
09836	Gonococcal endometritis, chronic	56	0
09837	Gonococcal salpingitis (chronic)	56	0
09839	Other chronic gonococcal infection of upper genitourinary tract	56	0
0984	Gonococcal infection of eye	N/A	0
09840	Gonococcal conjunctivitis (neonatorum)	171	0
09841	Gonococcal iridocyclitis	171	0
09842	Gonococcal endophthalmia	171	0

ICD9	Description	Line	Chronic
09843	Gonococcal keratitis	171	0
09849	Other gonococcal infection of eye	171	0
0985	Gonococcal infection of joint	N/A	0
09850	Gonococcal arthritis	56	0
09851	Gonococcal synovitis and tenosynovitis	56	0
09852	Gonococcal bursitis	56	0
09853	Gonococcal spondylitis	56	0
09859	Other gonococcal infection of joint	56	0
0986	Gonococcal infection of pharynx	56	0
0987	Gonococcal infection of anus and rectum	56	0
0988	Gonococcal infection of other specified sites	N/A	0
09881	Gonococcal keratosis (blennorrhagica)	56	0
09882	Gonococcal meningitis	56	0
09883	Gonococcal pericarditis	56	0
09884	Gonococcal endocarditis	56	0
09885	Other gonococcal heart disease	56	0
09886	Gonococcal peritonitis	56	0
09889	Gonococcal infection of other specified sites	186	0
099	Other venereal diseases	N/A	0
0990	Chancroid	56	0
0991	Lymphogranuloma venereum	56	0
0992	Granuloma inguinale	56	0
0993	Reiter's disease	50	0
0994	Other nongonococcal urethritis	N/A	0
09940	Other nongonococcal urethritis, unspecified	56	0
09941	Other nongonococcal urethritis, chlamydia trachomatis	56	0
09949	Other nongonococcal urethritis, other specified organism	56	0
0995	Oth venereal diseases due chlamydia trachomatis	N/A	0
09950	Other venereal diseases due to chlamydia trachomatis, unspecified site	56	0
09951	Other venereal diseases due to chlamydia trachomatis, pharynx	56	0
09952	Other venereal diseases due to chlamydia trachomatis, anus and rectum	56	0
09953	Other venereal diseases due to chlamydia trachomatis, lower genitourinary sites	56	0
09954	Other venereal diseases due to chlamydia trachomatis, other genitourinary sites	56	0
09955	Other venereal diseases due to chlamydia trachomatis, unspecified genitourinary site	56	0
09956	Other venereal diseases due to chlamydia trachomatis, peritoneum	56	0
09959	Other venereal diseases due to chlamydia trachomatis, other specified site	56	0
0998	Other specified venereal diseases	56	0
0999	Venereal disease, unspecified	56	0
102	Yaws	N/A	0
1020	Initial lesions of yaws	276	0
1021	Multiple papillomata due to yaws and wet crab yaws	276	0
1022	Other early skin lesions of yaws	276	0
1023	Hyperkeratosis due to yaws	276	0
1024	Gummata and ulcers due to yaws	276	0
1025	Gangosa	276	0
1026	Bone and joint lesions due to yaws	276	0
1027	Other manifestations of yaws	276	0
1028	Latent yaws	276	0
1029	Yaws, unspecified	276	0
480	Viral pneumonia	N/A	0
4800	Pneumonia due to adenovirus	623	0
4801	Pneumonia due to respiratory syncytial virus	623	0
4802	Pneumonia due to parainfluenza virus	623	0
4803	Pneumonia due to SARS-associated coronavirus	623	0
4808	Pneumonia due to other virus not elsewhere classified	623	0
4809	Viral pneumonia, unspecified	623	0
481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]	208	0
482	Other bacterial pneumonia	N/A	0
4820	Pneumonia due to Klebsiella pneumoniae	208	0
4821	Pneumonia due to Pseudomonas	208	0
4822	Pneumonia due to Hemophilus influenzae [H. influenzae]	208	0
4823	Pneumonia due to streptococcus	N/A	0
48230	Pneumonia due to Streptococcus, unspecified	208	0
48231	Pneumonia due to Streptococcus, group A	208	0
48232	Pneumonia due to Streptococcus, group B	208	0
48239	Pneumonia due to other Streptococcus	208	0
4824	Pneumonia due to staphylococcus	N/A	0
48240	Pneumonia due to Staphylococcus, unspecified	208	0
48241	Methicillin susceptible pneumonia due to Staphylococcus aureus	208	0
48242	Methicillin resistant pneumonia due to Staphylococcus aureus	208	0
48249	Other Staphylococcus pneumonia	208	0
4828	Pneumonia due to other specified bacteria	N/A	0
48281	Pneumonia due to anaerobes	208	0
48282	Pneumonia due to escherichia coli [E. coli]	208	0
48283	Pneumonia due to other gram-negative bacteria	208	0
48284	Pneumonia due to Legionnaires disease	208	0
48289	Pneumonia due to other specified bacteria	208	0
4829	Bacterial pneumonia, unspecified	208	0
483	Pneumonia due to other specified organism	N/A	0
4830	Pneumonia due to mycoplasma pneumoniae	208	0
4831	Pneumonia due to chlamydia	208	0
4838	Pneumonia due to other specified organism	208	0
484	Pneumonia infectious diseases classified elsw	N/A	0
4841	Pneumonia in cytomegalic inclusion disease	208	0
4843	Pneumonia in whooping cough	208	0
4845	Pneumonia in anthrax	208	0
4846	Pneumonia in aspergillosis	208	0
4847	Pneumonia in other systemic mycoses	208	0
4848	Pneumonia in other infectious diseases classified elsewhere	208	0
485	Bronchopneumonia, organism unspecified	208	0
486	Pneumonia, organism unspecified	208	0
487	Influenza	N/A	0
4870	Influenza with pneumonia	403	0
4871	Influenza with other respiratory manifestations	403	0
4878	Influenza with other manifestations	403	0
488	Influenza d/t certn identified influenza viruses	N/A	0
4880	Influenza due to identifid avian influenza virus	N/A	0
48801	Influenza due to identified avian influenza virus with pneumonia	403	0
48802	Influenza due to identified avian influenza virus with other respiratory manifestations	403	0
48809	Influenza due to identified avian influenza virus with other manifestations	403	0
4881	Influenza due to id novel h1n1 influenza virus	N/A	0
48811	Influenza due to identified 2009 H1N1 influenza virus with pneumonia	403	0
48812	Influenza due to identified 2009 H1N1 influenza virus with other respiratory manifestations	403	0
48819	Influenza due to identified 2009 H1N1	403	0

ICD9	Description	Line	Chronic
	influenza virus with other manifestations		
48881	Influenza due to identified novel influenza A virus with pneumonia	403	0
48882	Influenza due to identified novel influenza A virus with other respiratory manifestations	403	0
48889	Influenza due to identified novel influenza A virus with other manifestations	403	0
530	Diseases of esophagus	N/A	1
5300	Achalasia and cardiospasm	382	1
5301	Esophagitis	N/A	1
53010	Esophagitis, unspecified	519	1
53011	Reflux esophagitis	519	1
53012	Acute esophagitis	519	1
53013	Eosinophilic esophagitis	519	1
53019	Other esophagitis	519	1
5302	Ulcer of esophagus	N/A	1
53020	Ulcer of esophagus without bleeding	519	1
53021	Ulcer of esophagus with bleeding	519	1
5303	Stricture and stenosis of esophagus	382	1
5304	Perforation of esophagus	230	1
5305	Dyskinesia of esophagus	382	1
5306	Diverticulum of esophagus, acquired	519	1
5307	Gastroesophageal laceration-hemorrhage syndrome	60	1
5308	Other specified disorders of esophagus	N/A	1
53081	Esophageal reflux	519	1
53083	Esophageal leukoplakia	519	1
53084	Tracheoesophageal fistula	68	1
53085	Barrett's esophagus	519	1
53086	Infection of esophagostomy	427	1
53087	Mechanical complication of esophagostomy	427	1
53089	Other specified disorders of esophagus	519	1
5309	Unspecified disorder of esophagus	519	1
556	Ulcerative colitis	N/A	1
5560	Ulcerative (chronic) enterocolitis	32	1
5561	Ulcerative (chronic) ileocolitis	32	1
5562	Ulcerative (chronic) proctitis	32	1
5563	Ulcerative (chronic) proctosigmoiditis	32	1
5564	Pseudopolyposis of colon	32	1
5565	Left-sided ulcerative (chronic) colitis	32	1
5566	Universal ulcerative (chronic) colitis	32	1
5568	Other ulcerative colitis	32	1
5569	Ulcerative colitis, unspecified	32	1
590	Infections of kidney	N/A	0
5900	Chronic pyelonephritis	N/A	0
5901	Acute pyelonephritis	N/A	0
59010	Acute pyelonephritis without lesion of renal medullary necrosis	51	0
59011	Acute pyelonephritis with lesion of renal medullary necrosis	51	0
5902	Renal and perinephric abscess	51	0
5903	Pyeloureteritis cystica	51	0
5908	Oth pyelonephritis/pyonephrof not spec acut/chrn	N/A	0
59080	Pyelonephritis, unspecified	278	0
59081	Pyelitis or pyelonephritis in diseases classified elsewhere	N/A	0
5909	Infection of kidney, unspecified	278	0
591	Hydronephrosis	184	0
592	Calculus of kidney and ureter	N/A	0
5921	Calculus of ureter	355	0
5929	Urinary calculus, unspecified	355	0
593	Other disorders of kidney and ureter	N/A	0
5930	Nephroptosis	667	0
5931	Hypertrophy of kidney	667	0
5932	Cyst of kidney, acquired	561	0
5933	Stricture or kinking of ureter	184	0
5934	Other ureteric obstruction	184	0
5935	Hydroureter	184	0
5936	Postural proteinuria	667	0
5937	Vesicoureteral reflux	N/A	0
5938	Other specified disorders of kidney and ureter	N/A	0
59382	Ureteral fistula	234	0
5939	Unspecified disorder of kidney and ureter	343	0
594	Calculus of lower urinary tract	N/A	0
5940	Calculus in diverticulum of bladder	355	0
5941	Other calculus in bladder	355	0
5942	Calculus in urethra	355	0
5948	Other lower urinary tract calculus	355	0
5949	Calculus of lower urinary tract, unspecified	355	0
595	Cystitis	N/A	0
5950	Acute cystitis	278	0
5951	Chronic interstitial cystitis	331	0
5952	Other chronic cystitis	278	0
5953	Trigonitis	278	0
5954	Cystitis in diseases classified elsewhere	278	0
5958	Other specified types of cystitis	N/A	0
59581	Cystitis cystica	278	0
59582	Irradiation cystitis	278	0
59589	Other specified types of cystitis	278	0
5959	Cystitis, unspecified	278	0
596	Other disorders of bladder	N/A	0
5960	Bladder neck obstruction	331	0
5961	Intestinovesical fistula	234	0
5962	Vesical fistula, not elsewhere classified	234	0
5963	Diverticulum of bladder	331	0
5965	Other functional disorders of bladder	N/A	0
59652	Low bladder compliance	331	0
59655	Detrusor sphincter dyssynergia	331	0
59659	Other functional disorder of bladder	331	0
5966	Rupture of bladder, nontraumatic	84	0
5967	Hemorrhage into bladder wall	331	0
5968	Other specified disorder of bladder	N/A	0
59681	Infection of cystostomy	331	0
59682	Mechanical complication of cystostomy	331	0
59683	Other complication of cystostomy	331	0
59689	Other specified disorders of bladder	331	0
5969	Unspecified disorder of bladder	331	0
597	Urethritis not sexually trnsmtted&urethral synd	N/A	0
5970	Urethral abscess	209	0
5978	Other urethritis	N/A	0
59780	Urethritis, unspecified	586	0
59781	Urethral syndrome NOS	586	0
59789	Other urethritis	586	0
598	Urethral stricture	N/A	0
5980	Urethral stricture due to infection	N/A	0
59800	Urethral stricture due to unspecified infection	331	0
59801	Urethral stricture due to infective diseases classified elsewhere	331	0
5981	Traumatic urethral stricture	331	0
5982	Postoperative urethral stricture	331	0
5988	Other specified causes of urethral stricture	331	0
5989	Urethral stricture, unspecified	331	0
599	Other disorders of urethra and urinary tract	N/A	0
5990	Urinary tract infection, site not specified	278	0
5991	Urethral fistula	434	0
5992	Urethral diverticulum	434	0

ICD9	Description	Line	Chronic
5993	Urethral caruncle	586	0
5993	Urethral caruncle	598	0
5994	Urethral false passage	586	0
5995	Prolapsed urethral mucosa	586	0
5995	Prolapsed urethral mucosa	598	0
5996	Urinary obstruction	N/A	0
59960	Urinary obstruction, unspecified	576	0
59969	Urinary obstruction, not elsewhere classified	576	0
5997	Hematuria	N/A	0
59971	Gross hematuria	N/A	0
59972	Microscopic hematuria	N/A	0
5998	Other specified disorder urethra&urinary tract	N/A	0
59981	Urethral hypermobility	459	0
59982	Intrinsic (urethral) sphincter deficiency [ISD]	331	0
59983	Urethral instability	331	0
59984	Other specified disorders of urethra	331	0
59989	Other specified disorders of urinary tract	331	0
5999	Unspecified disorder of urethra and urinary tract	586	0
614	Inflam dz of ovary-tube-pelvic tissue-peritoneum	N/A	0
6140	Acute salpingitis and oophoritis	55	0
6141	Chronic salpingitis and oophoritis	536	0
6142	Salpingitis and oophoritis not specified as acute, subacute, or chronic	536	0
6143	Acute parametritis and pelvic cellulitis	55	0
6144	Chronic or unspecified parametritis and pelvic cellulitis	536	0
6145	Acute or unspecified pelvic peritonitis, female	536	0
6146	Pelvic peritoneal adhesions, female (postoperative) (postinfection)	536	0
6147	Other chronic pelvic peritonitis, female	536	0
6148	Other specified inflammatory disease of female pelvic organs and tissues	55	0
6149	Unspecified inflammatory disease of female pelvic organs and tissues	55	0
647	Infect-parasitic maternal cce-complicating pc/p	N/A	0
6470	Mtrn syphilis comp pg childbirth/the puerperium	N/A	0
64700	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64701	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64702	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64703	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64704	Syphilis of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication	1	0
6471	Mtrn gonorrhea comp pg childbirth/the puerperium	N/A	0
64710	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64711	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64712	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64713	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64714	Gonorrhea of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication	1	0
6472	Oth maternal venereal diseases-complicating pc/p	N/A	0
64720	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64721	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64722	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64723	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64724	Other venereal diseases of mother, complicating pregnancy, childbirth, or the puerperium,postpartum condition or complication	1	0
6473	Mtrn tb comp pg childbirth/the puerperium	N/A	0
64730	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	1	0
64731	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition	1	0
64732	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	1	0
64733	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	1	0
64734	Tuberculosis of mother, complicating pregnancy, childbirth, or the puerperium,postpartum condition or complication	1	0
6474	Mtrn malaria comp pg childbirth/the puerperium	N/A	0
64740	Malaria in the mother, unspecified as to episode of care or not applicable	1	0
64741	Malaria in the mother, delivered, with or without mention of antepartum condition	1	0
64742	Malaria in the mother, delivered, with mention of postpartum complication	1	0
64743	Malaria in the mother, antepartum condition or complication	1	0
64744	Malaria in the mother, postpartum condition or complication	1	0
6475	Mtrn rubella comp pg childbirth/the puerperium	N/A	0
64750	Rubella in the mother, unspecified as to episode of care or not applicable	1	0
64751	Rubella in the mother, delivered, with or without mention of antepartum condition	1	0
64752	Rubella in the mother, delivered, with mention of postpartum complication	1	0

ICD9	Description	Line	Chronic
64753	Rubella in the mother, antepartum condition or complication	1	0
64754	Rubella in the mother, postpartum condition or complication	1	0
6476	Oth mtrn virl dz comp pg chldbrth/the puerperium	N/A	0
64760	Other viral diseases in the mother, unspecified as to episode of care or not applicable	1	0
64761	Other viral diseases in the mother, delivered, with or without mention of antepartum condition	1	0
64762	Other viral diseases in the mother, delivered, with mention of postpartum complication	1	0
64763	Other viral diseases in the mother, antepartum condition or complication	1	0
64764	Other viral diseases in the mother, postpartum condition or complication	1	0
6478	Oth maternal infectious-parasitic dz-compli pc/p	N/A	0
64780	Other specified infectious and parasitic diseases of mother, unspecified as to episode of care or not applicable	1	0
64781	Other specified infectious and parasitic diseases of mother, delivered, with or without mention of antepartum condition	1	0
64782	Other specified infectious and parasitic diseases of mother, delivered, with mention of postpartum complication	1	0
64783	Other specified infectious and parasitic diseases of mother, antepartum condition or complication	1	0
64784	Other specified infectious and parasitic diseases of mother, postpartum condition or complication	1	0
6479	Uns maternal infection/infestation-compli pc/p	N/A	0
64790	Unspecified infection or infestation of mother, unspecified as to episode of care or not applicable	1	0
64791	Unspecified infection or infestation of mother, delivered, with or without mention of antepartum condition	1	0
64792	Unspecified infection or infestation of mother, delivered, with mention of postpartum complication	1	0
64793	Unspecified infection or infestation of mother, antepartum condition or complication	1	0
64794	Unspecified infection or infestation of mother, postpartum condition or complication	1	0
694	Bullous dermatoses	N/A	1
6940	Dermatitis herpetiformis	216	1
6941	Subcorneal pustular dermatosis	216	1
6942	Juvenile dermatitis herpetiformis	216	1
6943	Impetigo herpetiformis	216	1
6944	Pemphigus	216	1
6945	Pemphigoid	216	1
6946	Benign mucous membrane pemphigoid	N/A	1
69460	Benign mucous membrane pemphigoid without mention of ocular involvement	216	1
69461	Benign mucous membrane pemphigoid with ocular involvement	216	1
6948	Other specified bullous dermatoses	216	1
6949	Unspecified bullous dermatoses	216	1
6953	Rosacea	510	1
706	Diseases of sebaceous glands	N/A	1
7060	Acne varioliformis	528	1
7061	Other acne	528	1
7062	Sebaceous cyst	632	1
7063	Seborrhea	593	1
7068	Other specified diseases of sebaceous glands	665	1
7069	Unspecified disease of sebaceous glands	593	1
7090	Dyschromia	N/A	1
70900	Dyschromia, unspecified	665	1
70901	Vitiligo	665	1
70909	Other dyschromia	665	1
V027	Carrier or suspected carrier of gonorrhea	3	0
V6545	Counseling on other sexually transmitted diseases	3	0
V73	Special scr examination viral&chlamydial dz	N/A	0
V738	Screening oth specific viral&chlamydial diseases	N/A	0
V7388	Special screening examination for other specified chlamydial diseases	3	0
V7389	Special screening examination for other specified viral diseases	3	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

Policy Evaluation: Low Dose Quetiapine Safety Edit

Research Questions:

1. What is the general utilization trend of quetiapine and other mental health drugs since implementation of the clinical prior authorization (PA) in January 2011?
2. What was the ultimate disposition of any encounter to the policy (i.e. not requested, requested and approved, or requested or denied)?
3. How many patients experienced adverse outcomes as a result of the PA?

Conclusions:

- The low dose quetiapine safety edit policy appears successful at limiting off-label prescribing of low dose quetiapine.
- The policy was not associated with increased psychiatric-related harms. However, the high volume of requests and high approval rate of these requests suggest that policy adjustments may be necessary.

Recommendations:

- Implement a step-edit to automatically approve low dose quetiapine prescriptions for:
    - Patients with a claim for a second generation antipsychotic in the past six months;
    - Patients with prior medical claims evidence of schizophrenia or bipolar disorder;
    - Prescriptions identified as being written by a mental health provider when the claims system has this capability.

Background:

Quetiapine (Seroquel®) is a second generation antipsychotic that is FDA approved for the treatment of schizophrenia and bipolar disorder, and as adjunctive use in the treatment of major depressive disorder. Low-doses (<150 mg per day) of quetiapine are prescribed off-label to treat many conditions, including insomnia, anxiety, post-traumatic stress disorder, and dementia.[1] The evidence and safety of off-label use is not typically as strong relative to FDA-approved indications.[2] A recent systematic review update by the Agency for Healthcare Research and Quality found that there is increasing evidence of efficacy in some off-label uses such as dementia but the evidence for the majority of off-label uses is still of low quality or absent.[1]

There has been ongoing concern about the safety of low-dose quetiapine use. Quetiapine is associated with many adverse events such as an increase in cholesterol and triglycerides, glycemic abnormalities, and weight gain. [1,3] Other serious adverse events identified in trials of low dose quetiapine were fatal hepatotoxicity, restless leg syndrome, and akathisia.[4] However, despite these concerns, there has been an increase in off-label prescribing of many second-generation antipsychotics, including quetiapine. As a result the increase in off-label use, many Medicaid programs have restricted the use of low dose quetiapine.[5–10]

A drug use evaluation in 2010 showed 56% of OHP clients with claims for low-dose quetiapine for more than 60 days did not have an FDA approved diagnosis available suggesting the potential for considerable off-label use of quetiapine. Subsequently, the Oregon Medicaid program implemented a safety edit policy to identify patients who were using low-dose quetiapine off-label. All mental health drugs are paid for by the OHP fee-for-service program regardless if patients are enrolled in managed care or not. The goals of this analysis are to evaluate the effects of this policy on quetiapine and other mental drug utilization; to assess for possible harms and identify options to improve the policy.

Methods:

The safety edit for low-dose quetiapine was implemented on January 1, 2011. Claims for prescriptions with a calculated daily dose of less than 150 mg of quetiapine were denied with a message to the pharmacy to notify the prescriber to request an authorization by phone, fax, or electronically. Approval required a diagnosis of an FDA approved indication for quetiapine and a medically appropriate reason for low-dose use. The claims processor adjudicated all requests within 24 hours of receipt allowing all approvals to be paid at the pharmacy. The policy did not "grandfather" (automatically approve payment) for any patients, nor were concurrent quetiapine prescriptions looked for in claims history. This analysis included patients enrolled in the Oregon Medicaid program between January 1, 2009 and December 31, 2013 and that had a minimum of two months continuous Medicaid enrollment before and after an index event. For the policy group, the index event was the earliest date the patient had a low-dose quetiapine claim denied with a message of "PA required" between January 1, 2011 and December 31, 2011

Total utilization was quantified using paid claims per member per month (PMPM) of low dose quetiapine and other potentially substitutable drugs (see Appendix 1). To assess the impact of the PA policy on dose of quetiapine used, we converted filled quetiapine doses to daily dose and categorized these prescriptions into <150 mg doses (low-dose quetiapine) and ≥150 mg doses (lowest therapeutic dose of quetiapine).

Patients were followed longitudinally to assess if an authorization was requested by their prescriber, and the ultimate disposition of any request. Patient demographics, disease severity, and subsequent drug therapy were then characterized by final request disposition (i.e. not requested, requested and approved or requested and denied).

To assess harms, a policy group of patients who had a denied claim for low dose quetiapine claim (the index event) between January 1, 2011 and December 31, 2011 was compared to a historical comparison group including patients who had a paid low-dose quetiapine claim (the index event) between January 1, 2009 and December 31, 2009, and therefore were not affected by the policy. To ensure the groups were independent, patients in the comparison group (2009) were excluded if they were also in the policy group (2011). Patients were excluded if their demographic data (e.g. age, sex or ethnicity) were not available, they were less than 18 or greater than 64 years old at the time of the index event, if they had dual Medicare eligibility, or if they did not have continuous enrollment for 2 months prior to and 2 months after the month of their index event.

The primary outcomes were: a composite of an emergency department or hospitalization due to psychiatric illness within 30 days of the index event; a composite of emergency department or hospital claims due to schizophrenia within 30 days of the index event; a composite of emergency department or hospital claims due to bipolar disorder within 30 days of the index event; and all cause hospitalization and emergency department visits within 30 days of the index event. The analyses were repeated using a 60 day post index event assessment window.

Results:

Figure 1 shows aggregated prescriptions filled per member per month (PMPM) by drug type (see appendix 1 for a list of drugs in each category). After the policy was implemented (January 1, 2011), there appears to be a decrease in all second generation antipsychotics, but no significant changes in other classes.

Figure 1. Aggregated Prescriptions Filled Pmpm By Drug Type.

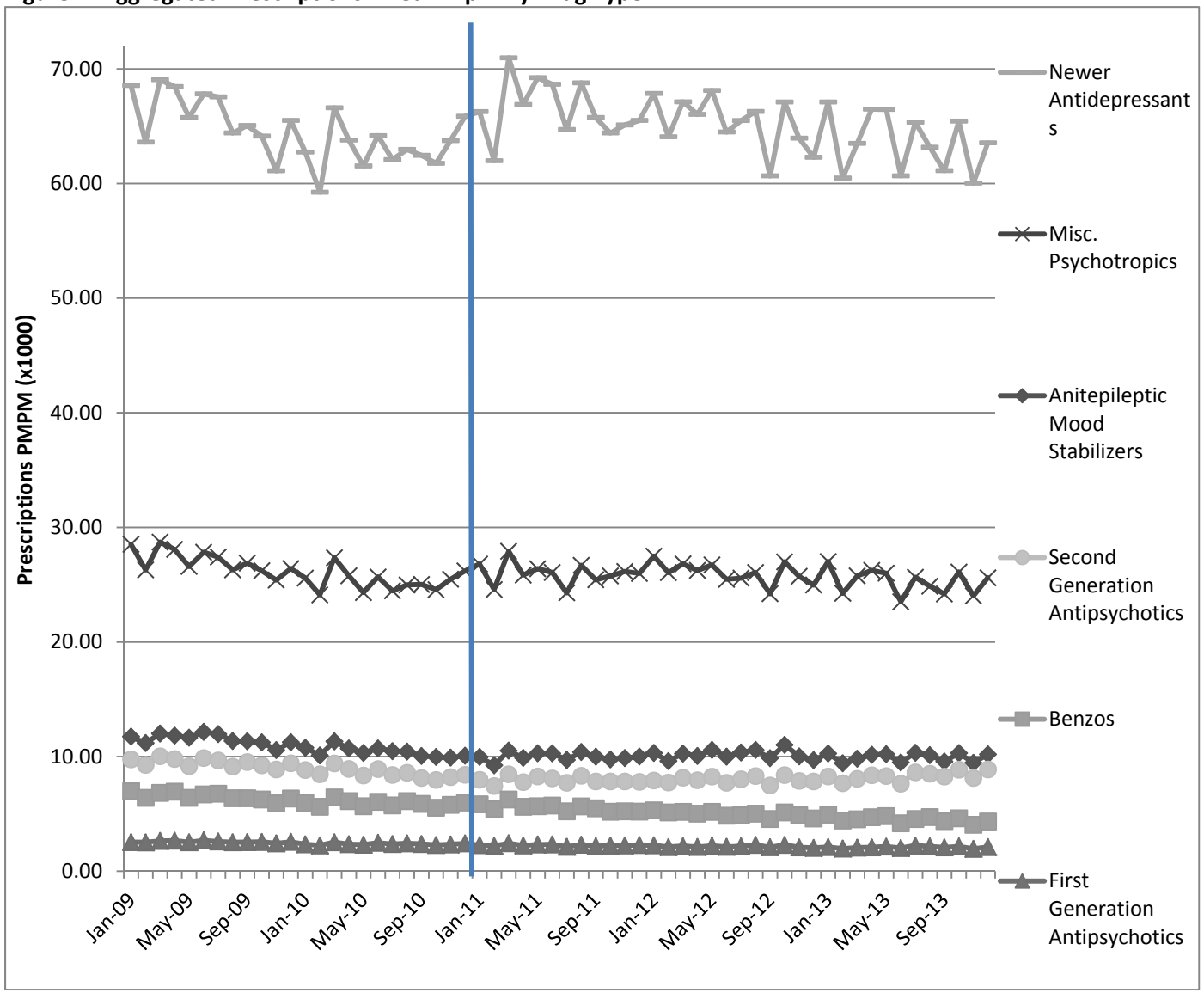
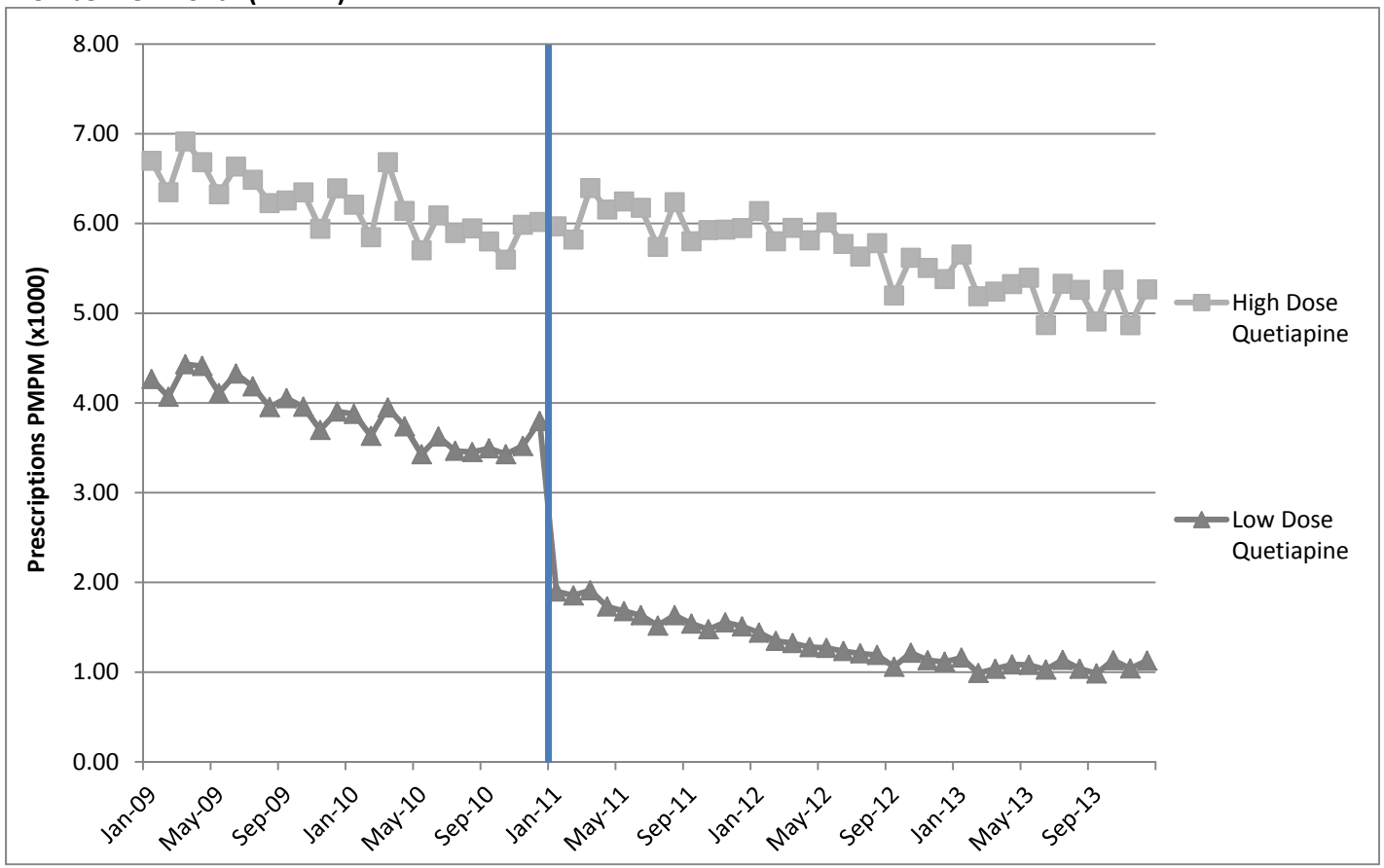


Figure 2 shows aggregated prescriptions filled PMPM for quetiapine, broken out by low dose prescriptions and non-low dose prescriptions. There is a sharp, sustained drop in the amount of low dose prescriptions filled after the policy was enacted. While there appears to be a small increase in the number of non-low dose prescriptions filled just after the policy was enacted, over time the number of prescriptions PMPM decreases.

Figure 2. Aggregated Prescriptions Of Non-Low Dose (≥150 Mg Per Day) And Low Dose (<150 Mg Per Day) Quetiapine Filled Per Enrolled Member Per Month (PMPM).



We evaluated all OHP clients who had a denied claim for low dose quetiapine in the first three years of the policy. A total of 7,749 clients had a denied claim in 2011-2013. Of these, 2,867 authorizations requests were submitted (37%). Only 7 requests were denied, resulting in a 99.8% approval rate for submitted request. No request was submitted for 4,882 clients (63%). There were no differences in the average age, sex, or racial demographics between those who had an approved request and those who had no request submitted. However, clients who had a request approved were more likely to be in managed care than fee-for-service and were more likely to have been prescribed the drug by a mental health provider.

Table 1. Baseline Characteristics Of All Patients With A Denied Claim For Quetiapine (2011-2013).

	Total (N=7,749)	Approval (N=2,860)	Denial (N=7)	No Request (N=4,882)
Average Age (min-max)	39 (4-101)	36 (4-82)	31 (6-49)	41 (4-101)
Female	4,823 (62%)	1,777 (62%)	3 (43%)	3,043 (62%)
Non-White	1,200 (15%)	433 (15%)	1 (14%)	766 (16%)
Enrollment at Index				
Fee-For-Service	1,517 (20%)	485 (17%)	4 (57%)	1,028 (21%)
Managed Care	6,125 (79%)	2,341 (82%)	3 (43%)	3,781 (77%)
Unknown	107 (1%)	34 (1%)	0 (0%)	73 (1%)
Long Term Care	766 (10%)	260 (9%)	0 (0%)	506 (10%)
Prescriber				
Primary Care	4,918 (63%)	1,709 (60%)	4 (57%)	3,205 (66%)
Mental Health	2,308 (30%)	992 (35%)	3 (43%)	1,314 (27%)
Other	262 (3%)	77 (3%)	0 (0%)	185 (4%)
Unknown	261 (3%)	82(3%)	0 (0%)	178 (4%)
Pharmacy Type				
Chain	4,759 (61%)	1,741 (61%)	4 (57%)	3,014 (62%)
Independent	1,842 (24%)	709 (25%)	3 (43%)	1,130 (23%)
Long Term Care	1,118 (14%)	394 (14%)	0 (0%)	724 (15%)
Mail Order	30 (0%)	16(1%)	0 (0%)	14 (0%)

For the harms analysis, there were 3,290 patients with index events for the policy group (2011) and 3,885 patients identified with index events for the comparison group (2009). After excluding patients less than 18 and greater than 64 years old or without baseline demographics (study n=0, control n=697), those covered by Medicare (study n= 162, control n=169), those without continuous eligibility (study n=334, control n= 246), and those in the intervention group from the comparison group (833), the final policy group was 2,794 patients and the comparison group was 1,940 patients. Table 1 displays the baseline characteristics of the groups, prescriber demographics and baseline pharmacy utilization. Baseline percentages of schizophrenia were similar, but more people in the comparison group had bipolar disorder than those in the policy group. Those who had a request approved were more likely to have a diagnosis of schizophrenia or bipolar disorder in the prior two months than those who had no request submitted.

Table 2. Baseline Characteristics For Harms Analysis.

	Comparison Group (N= 1,940)		Policy Group*					
			Total (N= 2,794)		Approval (N= 1,205)		No Request (N= 1,548)	
Demographics								
Average Age (min-max)	39.6	(18-64)	39.1	(18-60)	39.1	(18-60)	39.1	(18-60)
Female	1395	72%	1889	68%	808	67%	1079	68%
Non-White	309	16%	436	16%	170	14%	265	17%
Medications in Prior 2 months								
Antiepileptic Mood Stabilizers	238	12%	331	12%	168	14%	163	10%
Benzodiazepines	110	6%	117	4%	46	4%	71	4%
First Generation Antipsychotics	62	3%	72	3%	41	3%	31	2%
Misc. Psychotropics								
Non-Benzodiazepine Sedative	432	22%	574	21%	250	21%	324	20%
Hypnotics	4	0%	4	0%	2	0%	2	0%
Second Generation Antipsychotics	834	43%	1489	53%	757	63%	731	46%
Diagnosis in Prior 2 Months								
Bipolar	430	22%	482	17%	234	19%	248	16%
Schizophrenia	297	15%	416	15%	220	18%	196	12%
Major Depressive Disorder	703	36%	892	32%	360	30%	529	33%

*Denials not included in table

Table 3 displays the results of primary outcomes. There were 263 psych-related ED visits or hospitalizations during the 30 day follow-up period, 141 (5% of the population) in the policy group and 122 (6%) in the comparison group (OR 0.80, 95% confidence interval [CI] 0.62 to 1.03). There were 58 schizophrenia-related ED visits or hospitalizations during the 30 day follow-up period, 35 (1% of the population) in the policy group and 23 (1% of the population) in the comparison group (OR 1.06, 95% CI 0.61 to 1.86). There were 28 psych-related ED visits or hospitalizations during the 30 day follow-up period, 16 (1% of the population) in the policy group and 12 (1% of the population) in the comparison group (OR 0.93, 95% CI 0.41 to 2.09). There were 895 all cause ED visits or hospitalizations during the 30 day follow-up period, 488 (17% of the population) in the policy group and 407 (21% of the population) in the comparison group (OR 0.80, 95% CI 0.69 to 0.93). There were no significant differences in the primary endpoints at 60 days compared to 30 days.

Table 3. Primary And Secondary Outcomes 30 Days After Study Entry.

	Comparison Group (N= 1,940)		Policy Group* Total (N= 2,794)		Approval (N= 1,205)		No Request (N= 1,548)	
ED/Hospitalizations at 30 Days								
Primary: Psych-related	122	6%	141	5%	54	4%	87	5%
Schizophrenia	23	1%	35	1%	16	1%	19	1%
Bipolar	12	1%	16	1%	7	1%	9	1%
All Cause	407	21%	488	17%	198	16%	289	18%
ED/Hospitalizations at 60 Days								
Primary: Psych-related	176	9%	218	8%	88	7%	130	8%
Schizophrenia	32	2%	47	2%	21	2%	26	2%
Bipolar	16	1%	24	1%	11	1%	13	1%
All Cause	596	31%	756	27%	311	26%	444	28%

*Denials not included in table

Discussion:

In this analysis, patients encountering the safety edit did not experience more ED visits or hospitalizations for psych-related events, including for schizophrenia or bipolar disorder compared to patients who had a claim for low dose quetiapine prior to this policy. They had less all cause ED visits or hospitalizations, the cause of which is unknown. There were no significant differences between the subgroup of clients who encountered the safety edit and had a request submitted (and subsequently approved) and those who did not have a request submitted.

Policy group patients whose prescribers made a request were more likely to have a diagnosis of schizophrenia or bipolar disorder and were more likely to have had pharmacy claims for a second generation antipsychotic in the two months prior to the index event, suggesting the safety edit was effective at restricting use consistent with the FDA recommendation. The policy did decrease the overall use of low dose quetiapine.

Similar to other OHP fee-for-service PA analyses, only 37% of patients encountering the safety edit subsequently had a request for approval. That is, for a majority of cases no attempt was made by the prescriber to submit a request. It is difficult to infer causality between no request and subsequent adverse outcomes because having a request submitted was associated with increasing disease severity. Despite this limitation, rates of the primary outcomes were not different in the group that did not have a request submitted compared to the group that did have a request submitted. The rates of ED visits and hospitalizations for psych-related events, schizophrenia and bipolar disorder were similar to the comparison group at 30 days, while the rates of all cause ED visits and hospitalizations were lower in both intervention groups at 30 days; it is unclear if this decrease is related to the safety edit policy. It is also unclear what factors made the all cause hospitalizations and ED visits statistically significantly lower in the policy group compared to the historical comparison group.

References:

1. Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062- 1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 3, 2014.
2. Alexander, G. C., Gallagher, S. A., Mascola, A., Moloney, R. M. & Stafford, R. S. INCREASING OFF-LABEL USE OF ANTIPSYCHOTIC MEDICATIONS IN THE UNITED STATES, 1995-2008. *Pharmacoepidemiol. Drug Saf.* **20,** 177–184 (2011).
3. Newcomer, J. W. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J. Clin. Psychiatry* **68 Suppl 1,** 20–27 (2007).
4. Coe, H. V. & Hong, I. S. Safety of low doses of quetiapine when used for insomnia. *Ann. Pharmacother.* **46,** 718–722 (2012).
5. Indiana Medicaid DUR Board (Draft Minutes), 2007. Available at http://provider.indianamedicaid.com/medica/68893/20071019.pdf
6. Montana Department of Public Health & Human Services. September 3, 2008-Montana Healthcare Programs Notice. Available at http://medicaidprovider.hhs.mt.gov/pdf/pharmacy090308.pdf
7. State of Vermont-Department of Vermont Health Access. July 11, 2011 PDL Changes. Available at http://dvha.vermont.gov/for-providers/microsoft-word-2011-07-07-july-11-2011-pdl-changes-fax-blast-draft-nh.pdf
8. Idaho Medicaid Drug Utilization Review Program, 2011. Available at: https://idaho.fhsc.com/downloads/providers/IDRx_DUR_presentation_20110414.pptx. Accessed Oct 2, 2014.
9. Oregon Drug Use Review Board - Meeting Minutes, 2009. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/seroquel_due.pdf. Accessed October 2, 2014.
10. Drug Utilization Review (DUR) Board Meetings, Rhode Island Department of Human Services. Board Meeting Minutes. October 6 2010. Available at: http://www.dhs.ri.gov/Portals/0/Uploads/Documents/Public/Pharmacy/dur_oct10.pdf. Accessed Oct 2, 2014.

Appendix 1. Drug Classification Table.

Drug Class Code	Generic Drug Name
Second Generation Antipsychotic	Quetiapine
Second Generation Antipsychotic	Olanzapine
Second Generation Antipsychotic	Aripiprazole
Second Generation Antipsychotic	Ziprasidone
Second Generation Antipsychotic	Clozapine
Second Generation Antipsychotic	Risperidone
Second Generation Antipsychotic	Iloperidone
Second Generation Antipsychotic	Paliperidone
Second Generation Antipsychotic	Lurasidone
Second Generation Antipsychotic	Asenapine
Benzodiazepine	Oxazepam
Benzodiazepine	Alprazolam
Benzodiazepine	Lorazepam
Benzodiazepine	Diazepam
Benzodiazepine	Temazepam
Benzodiazepine	Clonazepam
Benzodiazepine	Clorazepate
Benzodiazepine	Chlordiazepoxide
Benzodiazepine	Diazepam
Benzodiazepine	Midazolam
Benzodiazepine	Triazolam
Benzodiazepine	Flurazpam
Antiepileptic Mood Stabilizer	Divalproex
Antiepileptic Mood Stabilizer	Lamotrigine
Antiepileptic Mood Stabilizer	Gabapentin
Antiepileptic Mood Stabilizer	Topiramate
Antiepileptic Mood Stabilizer	Carbamazepine
Antiepileptic Mood Stabilizer	Oxcarbazepine
Non-Benzodiazepine Sedative Hypnotic	Eszpiclone
Non-Benzodiazepine Sedative Hypnotic	Zaleplon

Non-Benzodiazepine Sedative Hypnotic	Ramelteon
Non-Benzodiazepine Sedative Hypnotic	Zolpidem
Miscellaneous Psychotropic	Mirtazapine
Miscellaneous Psychotropic	Amitriptyline
Miscellaneous Psychotropic	Doxepin
Miscellaneous Psychotropic	Nortriptyline
Miscellaneous Psychotropic	Trazodone
Miscellaneous Psychotropic	Hydroxyzine
Miscellaneous Psychotropic	Diphenhydramine
First Generation Antipsychotic	Chlorpromazine
First Generation Antipsychotic	Fluphenazine
First Generation Antipsychotic	Haloperidol
First Generation Antipsychotic	Loxapine
First Generation Antipsychotic	Perphenazine
First Generation Antipsychotic	Thioridazine
First Generation Antipsychotic	Thiothixene
First Generation Antipsychotic	Trifluoperazine

Low Dose Quetiapine

Goals:

- Promote and ensure use of quetiapine that is supported by the medical literature.
- Discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:

- Low dose quetiapine (extended or immediate-release formulations)

Length of Authorization:

- Up to 12 months (criteria-specific)

Requires PA:

- Quetiapine (HSN = 14015) doses <150 mg/day
- Auto-PA approvals for :
    - Patients with a claim for a second generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem and benzodiazepine sedatives are available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (Age ≥18 years) FDA-approved indications for Quetiapine.

Bipolar Disorder	296.0, 296.4, 296.6-296.8,296.89	
Major Depressive Disorder	296.2, 296.24, 296.3, 296.23, 296.33, 296.34, 296.5, 296.53, 296.54	For Seroquel XR® only, adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	295, 295.4, 295.44, 295.45, 295.6,295.62, 295.64, 295.85, 295.95, 295.80-295.82,295.40-295.42, 295.90-295.92	
Bipolar Mania	296.1, 296.3, 296.4, 296.43, 296.44	
Bipolar Depression	296.5	

Table 2. Pediatric FDA-approved indications.

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than 150 mg/day? (verify days' supply is accurate)	Yes: Go to #3	No: Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	Yes: Go to #4	No: Approve for titration up to maintenance dose (60 days).
4. Is reason for dose <150 mg/day due to any of the following: • Low dose needed due to debilitation from a medical condition or age; or • Unable to tolerate higher doses; or • Stable on current dose; or • Impaired drug clearance? • Any diagnosis in tables 1 or 2 above?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow for taper.

P&T/DUR Review: *9/15 (KK/AM); 9/10; 5/10*
Implementation: *TBA; 1/1/11*

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

Prior Authorization Review: Tesamorelin for injection

Background:
Human immunodeficiency virus (HIV)-infected persons who receive long-term anti-retroviral therapy (ART) often experience weight gain and abdominal body fat.[1] Tesamorelin is a growth hormone releasing factor (GRF) analog approved by the U.S. Food and Drug Administration (FDA) in 2010 to reduce excess abdominal fat in HIV-infected patients with lipodystrophy.[2] The Pharmacy and Therapeutics (P&T) Committee reviewed tesamorelin and approved Prior Authorization (PA) criteria in 2012 (see **Appendix 1**). A formal review was initiated to determine the clinical appropriateness of the implemented criteria.

When compared to placebo, tesamorelin decreases visceral adipose tissue (WMD -22.65 cm^2; 95% CI, -32.67 to -12.64 cm^2; $p<0.001$) but has no significant effect on subcutaneous adipose tissue mass (WMD 1.02 cm^2; 95% CI, -8.21 to +6.16 cm^2; $p=0.78$).[3] Use of tesamorelin leads to a weight-neutral effect and is not indicated for weight loss management.[2] Long-term cardiovascular benefit and safety of tesamorelin have not been studied, and there are no data to support improved compliance with anti-retroviral therapies (ART) in HIV-positive patients taking tesamorelin.[2]

No new indications, pertinent trials assessing clinically relevant outcomes (i.e., morbidity outcomes) or safety alerts were identified since the P&T Committee last reviewed this drug.

Recommendations:
No changes to the current PA criteria are recommended. No further review or research needed at this time.

References:
1. Shlay JC, Bartsch G, Peng G, et al. Long-term body composition and metabolic changes in antiretroviral naive persons randomized to protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or protease inhibitor plus nonnucleoside reverse transcriptase inhibitor-based strategy. *J Acquir Immune Defic Syndr*. 2007;44:506-517.
2. Egrifta® (tesamorelin for injection) [prescribing information]. Montreal, Quebec, Canada; Theratechnologies Inc., June 2015.
3. Sivakumar T, Mechanic OJ, Fehmie DA and Paul BT. Growth hormone axis treatments for HIV-associated lipodystrophy: a systematic review of placebo-controlled trials. *HIV Medicine*. 2011;12:453-462.

Tesamorelin (Egrifta®)

Goal:
- Restrict to indications funded by the OHP and supported by medical literature

Length of Authorization:
- Up to 12 months

Requires PA:
- Tesamorelin (Egrifta®)

Covered Alternatives:
- No preferred alternatives

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the indicated treatment for reduction of excess abdominal fat in HIV-infected patients with lipodystrophy (ICD9 272.6)?	Yes: Pass to RPh. Deny; not funded by the OHP.	No: Go to #3
3. RPh only: All other diagnoses must be evaluated as to funding level on OHP and evidence for must be provided by the prescriber that supports use. Evidence will be forwarded to Oregon DMAP for consideration.		

2

P&T/DUR Review: *9/15; 4/12*
Implementation: *7/12*

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

Prior Authorization Review: becaplermin topical gel

Background:
Human platelet-derived growth factor (PDGF) is a substance naturally produced in the body to help in wound healing. It promotes cellular proliferation and angiogenesis, helping to repair and replace dead skin and other tissues by attracting cells that repair wounds.[1] Becaplermin topical gel (Regranex®) is a genetically engineered product that mimics PDGF. It was approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of lower extremity diabetic neuropathic ulcers that have adequate blood supply and extend into the subcutaneous tissue and beyond.[2] The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The efficacy of becaplermin for lower extremity diabetic neuropathic ulcers has been established in clinical trials and confirmed in post-marketing experience.[3] No other indications have been approved by the FDA.

The efficacy of topical becaplermin has not been established for the treatment of pressure ulcers, venous stasis ulcers, or on exposed joints, tendons, ligaments and bone.[4] Off-label uses include management of necrotic mucosal flap after bone grafting;[5] necrobiosis lipoidica, a necrotizing skin condition is most frequently observed on the shins of both legs of patients with diabetes;[6] and hypertensive leg ulcers;[7] with insufficient or inconclusive evidence.

The FDA issued its strongest warning (Boxed Warning) in 2008 after increased rate of mortality secondary to malignancy distant from the site of application was observed in patients treated with 3 or more tubes of becaplermin gel in clinical studies and post-marketing use.[2] Though this risk has been disputed,[8] the FDA Boxed Warning and associated precautions are still in place.[4]

Recommendations:
Clerical changes to the current PA criteria are recommended. No further review or research needed at this time.

References:
1. Greer N, Foman N, Dorrian J, et al. Advanced wound care therapies for non-healing diabetic, venous and arterial ulcers: a systematic review. VA Evidence-based Synthesis Program Report, Washington (DC): Department of Veterans Affairs; November 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0054957/pdf/TOC.pdf . Accessed 10 June 2015.
2. Drugs@FDA. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed 10 June 2015.
3. Diabetic Foot Problems, NICE Clinical Guideline 119. National Institute for Health and Clinical Excellence (NICE); March 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0041804/pdf/TOC.pdf . Accessed 10 June 2015.
4. Regranex® (becaplermin) [prescribing information]. Fort Worth, TX; Smith & Nephew Inc., August 2014.
5. Calhoun CC, Cardenes O, Ducksworth J and Le AD. Off-label use of becaplermin gel (recombinant platelet-derived growth factor-BB) for treatment of mucosal defects after corticocancellous bone graft: report of 2 cases with review of the literature. *Journal of Oral and Maxillofacial Surgery*. 2009;67:2516-20.

Author: A. Gibler, Pharm.D. Date: September 2015

6. Tauveron V, Rosen A, Khashoggi M, et al. Long-term successful healing of ulcerated necrobiosis lipoidica after topical therapy with becaplermin. *Clinical and Experimental Dermatology*. 2013;38:745-47.
7. Senet P, Vicaut E, Beneton N, et al. Topical treatment of hypertensive leg ulcers with platelet-derived growth factor-BB: a randomized controlled trial. *Archives of Dermatology*. 2011;147:926-30.
8. Ziyadeh N, Fife D, Walker AM, et al. A matched cohort study of the risk of cancer in users of becaplermin. *Advances in Skin and Wound Care*. 2011;24:31-39.

Appendix 1: Current Prior Authorization Criteria

Becaplermin (Regranex®)

Goal(s):
- Restrict to indications funded by the OHP and supported by medical literature.

Length of Authorization:
- Up to 6 months

Requires PA:
- Becaplermin topical gel (Regranex®)

Covered Alternatives:
- No preferred alternatives

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have an ulcer(s) (ICD9 357.2; 707.11-19; 707.8; 707.9)?	Yes: Go to #3.	No: Pass to RPh. Deny; medical appropriateness.
3. Does the patient have diabetes mellitus (ICD9 249.xx; 250.xx)?	Yes: Approve ONLY 15 grams for 6-month supply.	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *09/15; _/_*
Implementation: ***TBD***; _/_

Author: A. Gibler, Pharm.D. Date: September 2015