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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, February 23, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

Meeting Agenda

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. OLD BUSINESS 1:05 pm – 1:15 pm
- a. Hepatitis C Follow-up from January* — K. Ketchum (OSU)
  1. Biopsy Recommendation
  2. Infergen (interferon alfacon-1) Recommendation
  3. Public Comment
  4. Discussion of Clinical Recommendation to OHA

III. DUR ACTIVITIES 1:15 pm – 2:05 pm
- a. DMAP Pharmacy Program Report — R. Magrish (DMAP)
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — R. Citron (OSU)
- d. Quarterly Utilization Reports — R. Citron (OSU)
- e. PDL Evaluation presentation — K. Ketchum (OSU)
- f. Oregon State Drug Reviews — K. Sentena (OSU)
  1. Atypical Antipsychotic Drug Class Review
  2. RSV Prophylaxis

BREAK 2:05 pm - 2:15 pm

IV. PRIOR AUTHORIZATION (PA) 2:15 pm – 2:50 pm
- a. New PA Criteria* — M. Herink (OSU)
  1. Hepatitis B PA Criteria
- b. Changes to existing PA Criteria* — R. Citron (OSU)
  1. Erythropoiesis Stimulating Proteins
  2. Proton Pump Inhibitors
  3. Topiramate
  4. Hormones – Testosterone (Androgens)
  5. Pulmonary Arterial Hypertension (PAH)
- c. Early Refill Threshold Change from 75% to 80%* — R. Citron (OSU)
- d. Public Comment
- e. Discussion of Clinical Recommendations to OHA

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

V. NEW BUSINESS 2:50 pm – 3:35 pm

a. Neuropathic Pain Class Update* M. Herink (OSU)
   1. DERP Report
   2. Public comment
   3. Discussion of clinical recommendations to OHA
b. COPD Medications New Drug Reviews* A. Burns (OSU)
   1. Daliresp (roflumilast)
   2. Arcapta (indacaterol)
   3. Public Comment
   4. Discussion of clinical recommendations to OHA
c. Drug Class Scans* M. Herink (OSU)
   1. Parkinson's Medications
   2. NSAIDS
   3. Analgesics for Gout
   4. Alzheimer's Medications
   5. Public Comment
   6. Discussion of clinical recommendations to OHA

VI. EXECUTIVE SESSION 3:35 pm

VII. RECONVENE for PUBLIC RECOMMENDATIONS*

VIII. FUTURE BUSINESS

Tentative Review Schedule and Prioritization

IX. ADJOURN

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

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Drug Use Review / Oregon Pharmacy & Therapeutics Committee
Thursday, January 26, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070
Meeting Minutes

Members Present: Andris Antoniskis, MD; Zahia Esber, MD; Phillip Levine, PhD; Meena Mital, MD; William Origer, MD; David Pass, MD; James Slater, PharmD
Members Present by Phone: Joshua Bishop, PharmD; Stacy Ramirez, PharmD
Staff Present: Dean Haxby, PharmD; Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA:HA; Kathy Sentena, PharmD; Ted Williams, PharmD, BCPS; Valerie Smith; Richard Holsapple, RPh; Ralph Magrish, MPA
Staff Present by Phone: Sherri Willard, PharmD
Audience Present: Mike Donabedion (Vertex); Dr. Jamie Tobitt, PharmD (Vertex); Sharon Yeske-Amato (Walgreens); Jeff Stockald (Walgreens); Dr. Rob Pearson (GSK); Lyle Laird, PharmD (Sunovion); Jeana Colabianchi, PharmD (Sunovion); Kathy Kirm (OPMC); Kerrie Boynton (DCIPA); Carin Mickelson (DOCS); B.M. Benson (Merck); Vic Benson (Merck); Venus Holder (Eli Lilly); Kristin Bugler (Merck); Jeff McDonald (Merck); Jim Hoover (Bayer); Don Stetcher (Novartis); Mary Kemhus (Novartis); Lorren Sandt (Caring Ambassadors); Laura Litzenberger (Janssen Scientific Affairs); Stephanie Kendall (J&J); Mike Willett (Pfizer); Richard McLeod (Pfizer)

I. CALL TO ORDER
- a. The meeting was called to order shortly after 2 pm and introductions were made.
- b. Conflict of interest declarations were reviewed; no new conflicts were disclosed.
- c. Minutes from the November 17, 2011 meeting were reviewed and one change noted.

ACTION: Minutes were approved with recommended change.

II. PROCESS
- a. The procedure document was reviewed and accepted as is, but noted that is a living document.

III. OLD BUSINESS
- a. Ms. Ketchum presented DUE on Methadone and Long-Acting Opioids. Public comment was presented during the November 17th meeting by Kathy Kirk and Kathy Hahn from the Oregon Pain Management Commission.

***ACTION:** Methadone – New Starts @ doses >20mg: approved with recommendation of adding UDS and strengthening language for co-administration with benzodiazepines.
***ACTION:** Opioids – Long-Acting: approved with recommendation of adding UDS.
***ACTION:** Opioids – Long-Acting – High Dose Limit: approved with recommendation of adding UDS.

IV. NEW BUSINESS
- a. Mr. Citron presented a dose consolidation concept for committee member comments.

***ACTION:** The committee recommended bringing a list of drugs or classes the Authority would like reviewed. The committee also recommended a dose consolidation review is done with each class review in the future.
- b. Mr. Magrish presented the New Drug Policy as specified in 410-121-0040(5)(a-c).

***ACTION:** Approved.

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c. Dr. Sentena presented DUE for adding Oral Anticoagulants class to the Preferred Drug List (PDL) and making Warfarin a preferred product.

***ACTION:** Approved.

1. Dr. Sentena presented DUE and recommended keeping Pradaxa (dabigatran) as non-preferred requiring prior authorization (Oral Direct Thrombin Inhibitors).

***ACTION:** Approved with recommendation to add GFR limits to #1 and add "unstable INR" to #6 after Executive Session.

2. Dr. Sentena presented DUE and recommended keeping Xarelto (rivaroxaban) as non-preferred requiring prior authorization (Oral Direct Factor Xa Inhibitors). Laura Litzenberger from Janssen Scientific Affairs presented public comment for Xaralto.

***ACTION:** Approved with recommendation of making 3rd line after Pradaxa after Executive Session.

d. Dr. Herink presented DUE and recommended expanding the current Hepatitis C drug class to include all agents for treatment of chronic Hepatitis C virus and maintain either one or both of peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (Pegintron) as preferred products and require prior authorization (Pegylated Interferon and Ribavirin). Lorren Sandt from Caring Ambassadors presented public comment on Hepatitis C.

ACTION: Committee asked to see cost evaluations per package size and bring back to February meeting.

1. Dr. Willard presented DUE and recommended prior authorization criteria (Hepatitis C Oral Protease Inhibitors/Triple Therapy) on Incivek (telaprevir). Dr. Jamie Tobitt form Vertex presented public comment on telaprevir.
2. Dr. Willard presented DUE and recommended prior authorization criteria (Hepatitis C Oral Protease Inhibitors/Triple Therapy)Victrelis (boceprevir). Vic Benson from Merck presented public comment on boceprevir.

***ACTION:** Hepatitis C Oral Protease Inhibitors/Triple Therapy: approved with recommendation of including the same exclusion criteria as in the studies presented and when variances apply use the more generous of the choice (e.g. male or female, platelet count, etc.) after Executive Session. Recommended monitoring these clients through the Disease Case Management or Medication Therapy Management programs.

e. Dr. Herink presented DUE on the ACE-Is/ARBs/DRIs class and recommended maintaining all DRI's and products containing a DRI as non-preferred; keeping Edarbi (azilsartan) as non-preferred ARB; and making PDL recommendations based on cost since no new significant clinical evidence exists since the class was last reviewed.

***ACTION:** Approved after Executive Session.

f. Dr. Herink presented drug class scans.
   1. HSV Antivirals
   2. Influenza Antivirals
   3. Beta Blockers
   4. Calcium Channel Blocker

ACTION: Approved after Executive Session.

VII. FUTURE BUSINESS

The next meeting will be on February 23, 2012 in Wilsonville. The March meeting will be held on the 29th instead of the originally scheduled 26th in Salem.

VIII. ADJOURN

The meeting adjourned at 4:25pm.

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Hepatitis C Class Review

Month/Year of Review: January 2012
PDL Class: Hepatitis C Agents
Suggested Revision: Expand current Hepatitis C PDL class to include all agents for treatment of Chronic Hepatitis C (CHC) Virus

Current Status of PDL Class:
PA Criteria for Pegylated Interferon and Ribavirin (Appendix 1)
Preferred Agents: Pegasys (peginterferon alfa 2a), Pegintron (peginterferon alfa 2b)

Background:
Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease and leading indication for liver transplantation in the United States (U.S.). Therefore, the goal of therapy for HCV infection is to prevent complications and death.[1]

An estimated 180 million people worldwide are infected with HCV. The prevalence of HCV infection in the U.S. between 1999 and 2002 was 1.6%, or about 4.1 million people positive for hepatitis C antibody (anti-HCV).[1]

About 55% to 85% of those who develop acute hepatitis C remain infected, rather than achieve spontaneous resolution.[1] An estimated 15 to 30% of patients with CHC develop cirrhosis within 30 years. One to three percent of patients per year with HCV-related cirrhosis develop hepatocellular carcinoma.[2]

U.S. guidelines have recommended combination peginterferon alfa (P) and ribavirin (R) as the standard of care (SOC) for CHC, with the optimal duration of treatment based on viral genotype. Response to treatment (i.e., SVR) with SOC is about 50% for Caucasians and 30% for African-Americans. Guidelines for treating HCV genotype 1 (HCV-1) were updated in fall 2011, following FDA approval of the direct acting antivirals (DAA) boceprevir (BOC) and telaprevir (TVR).[1,2]

HVC is classified into at least 6 major genotypes: genotype 1 (with subtypes 1a and 1b), which is the most common in the U.S.; genotypes 2 and 3, which are the next most common; and genotypes 4, 5, and 6, which are, thus far, the least common.[1] Genotype 1 accounts for >70% of CHC in the

U.S. and Europe and has the poorest response to treatment. Genotyping HCV is useful for predicting the likelihood of response to and duration of therapy.[3]

According to AASLD guidelines, widely accepted criteria for CHC treatment include HCV RNA serum positive, significant fibrosis, compensated liver disease, acceptable blood and biochemistry indices, willingness to be adherent to therapy, and no contraindications. Criteria contraindicating therapy include uncontrolled major depression, solid organ transplant, autoimmune hepatitis or autoimmune condition exacerbated by PR, untreated thyroid disease, pregnancy, inadequate contraception, severe concurrent medical illnesses, age <2, and hypersensitivity to drug therapies. However, these are not absolute and clinical judgment should be exercised in each case.[1]

Sustained virologic response (SVR) is associated with permanent virologic cure, long-term clearance of HCV infection, as well as improved morbidity and mortality in the vast majority of patients. RVR predicts a high likelihood of achieving an SVR. Those who achieve an RVR have an SVR rate of about 90%; however, only 15% to 20% of those with HCV-1 infection achieve RVR with peginterferon alfa. Early virologic response (EVR) is the most accurate predictor of non-response, as 97 to 100% of treatment-naïve HCV-1 patients who fail to reach EVR fail to achieve SVR. While end-of-treatment response (ETR) is an inaccurate predictor of achieving SVR, ETR is necessary for SVR to occur.[1,4]

On-treatment viral kinetics is used to guide the duration of therapy.[4] Studies have previously established patients with HCV-1 should be treated for 48 weeks with PEG-2a (180 µg/week sc) plus weight-based RIB (1000 or 1200 mg per day) or PEG-2b (1.5 µg/kg sc) plus weight-based RIB (800 mg, 1000 mg, 1200 mg, or 1400 mg).[7] Treatment may be discontinued in patients who do not achieve EVR. Forty to fifty percent of patients with HCV-1 treated with PEG and the standard weight-based dose of RIB for 48 weeks achieve SVR. The two FDA-approved PEGs (Pegasys, Roche, and PegIntron, Merck) have had similar efficacy and safety profiles in head-to-head comparisons.[4]

Summary:

The standard of care for the treatment of Chronic Hepatitis C (CHC) has been pegylated interferon (alfa 2a or alfa 2b) in combination with weight-based ribavirin (PR) for either 48 weeks or 24 weeks depending on genotype[1]. The American Association for the Study of Liver Disease recently published an update on the treatment of genotype 1 chronic hepatitis c virus infection guidelines to include the new direct acting antiviral (DAA) agents of BOC and TVR.[2] These were based on a review and analysis of published literature, guideline policies, and expert opinion. There is evidence showing a significant improvement in SVR rates in patients with genotype 1 CHC but the guidelines state that the recommendations are based on new data that is still quite limited and as more studies are conducted and become available the recommendations may need to be reconsidered.[2] Both BOC and TVR have evidence showing a significant improvement in demonstrating higher rates of virologic response compared with the current standard of treatment and also both in patients who had previously failed dual therapy, but at a significantly higher cost and with safety concerns including anemia, drug interactions, skin rashes, and adverse events[5].

The updated guidelines state:

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. (Class 1, Level A)
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. (Class 1, Level A).

The combination of pegylated interferon and ribavirin remains the standard of care for all other genotypes.[1] Oregon reviewed the interferons for CHC previously and developed PA criteria for treatment with peginterferon and ribavirin shown in Appendix 1. Both Peg-Intron and Pegasys are listed as preferred agents. There is comparative effectiveness evidence demonstrating that there are no significant differences in efficacy or safety between the two agents.[4] The introduction of these long-acting peginterferons has become the standard of care and have replaced the older non-pegylated infererons[1].

In 2010, the FDA approved an expanded indication for interferon alfacon-1 (Infergen) for retreatment of CHC in combination with ribavirin after failure to previous treatment with a pegylated interferon and ribavirin[6]. This approval was based on a single study (DIRECT trial) which was a randomized, open-label, study comparing the safety and efficacy of two doses of interferon alfacon-1 plus ribavirin in previous nonresponders[4]. The AASLD guidelines do not demonstrate any role of interferon alfacon-1 in the treatment of CHC and there is limited data to support its use.

There is currently no comparative evidence evaluating if there is a difference in either efficacy or safety between BOC and TVR. There were also differences in how the drug studies were conducted as well as major differences in side effect profiles, making a direct comparison difficult. Only telaprevir was studied in prior null responders to PR therapy, BOC was studied in combination with peginterferon alfa-2b while TVR was given with peginterferon alfa-2a, and although there is a high incidence of anemia associated with both drugs it was managed differently in clinical trials. Use of erythropoietin stimulating agents (ESAs) was excluded from TVR studies while ESAs were allowed for the management of anemia at the discretion of the clinician in the BOC studies.[2,3] Ongoing studies are further evaluating how the management of anemia including ESA use or R dose reduction affects outcomes with BOC treatment.

Recommendations:

- Expand current Hepatitis C antiviral PDL class to include all agents for treatment of Chronic Hepatitis C Virus
- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PegIntron) as preferred pegylated interferon products depending on price. These two agents are recommended in the current guidelines and have shown to be similar in terms of safety and efficacy.
- Designate interferon alfacon-1 (Infergen) as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.
- Develop PA criteria to support the judicious use of the oral protease inhibitors in patients with genotype 1 CHC in combination with pegylated interferon and ribavirin.

APPENDIX 1: Prior authorization criteria for pegylated interferon and ribavirin

Pegylated Interferon and Ribavirin

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #3.	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #4.	**No:** Go to #10
4. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #5
5. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment? Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #6
6. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy~~cytopenias~~ • untreated hyperthyroidism • severe renal impairment or transplant	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #7

• autoimmune disease • pregnancy • unstable CVD		
7. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #8	**No:** Deny; Pass to RPH (Medical Appropriateness)
8. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
12. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

Genotype	Approve for	Apply
1 or 4	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).
2 or 3	**An additional 12 weeks** or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).
For all genotypes and HIV co-infection	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).

No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.

Stage is indicative of fibrosis:			Grade is indicative of necrosis:	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild

Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate
Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ ~~Re-treatment of HCV or HBV previous non-responders or relapsers~~
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

References:

1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335-1374.

2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54(4):1433-1444.

3. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 202258Orig1s000 summary review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000SumR.pdf. Accessed September 26, 2011.

4. Rosen HRM. Chronic Hepatitis C Infection. *N. Engl. J. Med*. 2011;364(25):2429-38.

5. Tungol A, Rademacher K, Schafer JA. Formulary management of the protease inhibitors boceprevir and telaprevir for chronic hepatitis C virus. *J Manag Care Pharm*. 2011;17(9):685-694.

6. Infergen Package Insert. Kadmon Corporation, LLC. Available at: http://kadmon.com/files/infergen-pi.pdf.

ProDUR Alert Overview

DA Drug/Allergy Interaction: Triggers if there is an association between an ingredient and an allergy recorded in the recipient profile.

DC Inferred Disease Interaction: Triggers if there is a drug on the recipients profile that is indicated for a disease state that interacts with the drug being filled.

DD Drug to Drug Interaction: Triggers if there is an interaction between the drug being filled and another drug on the recipients profile.

ER Early Refill (Overutilization): Triggers if the drug being billed is too early based on previous billing and days supply. Allow filling when 75% of previous fill has been used.

HD High Dose: Triggers if the drug being billed, based on billed days supply, exceeds the maximum recommended daily quantity limit. **Currently only set for CNS Stimulants, Methadone, Asmanex, Lovenox, and the aspirin/APAP-narcotic combinations.**

ID Ingredient Duplication: Triggers if the drug being filled has a matching ingredient to another recently filled drug on the recipients profile.

LD Low Dose: Triggers if the drug being billed, based on billed days supply, is below the minimum recommended daily quantity limit. **Currently only set for Seroquel (quetiapine).**

LR Late Refill (Underutilization): Triggers if the drug being filled is late in being refilled for the recipient.

MC Drug to Disease Interaction: Triggers if there is a disease diagnosis on the recipients claim profile that interacts with the drug being filled.

MX Maximum Duration of Therapy: Triggers if the days supply on the claim is greater than the maximum days value.

NF Non-Formulary: Triggers if the drug being billed is not associated with the PDL.

PA Pediatric and Geriatric Age Limits: Triggers if the age of the recipient is less than the minimum (pediatric) or greater than the maximum (geriatric) age for the drug being billed.

PG Pregnancy/Drug Interaction: Triggers if the drug being filled is contraindicated for use in pregnancy and the patient profile indicates that the patient may be pregnant.

TD Therapeutic Duplication: Triggers if the class of drug being billed matches the drug class of another recently filled medication on the recipients profile.

ProDUR Alert Sequence

The order in which the ProDUR alerts are performed in the pharmacy claim process is as follows:

1. High Dose (**HD**)
2. Drug Pregnancy (**PG**) - Major and Moderate Severities
3. Overutilization (**ER**)
4. Low Dose **(LD)**
5. Therapeutic Duplication (**TD**)
6. Non-Formulary (**NF**)
7. Ingredient Duplication (**ID**)
8. Drug/Drug Interaction (**DD**) – Major Severity
9. Drug Age – Geriatric (**PA**) – Major Severity
10. Drug Age – Pediatric (**PA**) – Major Severity
11. Drug Disease (**DD**) – Major Severity
12. Drug Allergy (**DA**)
13. Excessive Duration (**MX**)
14. Underutilization (**LR**)

Overriding an ER, HD (select drugs), and PG (Severity 1) ProDUR Errors:

In the Oregon MMIS, four ProDUR alerts are set to deny: ER, PG Severity Level 1, HD (select drugs), and LD (Seroquel only)

Pharmacy providers may override the alerts by entering the appropriate Conflict Reason Code (ER, PG, HD) in NCPDP field **439-E4**, Professional Service Intervention Codes (O0, M0, P0, R0, 00) in NCPDP field **440-E5:**

M0 = Prescriber Consulted
P0 = Patient consulted
R0 = Other Consulted

And Result of Service/Outcome Code in NCPDP field **441-E6:**

- 1A – Filled As is, False Positive
- 1B – Filled Prescription As Is
- 1C - Filled, With Different Dose
- 1D – Filled, Different Direction
- 1E – Filled, With Different Drug
- 1F – Filled, Different Quantity
- 1G – Filled, Prescriber Approval

To override an HD (select drugs) denial, the appropriate Result of Service/Outcome Code of 2A or 2B is required. Pharmacists first cancel the HD denied claim by re-entering the HD code, appropriate intervention and outcome codes of 2A or 2b and re-submiting. This process cancels the claim and a new claim may be submitted with the corrected days supply or quantity. Result of /Service/Outcome Codes for HD are:

- 2A – Prescription Not Filled (HD Conflict Reason)
- 2B – Not filled-Direction Clarified (HD Conflict Reason)

The LD ProDUR for Seroquel can only be overridden by a prior authorization being entered.

ProDUR Report for November 2011-January 2012

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	46,099	13,857	408	31,765	58.73%
HD (High Dose)	1,227	33	491	692	1.53%
PG (Pregnancy/Drug Interaction)	3,688	2,554	16	1,076	4.60%
LD (Low Dose)	3,290	421	46	2,800	4.07%
ID (Ingredient Duplication)	12,912	4,430	35	8,310	16.47%
TD (Therapeutic Duplication)	6,309	2,075	36	4,038	7.97%

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

OHP FFS Average Cost PMPM Top 30 Drug Class – Fourth Quarter 2011

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Class Description**	**2011**	**2010**	**%**	**2011**	**2010**	**%**	**2011**	**2010**	**%**
1	7	Ataractics, Tranquilizers	$10.93	$10.57	3.3%	6.2	6.6	-6.8%	$177	$159	10.8%
2	33	Antivirals	$6.20	$2.37	161.6%	0.8	0.5	76.8%	$783	$525	49.2%
3	11	Psychostimulants, Antidepressants	$4.72	$4.59	2.8%	9.1	8.8	4.0%	$52	$52	-1.2%
4	15	Bronchial Dilators	$3.44	$3.71	-7.4%	3.5	4.0	-11.4%	$97	$93	4.4%
5	40	Narcotic Analgesics	$3.07	$4.12	-25.5%	7.4	8.7	-14.9%	$41	$47	-12.6%
6	99	Miscellaneous	$2.88	$3.43	-16.1%	1.5	1.5	5.5%	$182	$223	-18.6%
7	48	Anticonvulsants	$2.51	$2.91	-13.6%	5.4	5.7	-4.7%	$42	$45	-6.7%
8	10	CNS Stimulants	$2.34	$2.26	3.6%	1.9	1.9	-1.9%	$124	$117	5.6%
9	58	Diabetic Therapy	$2.29	$2.42	-5.4%	2.1	2.4	-13.1%	$109	$100	9.0%
10	71	Other Hypotensives	$2.07	$1.73	19.8%	2.8	3.1	-8.7%	$73	$57	30.0%
11	42	Antiarthritics	$1.35	$1.27	6.5%	2.1	2.3	-7.7%	$64	$56	14.2%
12	12	Amphetamine Preps	$1.30	$1.17	11.2%	0.9	0.9	5.3%	$137	$130	5.3%
13	51	Gluco Corticoids	$1.22	$0.94	28.9%	1.9	2.0	-5.3%	$63	$46	35.8%
14	1	Antacids	$1.18	$1.57	-24.8%	3.6	4.0	-10.0%	$33	$39	-16.4%
15	63	Oral Contraceptives	$1.15	$1.08	6.4%	2.6	2.4	8.6%	$44	$45	-2.0%
16	30	Antineoplastic	$1.14	$1.48	-23.1%	0.3	0.3	-1.2%	$290	$390	-25.8%
17	65	Lipotropics	$1.09	$1.02	6.7%	2.1	2.1	-2.5%	$52	$48	9.3%
18	27	Other Antibiotics	$1.04	$0.67	55.6%	0.8	0.9	-7.1%	$108	$70	54.0%
19	77	Anticoagulants	$0.97	$0.79	22.6%	0.5	0.6	-15.1%	$194	$135	44.3%
20	64	Other Hormones	$0.96	$0.70	36.5%	0.1	0.1	-11.5%	$783	$571	37.2%
21	41	Non-narcotic Analgesics	$0.89	$0.63	41.0%	5.1	4.8	5.8%	$17	$13	30.8%
22	87	Electrolytes and Misc Nutr	$0.66	$0.59	11.9%	2.9	3.0	-2.9%	$22	$19	15.8%
23	6	Laxatives	$0.66	$0.39	68.2%	5.4	5.3	2.0%	$12	$7	65.2%
24	23	Streptomycins	$0.43	$0.39	11.5%	0.0	0.0	-1.7%	$1,075	$886	21.4%
25	69	Enzymes	$0.41	$0.37	11.2%	0.0	0.0	-0.3%	$835	$764	9.4%
26	82	Multivitamins	$0.38	$0.23	66.3%	3.6	3.6	0.8%	$10	$6	64.1%
27	80	Fat Soluble Vitamins	$0.37	$0.23	60.7%	3.6	3.1	15.1%	$10	$7	39.8%
28	76	Other Cardiovascular Preps	$0.32	$0.38	-15.9%	1.8	2.2	-16.5%	$17	$17	-1.0%
29	88	Hematinics with/without Iron	$0.31	$0.19	63.6%	1.3	1.4	-4.1%	$17	$12	39.2%
30	14	Antihistamines	$0.30	$0.27	9.9%	2.5	2.6	-1.1%	$12	$11	12.2%
		Aggregate	$61.16	$57.18	7.0%	101.41	104.38	-2.8%	$77	$72	8.2%
		75th Percentile			36.5%			5.3%			37.2%
		50th Percentile (Median)			7.8%			-3.2%			10.1%

Last updated: January 18, 2012

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

OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - Fourth Quarter 2011

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	**Class Number**	**Brand Name**	**2011**	**2010**	**%**	**2011**	**2010**	**%**	**2011**	**2010**	**%**
1	7	ABILIFY	$3.33	$3.29	1.3%	0.56	0.59	-5.1%	$596	$558	6.8%
2	7	SEROQUEL	$2.24	$2.39	-6.5%	0.52	0.71	-27.2%	$430	$335	28.4%
3	11	CYMBALTA	$1.43	$1.16	22.5%	0.68	0.61	12.1%	$209	$191	9.3%
4	10	METHYLPHENIDATE HCL	$1.40	$0.02	7192.6%	1.05	0.11	875.0%	$133	$18	647.8%
5	71	REMODULIN	$1.32	$0.97	36.0%	0.01	0.00	22.0%	$21,681	$19,448	11.5%
6	33	SYNAGIS	$1.25	$0.70	78.8%	0.06	0.04	47.6%	$2,166	$1,786	21.3%
7	7	OLANZAPINE	$1.16			0.17			$662		
8	40	OXYCONTIN	$1.06	$1.12	-5.6%	0.21	0.28	-25.6%	$516	$407	26.8%
9	33	ATRIPLA	$1.02	$0.23	335.3%	0.06	0.02	298.6%	$1,633	$1,494	9.3%
10	33	TRUVADA	$0.93	$0.25	265.1%	0.10	0.03	212.2%	$971	$830	17.0%
11	7	GEODON	$0.88	$0.89	-1.6%	0.19	0.21	-10.8%	$463.92	$420.78	10.3%
12	7	ZYPREXA	$0.83	$1.61	-48.5%	0.11	0.27	-58.2%	$727.46	$591.09	23.1%
13	15	SINGULAIR	$0.76	$0.59	28.7%	0.50	0.45	9.9%	$152.87	$130.57	17.1%
14	11	LEXAPRO	$0.59	$0.57	3.8%	0.46	0.52	-12.6%	$130.00	$109.40	18.8%
15	7	SEROQUEL XR	$0.59	$0.44	32.8%	0.15	0.13	16.7%	$392	$345	13.7%
16	11	STRATTERA	$0.57	$0.54	6.0%	0.27	0.29	-3.7%	$207	$188	10.1%
17	58	LANTUS	$0.55	$0.58	-6.2%	0.29	0.32	-9.3%	$188.95	$182.71	3.4%
18	42	HUMIRA	$0.53	$0.48	12.3%	0.03	0.02	12.3%	$1,997.57	$1,997.34	0.0%
19	15	PROAIR HFA	$0.50	$0.51	-1.9%	0.94	1.08	-13.3%	$53.12	$46.95	13.2%
20	15	ADVAIR DISKUS	$0.49	$1.02	-52.5%	0.20	0.47	-57.8%	$244.64	$217.25	12.6%
21	51	FLOVENT HFA	$0.47	$0.36	31.5%	0.30	0.27	11.7%	$155.24	$131.92	17.7%
22	33	INCIVEK	$0.47			0.00			$16,410.22		
23	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.46	$0.39	18.2%	0.26	0.20	26.7%	$178.68	$191.59	-6.7%
24	33	REYATAZ	$0.45	$0.14	222.9%	0.05	0.02	173.2%	$876.10	$741.00	18.2%
25	65	LIPITOR	$0.43	$0.36	16.8%	0.27	0.29	-7.0%	$159.30	$126.86	25.6%
26	42	ENBREL	$0.42	$0.44	-3.5%	0.03	0.03	0.5%	$1,659.23	$1,729.45	-4.1%
27	40	HYDROCODONE-ACETAMINOPHEN	$0.41	$0.50	-18.5%	2.89	3.44	-16.0%	$14.23	$14.67	-3.0%
28	99	PULMOZYME	$0.41	$0.39	4.3%	0.02	0.02	-1.5%	$2,230.40	$2,104.82	6.0%
29	77	ENOXAPARIN SODIUM	$0.39	$0.22	75.2%	0.05	0.02	139.5%	$755.91	$1,033.96	-26.9%
30	33	PEGASYS	$0.38	$0.10	275.5%	0.01	0.00	179.5%	$2,755.57	$2,059.28	33.8%
31	15	SPIRIVA	$0.38	$0.29	33.4%	0.16	0.14	8.2%	$247.11	$200.60	23.2%
32	15	COMBIVENT	$0.38	$0.34	9.7%	0.18	0.21	-18.4%	$215.41	$160.45	34.2%
33	40	FENTANYL	$0.37	$0.37	0.2%	0.18	0.15	20.4%	$204.36	$245.63	-16.8%
34	12	VYVANSE	$0.37	$0.27	34.7%	0.23	0.19	22.7%	$158.04	$143.93	9.8%
35	58	NOVOLOG	$0.36	$0.35	2.8%	0.16	0.17	-8.2%	$224.76	$200.76	12.0%
36	11	PROVIGIL	$0.35	$0.28	28.0%	0.03	0.04	-10.2%	$1,070.50	$750.17	42.7%
37	23	TOBI	$0.35	$0.31	10.1%	0.01	0.01	4.6%	$4,435.88	$4,216.29	5.2%
38	11	INTUNIV	$0.34	$0.16	110.8%	0.19	0.10	86.5%	$176.39	$156.11	13.0%
39	58	HUMALOG	$0.32	$0.29	9.1%	0.12	0.12	5.3%	$256.35	$247.52	3.6%
40	33	ISENTRESS	$0.30	$0.07	322.8%	0.03	0.01	420.2%	$907.16	$1,115.45	-18.7%
		Aggregate	$61.16	$57.18	7.0%	101.41	104.38	-2.8%	$77	$72	8.2%
		75th Percentile			77.6%			18.5%			65.5%
		50th Percentile (Median)			10.4%			-4.7%			18.9%

Last updated: January 18, 2012

Drug Use Research & Management Program
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Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: January 2011 - December 2011

	2011												
	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	AVG/YTD
Eligibility													
Total Members	567,706	582,012	583,892	588,812	587,524	590,406	592,894	593,825	595,965	600,779	603,146	607,560	591,210
FFS Members	101,460	93,432	93,083	95,186	96,165	92,552	93,582	91,122	93,140	95,835	90,655	93,725	94,161
Standard	11,023	8,621	6,975	6,465	6,636	6,191	6,261	5,648	5,648	5,893	5,238	5,843	6,704
Plus	66,459	60,814	61,879	64,226	64,994	61,751	62,454	60,588	62,521	64,748	60,321	62,633	62,782
Medicare Wrap	23,978	23,997	24,229	24,495	24,535	24,610	24,867	24,886	24,971	25,194	25,096	25,249	24,676
Gross Figures													
Total Cost	$12,936,231	$12,608,046	$14,181,924	$13,434,890	$13,927,185	$14,019,094	$13,441,500	$14,406,998	$13,874,141	$13,696,222	$13,730,339	$14,022,722	$164,279,292
FFS Drugs	$3,977,251	$3,902,054	$4,370,565	$4,120,989	$4,279,429	$4,297,788	$4,152,647	$4,269,073	$4,234,164	$4,063,544	$4,091,975	$4,132,762	$49,892,241
Mental Health Carveout Drugs	$8,958,981	$8,705,992	$9,811,359	$9,313,900	$9,647,756	$9,721,306	$9,288,853	$10,137,924	$9,639,977	$9,632,678	$9,638,364	$9,889,960	$114,387,051
Total Rx	179,235	171,724	194,014	179,060	184,889	182,952	171,383	185,973	178,171	176,262	177,649	181,375	2,162,687
FFS Drugs	83,905	80,427	90,361	82,430	85,560	83,774	77,472	83,555	80,097	78,411	78,423	79,741	984,156
Mental Health Carveout Drugs	95,330	91,297	103,653	96,630	99,329	99,178	93,911	102,418	98,074	97,851	99,226	101,634	1,178,531
Cost/Rx	$72.17	$73.42	$73.10	$75.03	$75.33	$76.63	$78.43	$77.47	$77.87	$77.70	$77.29	$77.31	$75.98
FFS Drugs	$47.40	$48.52	$48.37	$49.99	$50.02	$51.30	$53.60	$51.09	$52.86	$51.82	$52.18	$51.83	$50.75
Mental Health Carveout Drugs	$93.98	$95.36	$94.66	$96.39	$97.13	$98.02	$98.91	$98.99	$98.29	$98.44	$97.14	$97.31	$97.05
Generic	$30.39	$30.61	$30.67	$31.21	$31.29	$31.23	$30.86	$30.13	$30.23	$30.14	$29.28	$28.50	$30.38
Brand	$289.00	$294.27	$294.98	$298.95	$300.12	$305.61	$318.12	$316.58	$315.51	$315.58	$318.94	$322.44	$307.51
PMPM Figures													
Cost PMPM	$54.98	$56.72	$63.76	$59.11	$60.92	$62.90	$60.04	$63.92	$61.64	$58.44	$61.12	$60.37	$60.33
Standard	$60.15	$69.36	$94.26	$120.50	$137.87	$157.46	$153.77	$168.38	$159.60	$144.12	$160.64	$161.45	$132.30
Plus	$63.57	$65.32	$72.68	$62.70	$64.19	$65.25	$61.57	$66.91	$64.08	$60.73	$64.23	$63.00	$64.52
Medicare Wrap	$16.37	$15.15	$16.50	$16.57	$15.54	$16.17	$14.95	$17.25	$15.94	$15.17	$16.81	$15.15	$15.96
FFS Drugs	$39.20	$41.76	$46.95	$43.29	$44.50	$46.44	$44.37	$46.85	$45.46	$42.40	$45.14	$44.09	$44.21
Mental Health Carveout Drugs	$15.78	$14.96	$16.80	$15.82	$16.42	$16.47	$15.67	$17.07	$16.18	$16.03	$15.98	$16.28	$16.12
Rx PMPM	0.99	1.02	1.15	1.03	1.06	1.07	0.99	1.09	1.02	0.98	1.03	1.02	1.04
Standard	1.28	1.48	2.02	2.01	2.11	2.20	1.98	2.31	2.16	2.00	2.21	2.07	1.99
Plus	0.92	0.95	1.04	0.91	0.93	0.94	0.86	0.95	0.91	0.84	0.90	0.88	0.92
Medicare Wrap	1.01	0.95	1.06	0.97	1.00	1.01	0.96	1.04	0.96	0.99	0.99	1.00	0.99
FFS Drugs	0.83	0.86	0.97	0.87	0.89	0.91	0.83	0.92	0.86	0.82	0.87	0.85	0.87
Mental Health Carveout Drugs	0.17	0.16	0.18	0.16	0.17	0.17	0.16	0.17	0.16	0.16	0.16	0.17	0.17
Utilization Percentages													
Generic %	83.8%	83.8%	83.9%	83.6%	83.6%	83.5%	83.4%	83.5%	83.3%	83.3%	83.4%	83.4%	83.6%
FFS Drugs	88.3%	88.3%	88.4%	88.3%	88.2%	88.0%	88.1%	88.2%	88.0%	88.1%	88.4%	88.5%	88.2%
Mental Health Carveout Drugs	79.9%	79.7%	80.0%	79.6%	79.7%	79.6%	79.6%	79.6%	79.5%	79.5%	79.5%	79.4%	79.6%
PDL %	80.1%	80.2%	80.2%	80.2%	80.1%	79.9%	80.0%	79.9%	79.8%	79.7%	80.7%	80.8%	80.1%

PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

Last Updated: January 18, 2012

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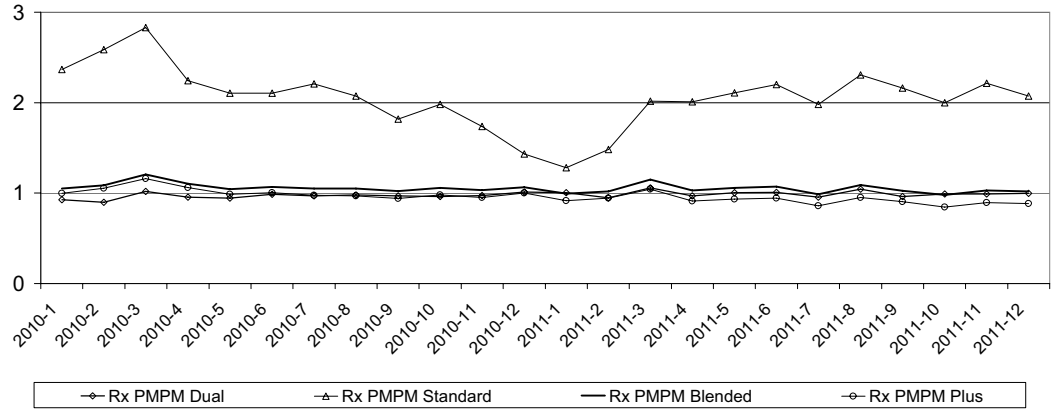
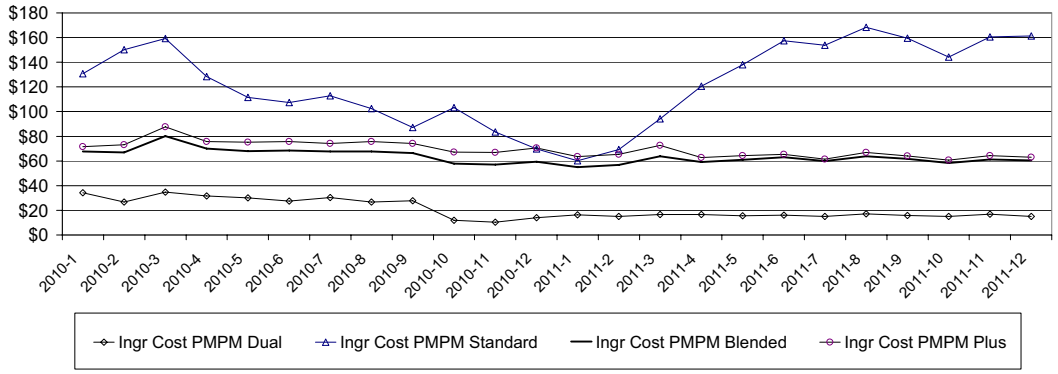
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: 2010-2011

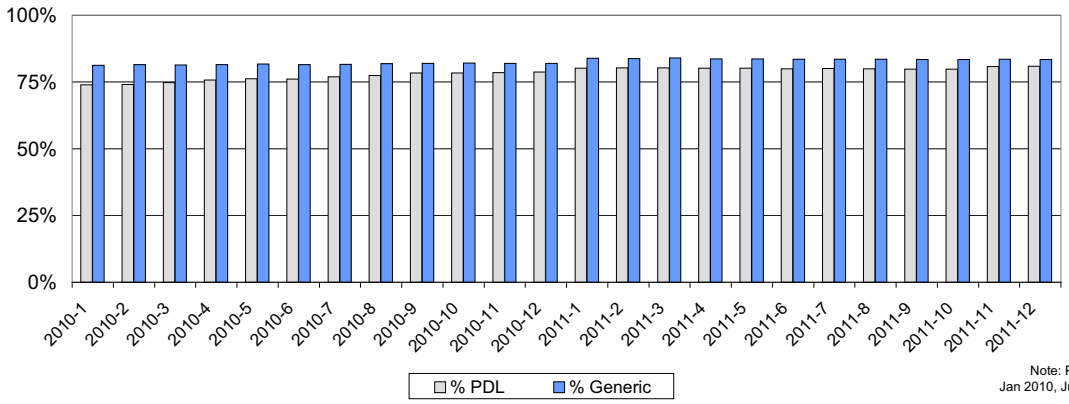
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

Oregon State University
College of Pharmacy

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

Policy Evaluation: HB 2126 – OHP Preferred Drug List Enforcement and Voluntary Mental Health Preferred Drug List

Executive Summary

- HB 2126 specifically allows the Oregon Health Authority to require prior authorization (PA[1]) for Oregon Health Plan fee-for-service physical health (PH) drugs not listed as preferred on the Preferred Drug List (PDL). This is called the PA-enforced PH PDL. A budget reduction of approximately $4 million total funds in OHP drug costs for the 09-11 biennium was assigned to the PA-enforced PH PDL.

- The PA-enforced PH PDL is estimated to have avoided $4.6 million for the 09-11 biennium. This total does not include CMS rebate revenues.
    - $3.8 million TF avoided costs avoided in pharmacy expenditures
    - $0.8 million TF increased supplemental rebate revenues
    - Unknown CMS rebate revenue changes due to the federal Affordable Care Act.

- HB 2126 specifically prohibits the Oregon Health Authority from requiring PA[1] for Oregon Health Plan fee-for-service mental health (MH) drugs not listed as preferred on the Preferred Drug List (PDL). This is called the Voluntary MH PDL. A budget reduction of approximately $3 million total funds was assigned to the Voluntary MH PDL.

- The Voluntary Mental Health PDL increased supplemental rebate revenues by only $260,000 TF for the 09-11 biennium.
    - Several manufacturers refused to extend supplemental rebates to Oregon in the absence of PA of non-preferred products despite high voluntary use of preferred drugs.
    - An estimated $2.4 million was unavailable to Oregon because of the voluntary nature of the MH PDL.

- The PA-enforced Physical Health PDL climbed to the target 90% use of preferred drugs November.
    - Statutory requirement to exempt prescriptions written prior to July 1, 2009 from prior authorization delayed the market share shift to preferred drugs.
    - Statutory requirement that prohibits the OHA from denying a prior authorization request for a non-preferred drug if no preferred drug was tried first has reduced expected use of preferred drugs.

- The statutory requirements of grandfathering prescriptions written prior to July 1, 2009, no denials for non-preferred drugs, and response to PA requests within 24 hours, were met.

[1] A glossary of acronyms can be found preceding the references.

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

Policy Evaluation: HB 2126 – Oregon Health Plan Preferred Drug List Enforcement and Voluntary Mental Health Preferred Drug List

HB 2126[1] was passed in the 2009 Oregon Legislature. It specifically allows the Oregon Health Authority to require prior authorization (PA) for Oregon Health Plan fee-for-service drugs not listed as preferred on the Preferred Drug List (PDL), also called the Practitioner Managed Prescription Drug Plan. There are several significant exceptions to the State's ability to require prior authorization for PDL placement:

1) mental health (MH) drugs are not subject to prior authorization
2) provider prevails; meaning the Oregon Health Authority cannot deny access to the non-preferred product if the prescriber requests a prior authorization and after consultation deems the non-preferred drug medically necessary,
3) grandfathering; meaning the original prescription is written prior to July 1, 2009 or the request is for a refill for seizures, cancer, HIV or AIDS; or an immunosuppressant,
4) a prior authorization is not responded to the prescriber within 24 hours
5) the drug is in a class not reviewed for the PDL.

A budget reduction of approximately $4 million in Oregon Health Plan drug costs (total funds - TF) for the 09-11 biennium was assigned to this bill. This budget target assumes 90% use of preferred products and a January 1, 2010 start date. Another $3 million (TF) was assigned to a voluntary mental health PDL.

HB 2126 mandates Oregon Health Authority report to the health related committees and the Joint Committee on Ways and Means of the Seventy-sixth Legislative Assembly on the implementation and effectiveness. This evaluation is an update of the preliminary evaluation done in January 2011[2] and will determine if HB 2126 budget targets were achieved, if target use rates of preferred products were realized, report on prior authorization requests made, approved and time to respond and highlight opportunities for improvement.

History of Oregon Health Plan PDL implementation

The Oregon Health Plan PDL was initially authorized by the 2001 Legislature.[3] The legislation mandated that drugs be publicly evaluated first for their clinical evidence and second for their relative cost. The Oregon Health Plan PDL is created using a combination of evidence from the medical literature and local clinician opinions. This is different from an insurance company formulary development because public comment is embedded at several locations in the process and the evidence evaluation is done using established, explicit and transparent standards.[4, 5] See Appendix A for a flow chart of the current PDL development process.

Drug cost is considered only after clinical recommendations are made. The net price includes two types of manufacturer rebates. CMS[6] mandated rebates, which are a condition of Medicaid participation, and Supplemental Rebates, which are negotiated in addition to the CMS Rebates. Supplemental Rebates are not *required* to be considered for PDL preferred status but are *considered* in the pricing. Both rebates

are proprietary and confidential and cannot be disclosed. See Figure 1 for an example of how rebates affect net price of brand and generic drugs. The base price per unit is based on the average cost per day of a brand drug and a generic drug. This model assumes a 30% CMS brand rebate, 13% generic CMS rebate, 3% brand supplemental rebate and 0% generic supplemental rebate. However, there is great variance in all of these costs and rates across the market.

Figure 1

Brand Drug Rebate Example

$11.30	Price per unit reimbursed to pharmacy by Oregon Health Authority
- 3.40	Less CMS rebate per unit paid by manufacturer to Oregon Health Authority for each unit reimbursed
$ 7.90	Net cost with CMS rebate
- 0.25	Less supplemental rebate per unit paid by manufacturer to Oregon Health Authority for each unit reimbursed
$ 7.65	Final Net-Net Cost per unit

Generic Drug Rebate Example

$ 1.70	Price per unit reimbursed to pharmacy by Oregon Health Authority
- 0.10	less CMS rebate per unit paid by manufacturer to Oregon Health Authority for each unit reimbursed
$ 1.60	Net cost with CMS rebate
- 0.00	Less supplemental rebate per unit paid by manufacturer to Oregon Health Authority for each unit reimbursed
$ 1.60	Final Net-Net Cost per unit

Supplemental rebates were rarely offered to Oregon by individual manufacturers prior to July 1, 2009 when the Oregon Health Authority contracted with the Sovereign States Drug Consortium (SSDC)[7] to negotiate Supplemental Rebates with manufacturers. Many manufacturers require prior authorization of non-preferred drugs in return for Supplemental Rebates but rarely require market share guarantees. The SSDC is a non-profit, multi-state, Medicaid purchasing pool. The January 2010 PDL update was the first update to use the SSDC Supplemental Rebate bids to determine net price.

The practice of requiring prior authorization for non-preferred drugs is commonly used by commercial insurance plans, Medicare Part D plans and the great majority of state Medicaid programs in order to increase market share of the preferred drugs used. Increased market share of preferred drugs saves money through increased use of high quality, lower cost drugs and provides leverage to negotiate lower net prices (aka Supplemental Rebates) from manufacturers. The process to access non-preferred drugs has varied from 2002 to present. See Table 1 for a summary.

Table 1 – Oregon Health Plan PDL Implementation Summary

Period	Process to Access Non-Preferred Drugs	Preferred Drug Use Rate[8]	Comments
Aug 2002 - Apr 2003	"Dispense as Written" noted on prescription	58% (PH only)	Technically challenging to administer with claim system; did not meet budget targets
May 2003 - Sep 2003	Prior authorization	82% (PH only)	Avoided ~ $500,000TF/month[9] but the legislature prohibited prior authorization in subsequent special session
Oct 2003 - Feb 2008	Voluntary with targeted provider education and use of Epocrates[10]	68%-76% (PH only)	Difficult to leverage supplemental rebates
Mar 2008 – Dec 2009	Copay & quantity incentives; Epocrates	76% - 82% (PH only)	Increased preferred drug use, but still not meeting target 90%; No voluntary MH PDL;
Jan 2010 - Mar 2010	Copay & quantity incentives; Epocrates; Voluntary MH PDL added	74% (PH / MH combined)	Addition of MH drugs decreased overall preferred use rate. MH drugs influence the rate significantly due to the MH drug carve-out from managed care. They also have a lower preferred drug use rate. PDL developed with supplemental bids included
Apr 2010 – Dec 2010	Prior authorization started for physical health (PH) PDL[11]; Voluntary MH PDL (no prior authorization); Copay & quantity incentives continue; Epocrates	74% - 76% (PH / MH combined)	Grandfathering & provider prevails in place per statute; Some MH supplemental bids not available without prior authorization
Jan 2011 - Present	42 new PH classes added to the PDL. PA continues for PH PDL only. MH PDL remains voluntary	76% - 80% (PH / MH combined)	

TF = total funds, PH = Physical Health, MH=Mental Health, PDL = Preferred Drug List

Methods

The total gross drug cost trend was derived from paid, clean, fee-for-service drug claims and was reported as the sum of the amount paid on the claim. PDL status is the list effective on the date of dispensing.

Cost avoidance is a function of increased use of lower cost drugs at the pharmacy and increased rebate revenues. A pharmacy reimbursement trend analysis was done for a 15 month period before the prior authorization implementation and 17 months following implementation. The pre period was; 1/1/09 – 3/31/10 (15 months) and the post period was; 5/1/10 – 9/30/11 (17 months). The expected monthly linear trend was compared with observed monthly trend. The difference in trend estimated the cost avoidance. The trend analysis was conducted in aggregate, grouped by physical health (PH) and mental health (MH) drugs, on a per member per month (PMPM) basis to control for changes in enrollment. The PH drugs excluded hemophilia drugs because payment policy changed during the evaluation period and they are not included in the PDL.

A CMS rebate revenue trend analysis for a 12 month period prior to implementation of the new PDL and 6 months following implementation of the new PDL was planned. However, two confounders made this analysis impossible. The Affordable Care Act (ACA) changed the minimum rebate that must be provided by manufacturers beginning January 1, 2010 and changed the percentage of the rebate retained by the states. Supplemental Rebate revenue is entirely new revenue and thus is simply reported as revenue for the quarters claimed.

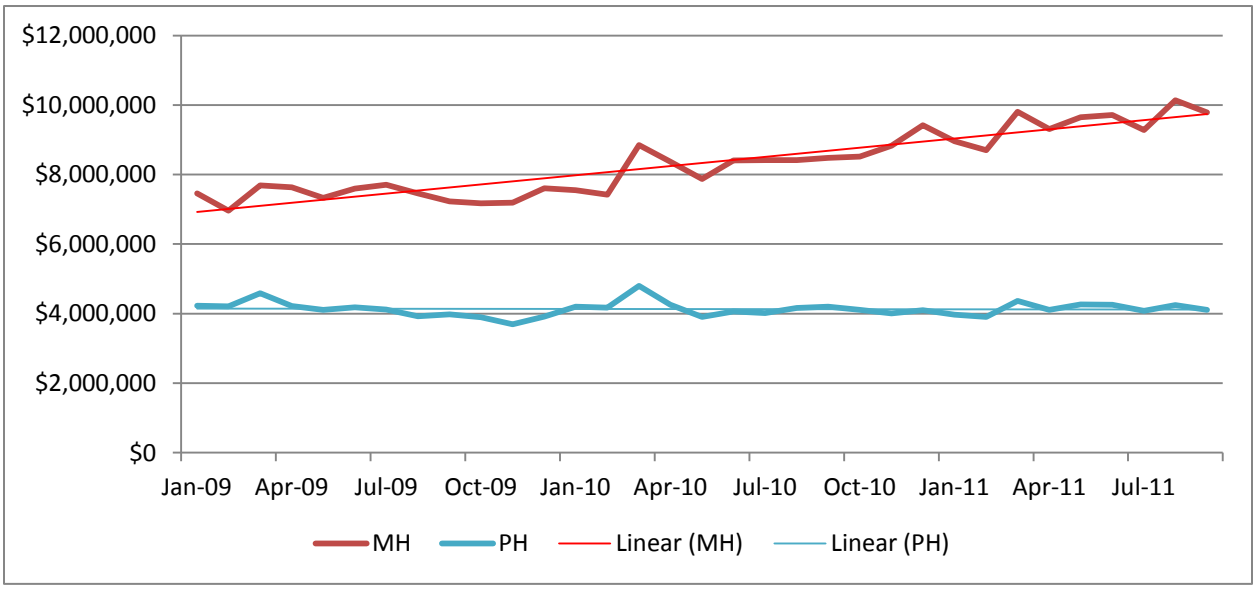
The preferred drug use rate was evaluated as the number of claims for preferred drugs over sum of the number of claims for both preferred and non-preferred drugs. This is reported as PA-enforced PH PDL and voluntary MH PDL separately.

Prior Authorization requests are reported by method of request and approval rate (i.e. number of prior authorizations approved divided by total prior authorizations requested).

Results

With the additional 42 classes added to the PDL January 1, 2011, the current Oregon Health Plan (OHP) PDL currently captures 78.5% of total OHP fee-for-service gross drug costs on average. The remaining 21.5% of costs are in classes that have not been reviewed for the PDL to date. The Voluntary MH PDL is associated with 60% of total OHP fee-for-service gross drug costs on average. This is because MH drugs are "carved-out" of Medicaid managed care contracts and thus all MH drugs for all OHP clients are paid for fee-for-service. Figure 2 displays that MH drugs continue to trend upwards at more than $1 million annually (14%). The PA-enforced PH PDL captures just 18.5% of total Oregon Health Plan fee-for-service gross drug costs and the trend is essentially flat.

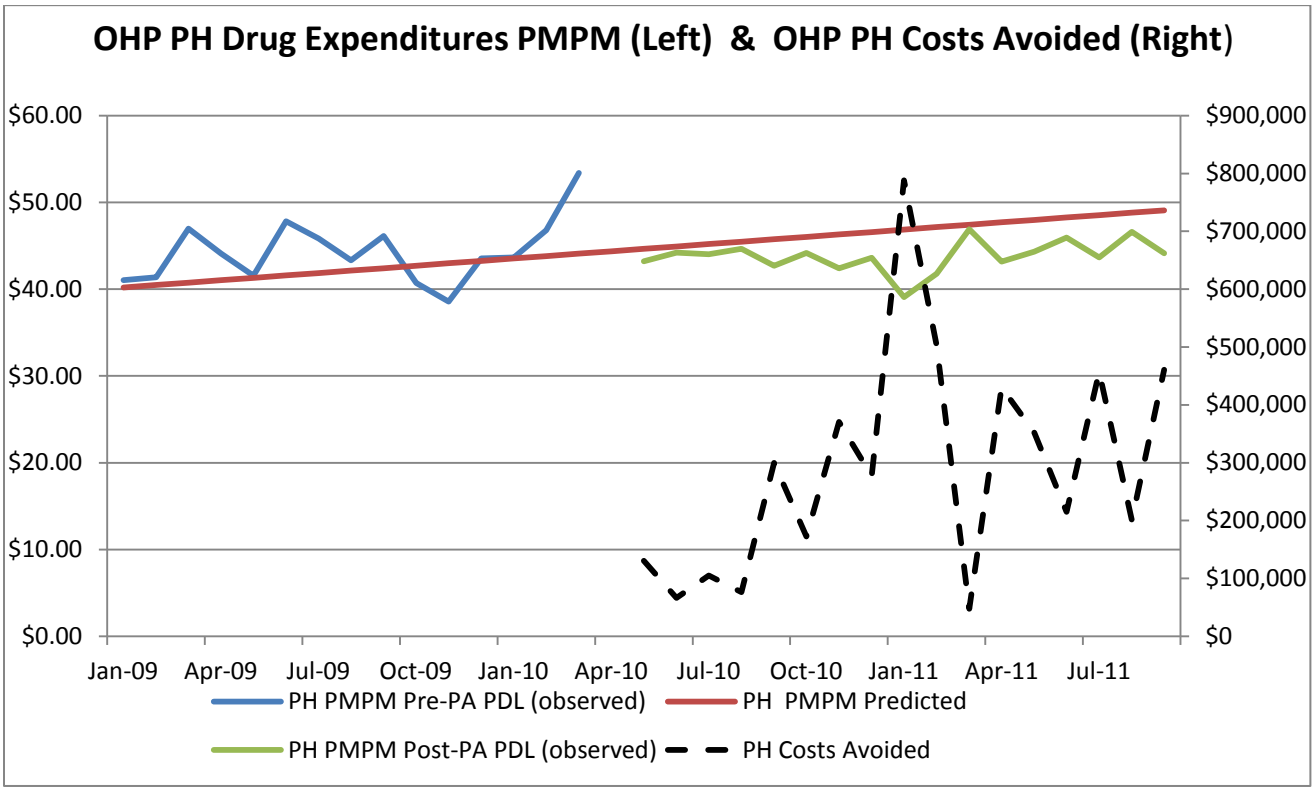
Figure 2 - Oregon Health Plan fee-for-service monthly gross drug cost trend[7]



PH = Physical Health; MH = Mental Health; Costs exclude all rebates

The trend analysis for the PA-enforced PH PDL expenditures PMPM is represented in Figure 3. Prior authorization enforcement was initiated April 13, 2010. For the first 17 months of the prior authorization enforcement an average of $291,000 per month was avoided. This is approximately $5 million total PH drug costs for the 17 months of evaluation and $3.8 million for the 14 months of the 09-11 biennia. However, it is likely that some of the savings in January 2011 should be attributed to a one-time change in pharmacy reimbursement implemented that month.

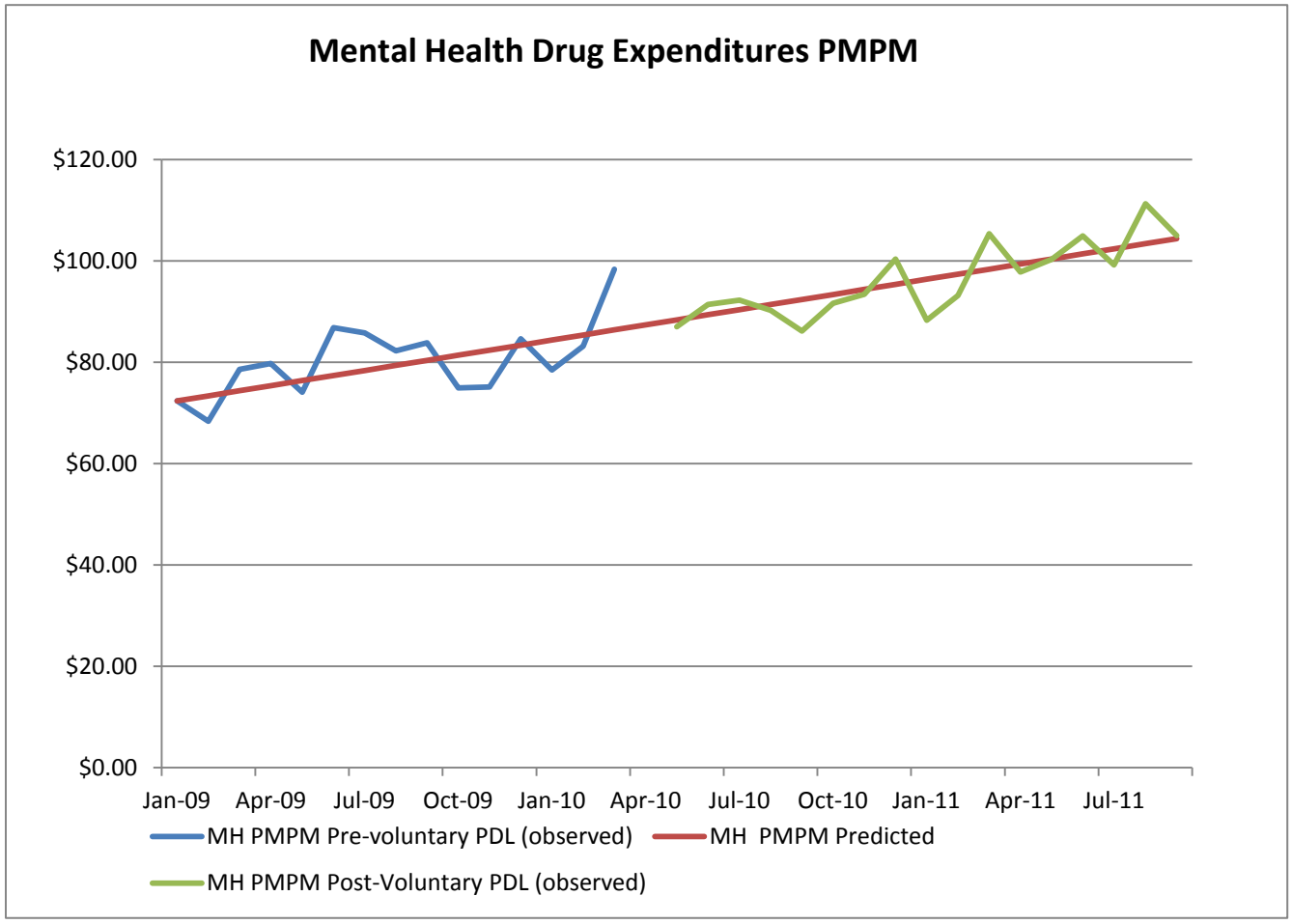
Figure 3 – Trend Analysis for PA-enforced PH PDL



PH = Physical Health; PMPM = per member per month; Costs exclude all rebates

The trend analysis for the voluntary MH PDL expenditures is represented in Figure 4. This group of drugs (60% of total FFS drug costs) is exempt from the prior authorization exception process and there is essentially no change in trend for the first 21 months (Jan 1, 2010 – Sep 30, 2011) of the voluntary MH PDL. Will there was a notable one-time effect from the January 2011 reimbursement change, the trend was not affected.

Figure 4 – Trend Analysis for Voluntary MH PDL



MH = Mental Health; PMPM = per member per month; Costs exclude all rebates

Prior to the SSDC[6] contract there were no supplemental rebate contracts in place. Calendar year Quarter 3 2009 was the first quarter of the new SSDC contract and invoices were prepared for the PH PDL in place at the time. Starting in Quarter 1 2010, the PH PDL was created using the supplemental bids and thus supplemental rebate revenues increased considerably from 1.5% to 3% of reimbursed PH PDL pharmacy costs. However, supplemental offers for branded drugs decreased dramatically in 2011 to 0.4% of reimbursed PH PDL pharmacy costs. This is likely due to the uncertainty created by the ACA and because many key drugs are going generic in 2011 and 2012.

There is an approximate 6-9 month delay from the time a drug is dispensed and paid for at the pharmacy to rebate collection. There is also considerable administrative burden to prepare contracts and invoices, track payments and settle disputes that is not captured in this analysis. Table 2 reports all the supplemental rebates collected for the PH PDL. There was $785,779 collected in the 2009-11 biennium since implementation of the PH PDL and with Quarter 2 2011 still outstanding.

Table 2 – Supplemental Rebates Invoiced for PH PDL Drugs

CY Quarter	Rebate Collected	Sum PH PDL Paid Claim Amount	Rebate Pct of PH PDL Costs
2009_3	$41,730	$3,197,885	1.3%
2009_4	$44,570	$2,994,814	1.5%
2010_1	$146,911	$4,477,253	3.3%
2010_2	$150,946	$4,021,537	3.8%
2010_3	$189,784	$4,091,650	4.6%
2010_4	$183,711	$4,056,110	4.5%
2011_1	$28,127	$7,231,306	0.4%

Table 3 reports MH drug supplemental rebate collections. There are several manufacturers of MH drugs that will not contract for supplemental rebates because there is no prior authorization in place for non-preferred drugs. Thus the collection rate for MH drugs is much lower (<0.3% of reimbursed MH PDL pharmacy costs). Two supplemental rebate bids for MH drugs that were not available to Oregon because of no prior authorization enforcement. These two bids amounted to almost $2.5 million for the 2009-11 biennia that went unrealized. Still, approximately $260,000 in MH drug supplemental rebates was collected in 2009-11.

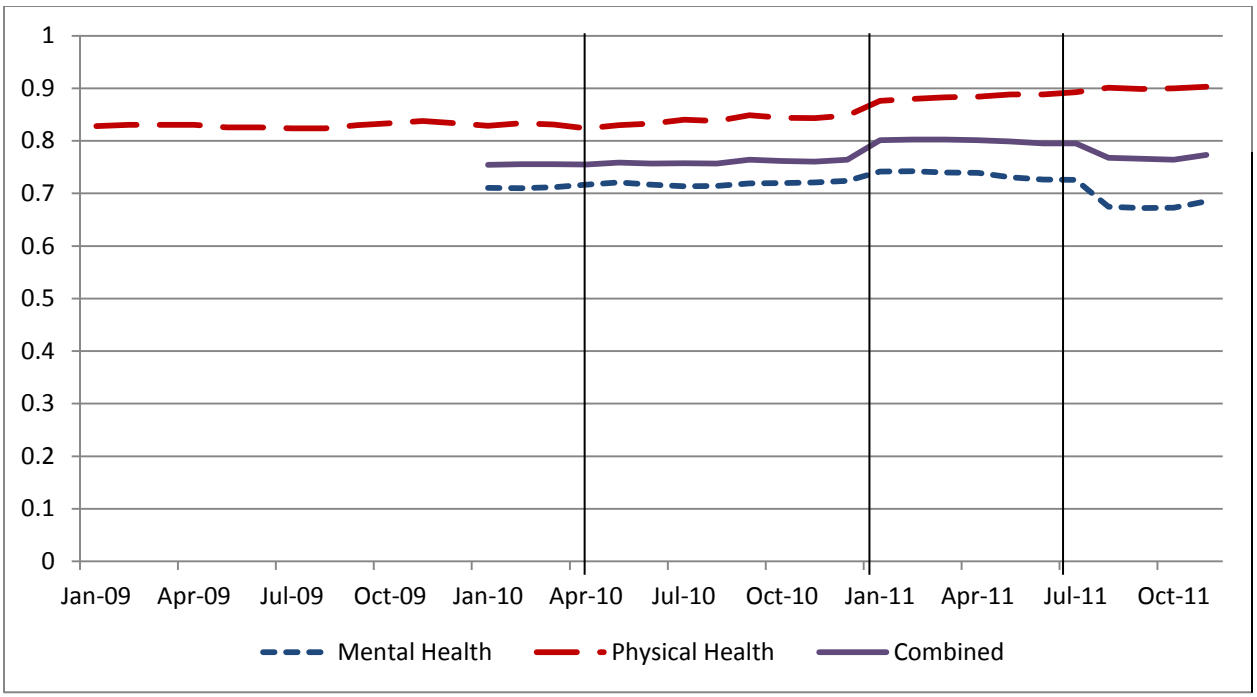
Table 3 – Supplemental Rebates Invoiced for MH PDL Drugs

CY Quarter	Rebate Collected	Sum MH PDL Paid Claim Amount	Rebate Pct of MH PDL Costs
2009_3			
2009_4			
2010_1	$43,978	$20,200,323	0.2%
2010_2	$67,448	$19,741,462	0.3%
2010_3	$69,319	$21,248,236	0.3%
2010_4	$45,682	$22,593,722	0.2%
2011_1	$33,858	$24,649,978	0.1%

Figure 5 depicts the preferred drug use rate for the PA-enforced PH PDL and the voluntary MH PDL. The pre-PA-enforced PH PDL preferred drug use rate was flat at 83%. The PA was implemented for the PH PDL in April 2010 with extensive grandfathering to accommodate patients that were stabilized on non-preferred drugs. Still, the preferred drug use rate of the PH PDL increased to 85% by July 2010. On January 2011 the PH PDL was revised accounting for an immediate increase to 87.5% preferred use rate and it has steadily increased to just over 90% in November 2011.

In contrast the voluntary MH PDL preferred drug use rate remained flat at 71% through 2010. It increased to 74% when with supplemental rebates that allowed two products be preferred through 7/1/2011 and decreased to 68% when both contracts were rescinded and those products were removed from the MH PDL.

Figure 5 –Rate of Preferred Drug Use for PH PDL, MH PDL and combined PDL



There are 72 drug classes captured by the PH PDL. Of these, 57 classes meet or exceed the target 90% preferred use rate. The preferred use rate for the remaining 15 classes is trending upward or has erratic utilization due to small numbers of claims.

HB2126 required that non-preferred prescriptions written prior to July 1, 2009 be exempt from prior authorization. To fulfill this mandate, the claims system was programmed to "grandfather" existing prescriptions for non-preferred drugs by generating and approving an "Auto-PA" for any client that had a paid claim for the non-preferred drug within the previous 90-days. The Auto-PA function was turned off in August 2010 when the statutory mandate had expired. Extensive grandfathering was also used to smooth implementation of 42 new classes in January of 2011. Table 4 reports the number of prior authorization requests made for non-preferred drugs by media type. Over 90% of prior authorizations

requested during the initial phases of prior authorization implementation were automatically generated and approved and this reflects the "grandfathering" policy. Both the total number of prior authorization requests and Auto-PA requests decline precipitously in September 2010 and April 2011 but there is not a consequent increase of other forms of prior authorization requests of similar magnitude. This change is also reflected in Figure 3 where the cost avoidance in September and October 2010 increases relative to previous months. Some non-preferred PDL drugs also have appropriate use prior authorization requirements imposed by Pharmacy and Therapeutics Committee recommendation that apply. This data does not differentiate between "appropriate use prior authorization" and "non-preferred drug prior authorization".

Table 4 - Total Non-Preferred Drug PAs Requested by Media Type

Total Non-Preferred Drug PAs								
Month	AUTO PA	ELEC TXN	FAX	ONLINE	PAPER	PHONE	WEB	TOTAL PA's ADJUD.
2010_01	103	0	30	5	0	38	0	176
2010_02	377	0	31	5	0	40	1	453
2010_03	257	0	57	4	0	53	1	371
2010_04	4,225	0	62	1	0	72	3	4,360
2010_05	1,822	1	71	3	0	50	6	1,947
2010_06	828	2	76	0	0	47	5	953
2010_07	1,023	0	44	0	0	56	4	1,123
2010_08	829	0	76	0	0	61	4	966
2010_09	37	0	97	1	0	101	12	236
2010_10	31	0	113	1	0	88	3	233
2010_11	26	0	86	1	0	77	5	190
2010_12	29	0	67	0	0	74	5	170
2011_01	5,748	0	148	5	1	170	14	6,072
2011_02	2,254	0	132	1	0	146	11	2,533
2011_03	1,580	0	171	1	1	122	15	1,875
2011_04	964	0	115	2	0	148	12	1,229
2011_05	388	1	246	3	0	238	21	876
2011_06	118	0	215	0	1	201	21	535
2011_07	206	0	128	1	0	143	11	478
2011_08	271	0	206	4	1	183	18	665
2011_09	89	0	153	4	0	154	13	400
2011_10	30	0	114	3	1	162	11	310
Totals	21,235	4	2,438	45	5	2,424	196	26,151
Pct	81.20%	0.02%	9.32%	0.17%	0.02%	9.27%	0.75%	100.00%

	PDL implemented 1/1/11 with only classes with existing clinical criteria enforced (Long Acting Opioids & Singulair™ primarily)
	All remaining physical health PDL PA- enforced beginning 4/13/2010
	PDL updated with changes on 7/1/2010
	42 new PH classes added to the PH PDL with grandfathering of existing patients stabilized on non-preferred products

Table 5 reports the percent of prior authorization requests that were approved. Over 99% of requests are approved and reflects the "provider prevails" requirement of the statute.

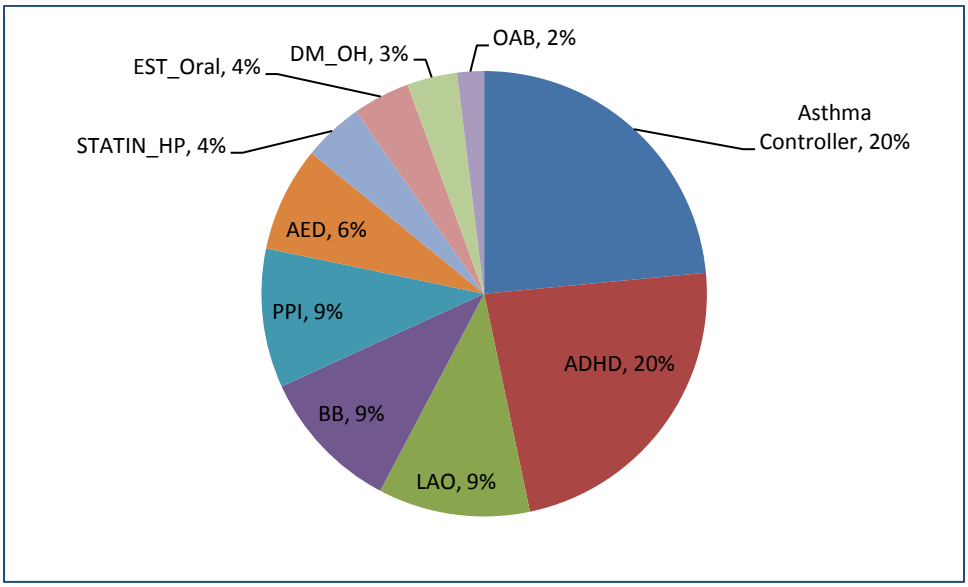
Table 5 - Total Non-Preferred Drug PAs Approved - as Percent of Total Requested

Approved - as Percent of Total Requested								
Month	AUTO PA	ELEC TXN	FAX	ONLINE	PAPER	PHONE	WEB	TOTAL PA's ADJUD.
2010_01	99%	-	100%	100%	-	100%	-	99%
2010_02	100%	-	100%	100%	-	100%	100%	100%
2010_03	100%	-	98%	100%	-	100%	100%	99%
2010_04	100%	-	97%	100%	-	100%	100%	100%
2010_05	100%	100%	99%	100%	-	100%	100%	100%
2010_06	100%	100%	100%	-	-	100%	100%	100%
2010_07	100%	-	98%	-	-	98%	100%	100%
2010_08	100%	-	99%	-	-	100%	100%	100%
2010_09	100%	-	99%	100%	-	99%	100%	99%
2010_10	100%	-	100%	100%	-	99%	100%	100%
2010_11	100%	-	100%	100%	-	97%	100%	99%
2010_12	100%	-	100%	-	-	97%	100%	99%
2011_01	100%	-	100%	100%	100%	99%	100%	100%
2011_02	100%	-	99%	100%	-	100%	100%	100%
2011_03	100%	-	99%	100%	100%	99%	100%	100%
2011_04	100%	-	100%	100%	-	100%	100%	100%
2011_05	100%	100%	100%	100%	-	100%	100%	100%
2011_06	99%	-	100%	-	100%	100%	100%	100%
2011_07	100%	-	100%	100%	-	99%	100%	100%
2011_08	100%	-	100%	100%	100%	99%	100%	100%
2011_09	100%	-	99%	100%	-	99%	92%	100%
2011_10	100%	-	99%	100%	100%	99%	100%	99%
	100%				100%	99%	99%	100%

	PDL implemented 1/1/11 with only classes with existing clinical criteria enforced (Long Acting Opioids & Singulair primarily)
	All remaining physical health PDL PA- enforced beginning 4/13/2010
	PDL updated with changes on 7/1/2010
	>40 new classes added to the PH PDL with grandfathering of existing patients stabilized on non-preferred products

Figure 6 reports the top 10 classes by prior authorization requests made. Notably, 4 of the top 5 classes (Asthma Controllers, ADHD, LAO and PPI) have clinical criteria for appropriate use recommended by the Pharmacy and Therapeutics Committee associated with them.

Figure 6 – Top 10 Classes by PAs Requested (Percent of Total PA requests)



A glossary of acronyms can be found preceding the references.

Table 6 reports the Oregon Pharmacy Call Center statistics for 2010-11. It includes calls for prior authorizations and technical claim processing or trouble-shooting questions. There was a spike in call volume in Q1-2011 when 42 new classes were implemented but this has dropped off subsequently. Notably, 100% of prior authorization requests were processed within 24 hours.

Table 6 – Pharmacy Call Center Statistics

	Q1-2010	Q2-2010	Q3-2010	Q4-2010	Q1-2011	Q2-2011	Q3-2011	Q4-2011
Messages Received	577	218	152	128	333	56	403	217
Total Calls Received	12939	12515	13228	13079	18067	16937	14919	14706
Total Calls on Hold > 5 min	19	6	5	2	15	3	6	3
Abandoned Call Rate	4%	5%	5%	5%	6%	7%	9%	4%
% PA Requests Processed in 24 hrs	100%	100%	100%	100%	100%	100%	100%	100%

Discussion

The PA-enforced PH PDL avoided $3.8 million in pharmacy expenditures and increased supplemental rebate revenues by $0.8 million (total of $4.6 million TF). This exceeds the $4 million budget reduction assigned to HB 2126. It does not include CMS Rebate revenue changes, which cannot be captured due to the ACA changes. The PA-enforced PH PDL preferred drug use rate is at the projected target rate of 90%. Both the "provider prevails" requirement and extensive grandfathering during implementation reduce the potential preferred drug use rate. Other Medicaid programs and managed care plans that use PA

enforcement of their PDLs can achieve 95% preferred rates. Cost avoidance and preferred drug use rate are expected to increase as the program matures under the current policy.

Only $260,000 TF in supplemental rebates were collected for the voluntary MH PDL. This is far short of the $3 million TF assigned to the voluntary MH PDL. Several manufacturers refused to extend supplemental rebates to Oregon in the absence of prior authorization enforcement of non-preferred products despite high voluntary use of preferred drugs. An estimated $2.4 million was unavailable to Oregon during the biennium because of the MH PDL prior authorization exemption. The voluntary MH PDL preferred use rate remains almost flat at 71-72%.

The great majority of prior authorization requests made were automatically generated and approved under the grandfathering policy. Prior authorization requests dropped below 300 per month after the initial grandfathering requirement expired and under 500 after the 2011 PDL expansion. Most prior authorization requests were for Asthma Controller drugs, followed by ADHD drugs. Close to 100% of prior authorization requests are approved, reflecting the "provider prevails" requirement. The few that are denied are done so based upon Pharmacy and Therapeutics Committee recommendations for appropriate use requirements.

Conclusions:

The PA-enforced PH PDL met budget and preferred drug use targets. The Affordable Care Act changes to CMS rebates likely will increase total fund CMS revenues but there may be a reduction in the state revenues.

The voluntary MH PDL is not meeting its budget targets. This is primarily because supplemental rebates were not extended to Oregon by manufacturers in the absence of a prior authorization requirement for non-preferred drugs. Additionally, without the use of prior authorization to inform clinicians and clients of preferred options, market share has not moved to the higher value preferred options.

The statutory requirements of grandfathering, provider prevails, and response to prior authorization requests within 24 hours, were met.

Glossary of Acronyms	
ACA	Affordable Care Act
ADHD	Attention Deficit Hyperactivity Disorder
AED	Antiepileptic Drugs
AIDS	Auto-Immune Deficiency Syndrome
BB	Beta-Blockers
CMS	Center for Medicare and Medicaid Services
DM_OH	Diabetes Mellitus, Oral Hypoglycemic
Est_Oral	Oral Estrogens
FFS	fee-for-service
HIV	Human immunodeficiency virus
LAO	Long-Acting Opioids
MH	Mental Health
OAB	Overactive Bladder
OHA	Oregon Health Authority
OHP	Oregon Health Plan
PA	Prior Authorization
PDL	Preferred Drug List
PH	Physical Health
PMPDP	Practitioner Managed Prescription Drug Plan
PMPM	per member per month
PPI	Proton Pump Inhibitors
SSDC	Sovereign States Drug Consortium
Statin_HP	Statins - High Potency
TF	Total Funds

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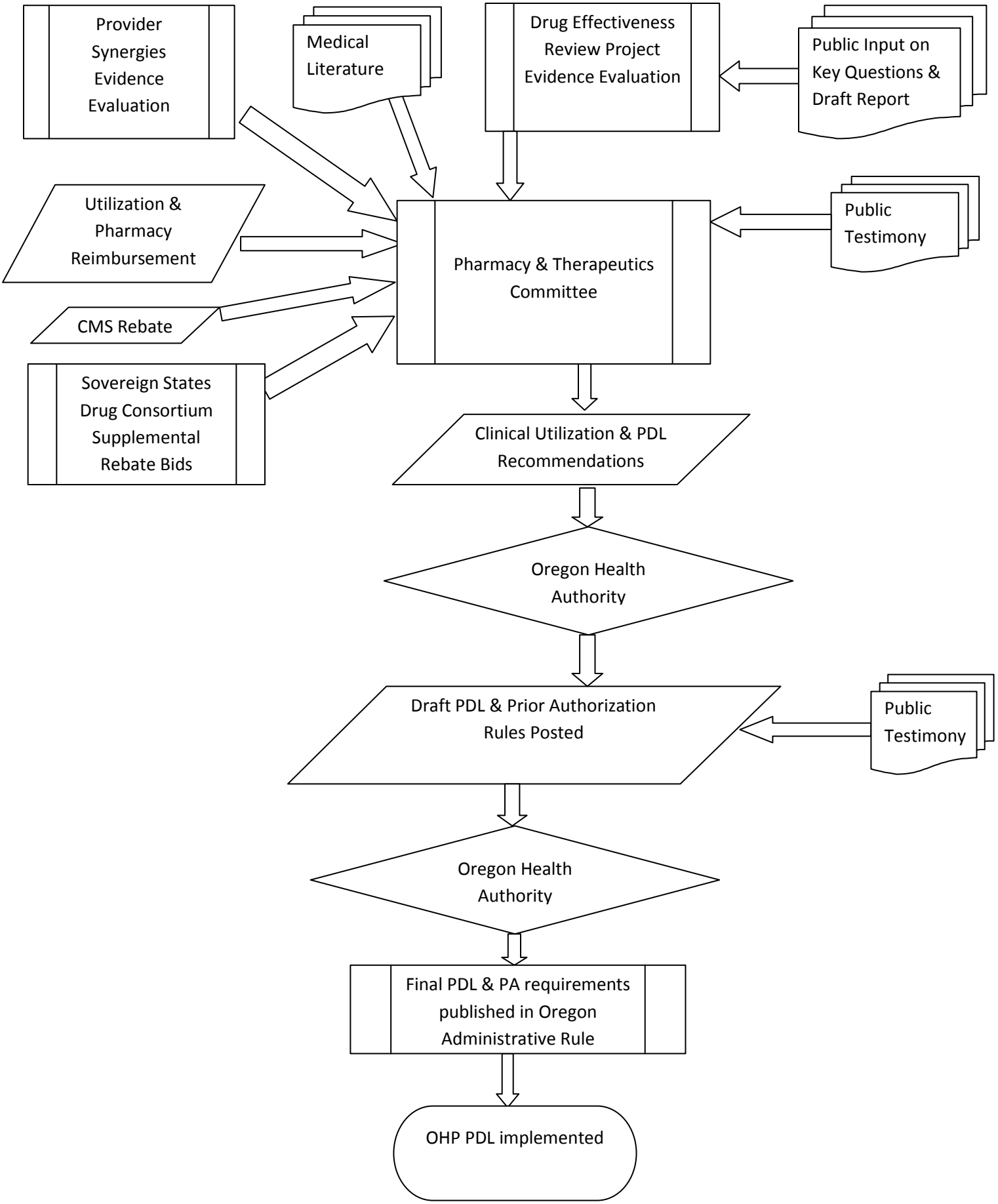
Appendix A – Current PDL Development Process



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November 2011 Volume 1, Issue 1

Atypical Antipsychotic Drug Class Review Summary of Findings

By Ann Hamer, PharmD, BCPP, OptiumHealth Behavioral Solutions & OSU College of Pharmacy

With the relatively recent approval of three new atypical antipsychotics, there are now ten different atypical agents available. Some have a variety of dosage forms (orally disintegrating tablets or long-acting injectables) and many have an assortment of approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment for schizophrenia in adults). This article will cover a summary of findings from the most recent Drug Effectiveness Review Project (DERP) drug class review on atypical antipsychotics and a brief review of the three newest atypical antipsychotics.

Summary of DERP Atypical Antipsychotics Review Findings (July 2010)[1]

Schizophrenia and Related Psychoses:

- In patients with schizophrenia, differences in short-term efficacy are not apparent among the atypical antipsychotics.
- In patients with schizophrenia, clozapine reduces suicidal behavior in patients at high risk, but results in more discontinuations due to adverse events compared to other atypical antipsychotics.
- Clozapine and olanzapine treatment result in lower rates of drug discontinuation for any reason over periods of up to 2 years.
- While risperidone and extended-release paliperidone resulted in higher rates of extrapyramidal symptoms in some studies, the majority of studies found no differences among the drugs.
- Risperidone was found to result in more frequent or more severe sexual dysfunction symptoms than quetiapine, but was similar to extended-release paliperidone or ziprasidone.
- Very limited evidence existed regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. Among adolescents with schizophrenia, quetiapine was not superior to placebo based on response rate, but was superior based on improvements measured by the Positive and Negative Syndrome Scale. There were no differences by race were found. Compared with men, women had greater improvements with clozapine on a global impression scale, and with olanzapine on a quality of life scale.

Bipolar Affective Disorder:

- In adults with bipolar disorder, no significant differences were found between risperidone and olanzapine or asenapine and olanzapine in quality of life, remission, or response outcomes.
- Olanzapine resulted in greater mean weight gain compared with asenapine and risperidone, respectively.
- Asenapine appears to have a higher risk of drug discontinuations due to adverse events than olanzapine.
- There were no significant differences between risperidone and olanzapine or between asenapine and olanzapine in extrapyramidal symptoms or between risperidone and olanzapine in discontinuations due to adverse events.
- Evidence is limited in children and adolescents with bipolar disorder.

Major Depressive Disorder:

- In adults with major depressive disorder, the majority of studies evaluated the adjunctive use of atypical antipsychotics in patients with an inadequate response to prior standard antidepressants. These studies provided insufficient evidence for determining their comparative effectiveness and efficacy.
- Evidence from both observational studies and randomized controlled trials of atypical use in major depressive disorder have indicated that weight gain was greatest with adjunctive olanzapine.

Behavioral and Psychological Symptoms of Dementia:

- The best evidence found similar rates of response and withdrawal, and no differences in clinical outcome measures for olanzapine, risperidone, and quetiapine in patients with behavioral and psychological symptoms of dementia.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders:

- Compared to placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders.
- Compared to placebo, risperidone and quetiapine showed efficacy in children and adolescents with disruptive behavior disorders.

Serious Harms:

- Based on randomized controlled trials and observational studies, olanzapine demonstrated greater weight gain than other drugs (6-13 pounds more) and a 16% increased risk of new-onset diabetes.
- In the review, risperidone was identified as having an increased risk of new-onset tardive dyskinesia.
- While clozapine has been shown to be associated with increased risk of seizures and agranulocytosis, differences among the drugs in other serious harms have not been clearly shown.
- Evidence on the long-term harms for the newest drugs is lacking.

Newest Atypical Antipsychotics

The following section provides a brief overview of the newest atypical antipsychotics. A review of clinical findings (Positive and Negative Syndrome Scale—PANSS) from published trials are available in Table 1.

Asenapine[2,3]

Brand Name: Saphris

Indications: Asenapine is approved for the treatment of schizophrenia and as monotherapy or as an adjunct to lithium or valproate for the treatment of bipolar manic or mixed episodes.

Overview: Asenapine is only available as a sublingual (SL) tablet due to its bioavailability (bioavailability is 35% when taken sublingually, but < 2% if ingested). Similar to other second-generation antipsychotics, asenapine's binding profile includes serotonin type 2A (5-HT2A) and dopamine type 2 (D2) antagonism. Binding at the alpha-1 adrenergic and histamine H1 receptors predicts asenapine's propensity to cause orthostasis and sedation in some patients.

Side Effects: Commonly occurring adverse events reported with asenapine (incidence ≥ 5% and at least twice that for placebo) were: akathisia, oral hypoesthesia and somnolence in schizophrenia trials, and dizziness, and extrapyramidal symptoms (other than akathisia) in bipolar trials. Weight gain was greater than placebo, but less than with risperidone and olanzapine in short 6-week trials. In addition, increases in the QTc interval ranging from 2 to 5 milliseconds have occurred. Per the package insert, concomitant use of asenapine with other drugs known to prolong the QTc interval should be avoided.[8]

Dosing: The recommended starting and target dose is 5 mg twice daily sublingually for schizophrenia and 10 mg SL twice daily for bipolar affective disorder (dose should be reduced to 5 mg twice daily if adverse effects occur). The dose should be allowed to dissolve within seconds, but food and drink should be avoided for 10 minutes after ingesting. Use should be avoided in severe hepatic impairment (Child-Pugh C) as asenapine drug concentrations can increase dramatically when used in this population.

Iloperidone[4,5]

Brand Name: Fanapt

Indications: Iloperidone is approved for the treatment of schizophrenia in adults.

Overview: Iloperidone is chemically related to risperidone and its proposed mechanism of action is thought to be mediated through a combination of D2

and 5-HT2 antagonisms. The manufacturer warns that the medication may not be first-line due to (1) its risk to prolong the QT and (2) its slow dose titration that can delay the control of symptoms in the first couple of weeks. Based on current evidence, the DERP summary reported that discontinuation rates are higher with iloperidone compared to risperidone.[1]

Side Effects: Reported adverse effects occurring in at least 5% of patients and at least twice as often as placebo were: dizziness, dry mouth, somnolence, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain.

Due to risks of QTc prolongation, it is also recommended to avoid using iloperidone with other drugs known to prolong the QTc interval. Monitoring of serum potassium and magnesium in patients at risk for electrolyte disturbances should be considered.[2]

Dosing: Dose titration must occur slowly in order to avoid orthostatic hypotension and should begin with 1 mg twice daily on day 1 with subsequent doubling of the daily dose everyday thereafter to reach a target dose after 1 week of 10-12 mg twice daily. Dosing in hepatic impairment has not been evaluated.

Lurasidone[6,7]

Brand Name: Latuda

Indications: Lurasidone is approved for the treatment of adult schizophrenia.

Overview: Lurasidone is a benzoisothiazol derivative thought to work through D2 and 5HT2A antagonism. Comparative data are lacking, but it appears to be effective in the treatment of schizophrenia and in short-term trials it appears to be well tolerated with minimal metabolic effects. Longer-term trials are needed to further assess long-term efficacy and harms.

Side Effects: Commonly observed adverse effects include: somnolence, akathisia, nausea, parkinsonism, and agitation. Electrocardiogram changes exceeding 500 milliseconds were not reported. Weight gain in short-term trials appears to be similar to placebo.

Dosing: Although dose titration is not required, the recommended starting dose is 40 mg once daily with food (minimum of 350 calories). The maximum recommended daily dose is 80 mg. Maximum daily dosing in patients with hepatic or renal impairment is 40 mg daily.

Treatment Selection:

The findings from the DERP Drug Class Review on Atypical Antipsychotics demonstrate that in terms of short-term efficacy, few differences exist among the atypical antipsychotics.[1] Aside from comparative effectiveness and the quality and quantity of clinical trial data, the American Psychiatric Association's guidelines for the treatment of schizophrenia also recommend considering side effects and co-morbid psychiatric and medical diagnoses.[8,9] A comparison of side effects associated with second-generation antipsychotics are included in Table 2.[6]

Table 1. Change in Total PANSS Score from Published Trials

Study	Treatment	Change in PANSS Total
Asenapine[10,11]		
6 weeks N=458	5mg BID	-16.2 (SS)
	10mg BID	Not SS
	Placebo	-10.7 (SS)
	Haloperidol 4mg BID	-15.4 (SS)
6 weeks N=174	5mg BID	-15.9 (SS)
	Placebo	-5.3 (SS)
	Risperidone 3mg BID	-10.9
Iloperidone[12,13]		
4 weeks N=593	12mg/day BID	-12.0 (SS)
	Placebo	-7.1
	Ziprasidone 80mg BID	-12.3 (SS)
6 weeks N=621	2mg BID	-9.0
	4mg BID	-7.8
	6mg BID	-9.9 (SS)
	Haloperidol 15mg*	-13.9
	Placebo	-4.6
6 weeks N=616	2-4mg BID	-9.5 (SS)
	5-8mg BID	-11.1 (SS)
	Risperidone 2-4mg BID	-16.6 (SS)
	Placebo	-3.5
6 weeks N=706	6-8mg BID	-11.0 (SS)
	10-12mg BID	-14.0 (SS)
	Risperidone 3-4mg BID	-18.8 (SS)
	Placebo	-7.6
Lurasidone[14]		
6 weeks N=180	80mg QD	-14.1 (SS)
	Placebo	-5.5

* Given as two divided doses, SS=statistically significant

Table 2. Adverse Effects Comparison Atypical Antipsychotics[6]

Drug	Diabetes	EPS	Elevated Prolactin	QTc Prolongation	Weight Gain
Aripiprazole	+/-	+	+/-	+/-	+
Asenapine	+	+++	++	+	++
Clozapine	++++	+/-	+/-	+	++++
Iloperidone	++	+	+/-	++	++
Lurasidone	+/-	++	+	+/-	+/-
Olanzapine	++++	+	+	+	++++
Paliperidone	++	+++	+++	+	+++
Quetiapine	++	+/-	+/-	+	+++
Risperidone	++	+++	+++	+	+++
Ziprasidone	+/-	+	+	++	+/-

Conclusion:

While relatively few differences exist between the atypical antipsychotics in terms of clinical efficacy, side effects are often key differentiators in treatment selection. The three newest atypical antipsychotics appear to offer little clinical advantage over the other atypical antipsychotics, but longer-term studies are needed.

Reviewed By: Cydreese Aebi PhD, RPh. Clinical Pharmacy Coordinator, Oregon State Hospital, Salem, Oregon and William Nunley, MD, MPH, Associate Medical Director, CareOregon, Portland, Oregon.

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THE OREGON STATE DRUG REVIEW©
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January 2012 Volume 2, Issue 1

RSV Prophylaxis: Updates and Recommendations

Kathy Sentena, Pharm D, OSU College of Pharmacy- Drug Use Research and Management Group

The Respiratory Syncytial Virus (RSV) is a prevalent virus within the community, affecting patients of all ages. RSV is common amongst children, causing serious respiratory tract infections in a small percentage of pediatric patients. Although RSV infection usually manifests as upper respiratory tract illness most infected patients are asymptomatic, some conditions may increase the risk and severity of RSV, such as prematurity; cyanotic or complicated congenital heart disease (CHD); and chronic lung disease (CLD, formerly called bronchopulmonary dysplasia).[1]

The Respiratory Syncytial Virus (RSV) season begins nationally between October and December and ends February to mid-April, lasting a median duration of 17 weeks or less.[1] Differences in RSV infections rates are thought to be due to weather conditions affecting the transmissibility and viability of the virus.[2] Population density and other demographic factors may also contribute to the variability seen in RSV seasons throughout the nation. The National Respiratory and Enteric Virus Surveillance System (NREVSS) monitors and reports geographical patterns associated with RSV. In the Northwest Region, consisting of Alaska, Idaho, Oregon and Washington, the RSV season onset is variable, starting anytime between October and December and ending around April.[2]

Within Oregon a variety of population densities and weather variations exist, influencing RSV seasons. This variability has made it difficult to define the most appropriate months to initiate and discontinue immunoprophylaxis vaccinations with palivizumab for high risk pediatric patients. The 2010-2011 RSV season started in the beginning of October.[3] Earliest virus detection, meeting onset criteria, was in the Columbia Gorge/North East Oregon Region, while all other regions had yet to meet onset criteria. All regions experienced RSV onset by late December. Season offset was met initially by the North West Oregon/South West Washington region in the third week of April while other regions still had active RSV rates >10% into May.

Palivizumab

Palivizumab (Synagis®) is a monoclonal antibody currently FDA approved for prevention of serious lower respiratory tract infections caused by RSV in pediatric patients at high risk of RSV disease.[4] Palivizumab is dosed based on body weight, 15mg/kg, and provided in vials of 50mg and 100mg to be injected intramuscularly. Palivizumab is given monthly and concentrations remain high enough to be effective 30 days after the last dose. This translates into 5 doses providing protective concentrations for more than 20 weeks.[1] The safety and efficacy of palivizumab has been demonstrated in infants born at or prior to 35 weeks gestational age, infants with CLD and in children with hemodynamically significant CHD.

Palivizumab effectiveness was evaluated in two randomized, placebo-controlled, double blind trials.[5,6] The IMpact-RSV study was done in 1,502 children who were ≤35 weeks gestation and ≤6 months old at the beginning of RSV season (starting in November) or in children with CLD that were ≤ 24 months at the beginning of RSV season.[5] The primary endpoint was hospitalization with confirmed RSV infection. Palivizumab prophylaxis resulted in an absolute risk reduction (ARR) of 5.8% in RSV-related hospitalizations compared to placebo Patients in the prematurity subgroup benefitted the most from palivizumab prophylaxis with an ARR of 6.3% while children with CLD experienced an ARR of 4.9%, versus placebo.

Feltes, et al, studied palivizumab prophylaxis in children with hemodynamically significant CHD.[6] A total of 1,287 children received 5 weight adjusted doses of palivizumab, starting in November, and followed for 150 days. The primary endpoint was antigen-confirmed RSV hospitalizations. Palivizumab prophylaxis was associated with an ARR of 4.4% (p= 0.003), compared with placebo.

There have been no good quality studies that have shown a decrease in RSV related mortality or recurrent wheezing, after an RSV infection, as a result of palivizumab administration.[1]

2009 Guideline Recommendations

In 2009 the The American Academy of Pediatrics (AAP) updated their guidelines for using palivizumab for RSV prevention, with the goal of targeting those children at highest risk for severe disease. Recommendations changed from previous years by taking into account the seasonality of RSV in different regions and the impact on initiation and termination of prophylaxis; targeting those children with the highest risk of severe disease; reducing the number of risk factors to qualify for prophylaxis and changing the maximum recommended doses for certain populations.

Recommendation for Use of Palivizumab for Prevention of RSV[1]

1. Infants with CHD, CLD of prematurity, or birth before 32 weeks 0 days gestation.
2. Infants with a gestational age of 32 weeks 0 days through 34 weeks 6 days born within 3 months before the start of RSV season or at any time throughout the RSV season with at least one of the following risk factors:
    a. Infant attends child care; OR
    b. 1 or more siblings or other children younger than 5 years live permanently in the child's household.
3. Infants born between 32 weeks 0 days and 34 weeks 6 days gestation without hemodynamically significant CHD or CLD who qualify for prophylaxis should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first). This is a change from previous recommendations of 5 months of prophylaxis.
4. Regardless of the month in which the first dose is administered the maximum number of 5 doses is recommended for all regions.(Table 1)

The AAP has determined a maximum of five monthly palivizumab doses is adequate to provide coverage for most areas of the United States, beginning in November with the last dose in March.(Table 1)

Table 1. Maximum Number of Monthly Doses of Palivizumab for RSV Prophylaxis[1]
Infants Eligible for a Maximum of 5 Doses
Infants with CLD, <24 months of age, and require medical therapy
Infants with CHD, <24 months of age and require medical therapy
Premature infants born at ≤31 weeks 6 days
Certain infants with neuromuscular disease or congenital abnormalities of the airways
Infants Eligible for a Maximum of 3 Doses
Premature infants with a gestational age of 32 weeks 0 days to 34 weeks 6 days with at least 1 risk factor and born 3 months before or during RSV season

Cost

Studies have shown that immunoprophylaxis with palivizumab can reduce hospitalizations, especially during peak viral activity. Due to the cost of palivizumab, which is estimated at $1661-2584 a dose (dependent upon the child's weight), it is important that palivizumab be used judiciously.[7]

Many cost effectiveness analyses on prophylaxis against RSV infection with palivizumab have been preformed.[7,8,9,10,11,12,] Two studies in Medicaid populations have shown reductions in hospitalizations and hospitalization costs, but failed to show cost-effectiveness or decreases in direct costs.[8,9] Systematic reviews have found that cost-effectiveness ratios tend to fall below accepted thresholds, yet, accepted cost-effectiveness has been achieved when high-risk infants with risk factors are targeted.[10,11,12]

Cost-effectiveness analyses are subject to limitations including changing practice recommendations that may influence conclusions. None of the published cost-effectivness studies include the most current AAP recommendations for palivizumab prevention of RSV, which targets children at the highest risk. Additional study limitations are listed below (Table 2).

Table 2. Limitations of Cost-Effective Analyses
1. Cost data sources are variable (acquisition costs and hospitalization costs)
2. Criteria for hospitalization not reported in all analyses.
3. Differences in RSV rates, depending on year and geographic region.
4. Use of sub-group efficacies versus overall efficacies in determining costs.
5. Perspective of analyses varies (society, payer or provider).

A recent example of a study whose conclusions are limited by the above study design issues is a cost-effectiveness analysis by Hampp, et al, which studied palivizumab for RSV prophylaxis for various indications.[7] Data from 159,790 children, ages 0 to 2 years, from the Florida Medicaid system during the 2004-2005 RSV season were analyzed. A decision tree analysis was used to compare children with the following indications: CLD, CHD, or prematurity (≤ 32 weeks gestation) and children with none of these indications. Children were compared using palivizumab prophylaxis versus no prophylaxis with the outcome measure being incremental cost (2010 US dollars) per hospitalization for RSV infection avoided. Medicaid payment amounts, based on National Drug Codes, were used to generate mean palivizumab costs and hospitalization expenses were based on inpatient claims paid by Medicaid.

Almost three thousand children received palivizumab, totaling 9805 doses. Mean palivizumab cost per dose ranged from $1,661 for infants younger than 6 months to $2,584 for children up to 2 years of age. Hospitalizations related to RSV occurred in 1,116 children, with high risk children accounting for 98 visits. Costs associated with RSV ranged from $5,069 in children with no indication to $12,103 in children with CLD. Palivizumab was most cost-effective in children of younger age and with multiple indications. In children 0-2 years old, with an indication for prophylaxis, the incremental cost-effective ratios ranged from $302,103 to over $1.3 million per RSV-related hospitalization avoided. The most cost-effective sub-group was premature infants, 6 months or younger, with no other indications. To prevent one RSV-related hospitalization in this group, palivizumab prophylaxis cost $302,103 (95% Confidence Interval (CI), $141,850-$914,798). Palivizumab immunoprophylaxis would be cost neutral at a per-dose cost of $47, given the mean cost of a RSV related hospitalization in this population being $8,910. This analysis included children identified for prophylaxis according to older guideline recommendations and children that were prescribed palivizumab inappropriately, creating potential bias to favor a less cost-effective scenario. Utilizing Florida demographic data, which is known for a unique onset and offset of the RSV season, may lend the results to being less applicable to other areas of the United States.

The Canadian Agency for Drugs and Technologies in Health (CADTH) examined the data in a 2006 report on palivizumab prophylaxis for RSV. This report included clinical effectiveness data as well as cost and economic evaluations. CADTH concluded that palivizumab should be considered for children at highest risk, such as those with CLD and premature infants, ≤32 weeks gestation.[13]

Summary

Palivizumab is an effective prophylactic measure against RSV in select, high risk patients. AAP guidelines reiterate the importance of utilizing palivizumab in identified high risk infants and children. By identifying infants and children appropriately and limiting the number of palivizumab doses to five a season, palivizumab prophylaxis will be used to its maximum benefit.

Peer Reviewed By: Arthur Jaffe, MD, Professor, Division of General Pediatrics, Oregon Health and Science University; Nancy Gadd, PharmD, BCPS, Pediatric Clinical Pharmacist Doernbecher Children's Hospital and Oregon Health and Science University

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

Hepatitis B Antivirals PA Criteria

Month/Year of Review: February 2012
Last Oregon Review: September 2010 (Provider Synergies)

The Oregon Health Resources Commission reviewed this class of agents for Chronic Hepatitis B (CHB) for addition to the Oregon PDL last September. The full source document can be found on the HRC website: http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/ps-2009-11-hep-b.pdf.

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harms/adverse events
3. Recommend including this class on the PDL and consider including entecavir (Baraclude) and tenefovir disoproxil fumarate (Viread)
4. Recommend establishing PA criteria for non-preferred products

Summary:
There are currently five oral nucleoside/nucleotide analogues (NA) available: lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. The long term clinical goals of antiviral therapy in CHB include reducing the development of cirrhosis, hepatocellular carcinoma, and death. There is moderate evidence suggesting that all of the NA have positive effects on one or more intermediate biomarkers associated with CHB including suppression of Hepatitis B Virus (HBV) DNA, normalization of serum alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg) loss or seroconversion, and hematologic response of improved necroinflammatory and fibrosis scores but no one treatment has shown to improve all biomarkers and there remains controversy over how these intermediate outcomes are related and if they predict clinical long term outcomes. The high-quality systematic review prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Minnesota Evidence-based Practice center concluded that observational studies suggest that male gender, coinfection with Hepatitis C, D, or HIV, increased HBV DNA, and cirrhosis were associated with an increased risk of hepatocellular carcinoma and death.[1] Although, there is limited direct evidence that any anti-HBV therapies have a beneficial impact on these clinical outcomes, there is growing evidence that prolonged and effective suppression of HBV DNA can decrease the risk of cirrhosis and hepatocellular carcinoma. This supports the current trend to use long term antiviral therapy. [2]

In addition to comparative efficacy evaluated in the Provider Synergies review,[3] randomized controlled trials demonstrated that tenofovir treatment resulted in statistically significant improvements in Hepatitis B viral suppression compared to adefovir in both HBeAg+ (76% vs. 13%, RR 5.8, 95% CI 3.35,9.73) and HBeAg- patients (93% vs. 63%, RR 1.5, 95% CI 1.28, 1.69).[4] It was also reviewed and recommended by the Canadian Agency for Drugs and

Technologies in Health (CADTH) as well as recommended in current treatment guidelines.[5] Guidelines from the Association for the Study of Liver (EASL), the American Association for the Study of Liver Disease (AASLD), the National Institute of Health (NIH), and a panel of US expert hepatologists have all published guidelines or consensus statements for the management of CHB. These all recommend peginterferon alfa, entecavir, and tenofovir as preferred first-line drugs for CHB based largely on efficacy and a lower risk of the development of drug resistance.[6–8] While these newer antiviral agents have the potential for prolonged effective viral suppression, more studies on the safety profiles and efficacy on long term use of these newer agents are needed. Future clinical trials should incorporate long term outcomes to align treatment with the surrogate markers and whether these markers reflect important clinical outcomes.

Other Considerations:

- Lamivudine has the most robust long term safety data and still has a place in therapy in those with favorable parameters and low risk of resistance. It can also be recommended in clinical situations which a finite prophylaxis course is needed.
- Combination therapy with NA has not has not proven to be superior to monotherapy in inducing a higher rate of sustained response.

Recommendations:

Consider establishing prior authorization criteria for the non-preferred agents in this class to promote the use of the preferred and recommended products when feasible.

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Suggested PA Criteria

Hepatitis B Antivirals

Goal(s):

- **Cover hepatitis B agents according to OHP guidelines. Cover preferred products when feasible for covered diagnosis.**
- **Preferred products are selected based on evidence based reviews.**

Length of Authorization: Up to 1 year. Quantity limited to a 30 day supply per dispensing.

Pediatric age restrictions:

A. lamivudine (Epivir HBV)-2 years and up
B. adefovir dipivoxil (Hepsera)-12-17 years
C. entecavir (Baraclude)-16 years and up
D. telbivudine (Tyzeka)-safety and effectiveness not approved in pediatrics

Covered Alternatives that do not require a PA: See PDL list at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Is the request for treatment of Chronic Hepatitis B?	Yes: Go to #4	No: Pass to RPh, Deny for Appropriateness
4. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin."***	Yes: Go to Renewal Criteria	No: Go to #5
5. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	Yes: Document intolerance or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30 days supply.	No: Go to #6
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness &	Yes: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	No: Approve requested treatment for 6 months with monthly quantity limit of 30 days supply.

safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.		

Renewal Criteria		
1. Is client compliant with requested treatment? (see refill history).	Yes: Go to 2.	No: Deny. Forward to RPH for provider consult.
2. Is HBV DNA undetectable?	Yes: Approve for up to 1 year with monthly quantity limit of 30 days supply	No: Deny. Forward to RPH for provider consult.

Erythropoiesis Stimulating Proteins (Hematopoietic Agents)

Goal(s):

- Promote evidence based preferred drug list (PDL) options for covered diagnoses

Length of Authorization:

- Up to 12 months
- Quantity limit of 30 day per dispense

Requires PA:

- All erythropoiesis stimulating proteins require PA for clinical appropriateness.

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis	Yes: Go to #3	No: Pass to RPH; Deny (not covered by the OHP)
3. Does the patient meet **both** of the following criteria • HGB less than 10g/dL and/or HCT less than 30% • Transferrin saturation greater than 20% and/or ferritin greater than 100ng/mL	Yes: Go to #4	No: deny (medical appropriateness)
4. Is the anemia due to one of the following: • Chronic renal failure • Chemotherapy • HIV/AIDS **and** o endogenous erythropoietin less than or equal to 500 IU/L o Member not receiving Zidovudine exceeding 4200mg per week • Interferon-ribavirin treatment (e.g. Pegasys®, Peg-Intron, etc) **and** o Despite a dose reduction in ribavirin of 200 mg/day from initial dose, anemia has persisted for at least two weeks.	Yes: Go to #5	No: deny (medical appropriateness)

Approval Criteria		
5. Will the Prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class. Go to #6	No: Go to #6
6. Approval length based on diagnosis	Chronic Renal Failure: • 12 months or length of prescription, whichever is less HIV/AIDS: • 12 months or length of prescription, whichever is less Chemotherapy: • 6 months or length of prescription, whichever is less Interferon-ribavirin therapy: • 6 months or length of prescription, whichever is less	

References:

1. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target

2. Use of Epoetin and Darbepoetin in Patients with Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update

3. Erthropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions Medicare National Cover Determinations. Centers for Medicare & Medicaid Service (CMS). January 14, 2008

4. Recombinant Erythropoietin Criteria for Use for Hepatitis C Treatment-Related Anemia. VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. April 2007

Guideline notes for the April 1, 2010 Prioritized List of Health Services

Guideline Note 7. Erythropoietin Guidelines:

Lines: 33,65,78,101,102,105,123-125,131,138,144,159,166-168,170,181,197,198,206-208,219,221, 222,229,230,232,236,243,249,252,275-278,280,286,291,309-311,313,319,337-339,350,354, 365,452,611

1. Indicated for anemia (Hgb less than 10gm/dl or Hct less than 30%) induced by cancer chemotherapy given within the previous 8 weeks or, in the setting of myelodysplasia.

    A. Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, EPO ESAs should be titrated to maintain a level between 10 and 12.

    B. Not indicated for anemia in cancer patients not undergoing chemotherapy.

2. Indicated for anemia (Hgb less than 10gm/dl or HCT less than 30%) associated with HIV/AIDS.

    A. An endogenous erythropoietin level less than 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) greater than 4200 mg/week.

    B. Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, EPO ESAs should be titrated to maintain a level between 10 and 12.

3. Indicated for anemia (Hgb less than 10gm/dl or Hct less than 30%) associated with chronic renal failure, with or without dialysis.

    A. Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, EPO ESAs should be titrated to maintain a level between 11 and 12.

DATE(s)
DUR Board Action: 09/16/2010 (DO)
Revision(s):
Initiated: 1/1/11

Proton Pump Inhibitors (PPI)

Goal(s):

- Promote preferred drug list (PDL) Options
- Restrict chronic use (>eight weeks) to patients who
  - Failed H2-antagnoist therapy
  - Failed Preferred drug list (PDL) PPI
  - Have severe disease (e.g. Barrett's esophagus , Zollinger-Ellison's disease)
- Restrict BID use to patients with severe disease, H. pylori, or pediatric patients.

Length of Authorization:

Two weeks to lifetime (criteria specific)

Requires PA:

- Non-preferred drugs
- Increasing from once daily to twice daily dosing

Covered Alternatives:

- Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
- Individual components for treatment of H. pylori that are preferred products

Common Proton Pump Inhibitor Formulations and Packaging

BRAND	GENERIC	FORMULATIONS
Nexium	Esomeprazole	• Capsules, delayed-release: 20, 40mg • Suspension, delayed-release pkts: 10, 20, 40mg
Prevacid	Lansoprazole	• Capsules, delayed-release: 15, 30 mg • Enteric coated granules for oral suspension, delayed release: 15, 30mg • Solu Tab: 15, 30 mg orally disintegrating tablet
Prevacid NapraPAC	Lansoprazole + Naproxen	• Delayed release capsules + naproxen tablets kit - 15 – 375, 15 -500
Zegerid	Omeprazole	• Packet for solution: 20, 40mg • Capsules: 20, 40mg
Dexilant	Dexlansoprazole	• Capsules, delayed-release: 30, 60mg
Protonix	Pantoprazole	• Tablets, delayed-release: 20 mg, 40 mg • Suspension, delayed-release: 40mg

Common Proton Pump Inhibitor Formulations and Packaging		
BRAND	**GENERIC**	**FORMULATIONS**
Helidac	bismuth subsalicylate, metronidazole, tetracycline	metronidazole 250 mg + tetracycline 500 mg + bismuth subsalicylate 525 mg, each given four times a day **add an H2 receptor antagonist
Prevpac	lansoprazole, amoxicillin, clarithromycin	lansoprazole 30 mg + amoxicillin 1 gm + clarithromycin 500 mg, each given twice a day
Pylera	bismuth subcitrate potassium, metronidazole, tetracycline	bismuth subcitrate potassium 140mg + metronidazole 125 mg +tetracycline HCl 125 mg, 3 capsules given four times a day **add omeprazole 20 mg twice a day

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the drug requested preferred?	Yes: Go to #4	No: Go to #3
3. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in the class	No: Go To #4
4. Is diagnosis • Zollinger-Ellison (251.5)? • Barrett's esophagus (530.85)? • Multiple Endocrine Adenoma (237.4)? • Malignant Mastoma (202.6)? • MEN Type I (258.01)?	Yes: Approve for lifetime; BID dosing OK.	No: Go to #5

Approval Criteria		
5. Is the diagnosis dyspepsia (536.8)?	Yes: Pass to PRH; Deny (OHP coverage) – Diagnosis is below the line. Preferred agents are available without a PA.	No: Go to #6
6. Has patient tried and failed omeprazole 40mg/day for 8 week trial (2 weeks for H. Pylori)?	Yes: Go to #7	No: Go to #12
7. Is the diagnosis H. pylori?	Yes: Approve for 2 weeks – BID dosing OK. May also approve 1 pack of Helidac®, Prevpac®, or Pylera®	No: Go to #8
8. Is diagnosis active G.I. bleed? (531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2)	Yes: Approve for 8 weeks – BID dosing OK	No: Go to #9
9. Is diagnosis Gastric or Duodenal Ulcer • (531.3-531.9, 531.3-532.9, 533.3-533.9, 534.3-534.9) and/or does patient have 2 or more of the following risk factors: o > 65 years o requires > 3 months of NSAIDs, aspirin or steroids o anticoagulation therapy (warfarin, enoxaparin, etc.) o History of GI bleed or ulcer	Yes: Approve once daily for one year. If previously failed an 8 week, once daily trial at the highest dose then BID for one year may be approved. May approve BID dosing for pediatrics under 12 years old	No: Go to #10
10. Is the diagnosis symptomatic GERD (530.81, 530.10 – 530.19)	Yes: Approve once daily for one year. If previously failed an 8 week, once daily trial at the highest dose then BID for one year may be approved. May approve BID dosing for pediatrics under 12 years old	No: Go to #11

Approval Criteria		
11. Is diagnosis: • Ulcer of esophagus (530.2x) • Stricture & stenosis of esophagus (530.3) • Perforation of esophagus (530.4)	Yes: Approve up to BID for one year	No: Go to #13
12. Is the request for tube administration (e.g. solution, orally disintegrating tablets, etc.)?	Yes: Approve once daily for 1 year. May approve BID dosing for pediatrics under 12 years old	No: Pass to RPH. Deny (Cost-effectiveness). Recommend omeprazole 20mg once or twice daily
13. All other diagnoses will need to be evaluated by a pharmacist for appropriateness and OHP line coverage.	• Diagnoses above the line and where PPI is appropriate can be covered. • Diagnoses below the line and where PPI is appropriate should be denied as not covered. • Diagnoses above the line but where PPIs are not appropriate should be denied and not medically appropriate.	

DUR Board Action: *2/23/12, 09/16/10 (DO), 3/18/10 (KK), 12/03/09 (DO/KK), 5-21-09; 5-7-02; 2-5-02; 9-7-01, 9-11-98*
Revision(s) *1/11/12, 1/1/11, 4/23/10 (DO), 1/1/10; 9-1-06, 7-1-06, 10-14-04, 3-1-04*

Topiramate

Goal(s):

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

Length of Authorization:

90 days to lifetime

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the client have a diagnosis of epilepsy? (ICD-9 code 345.0-345.9, 780.39, or 907.0)?	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3
3. Does the client have a diagnosis of migraine (ICD9 346)?	Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	No Go to #4
4. Does the client have a diagnosis of bipolar affective disorder or schizoaffective disorder? • (ICD9 296 and subsets) • (ICD9 295 and subsets)	Yes: Go to #5	No: Go to #6
5. Has the client tried or are they contraindicated to at least two of the following drugs: • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic **Document drugs tried or contraindications.**	Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	No: Pass to RPH; Deny, (Medical Appropriateness) Recommend trial of covered alternative.
6. Is the client using the medication for weight loss? (Obesity ICD9 278.0, 278.01)?	Yes: Pass to RPH; Deny, (Not covered by the OHP)	No: Go to #7

Approval Criteria	
7. Pass to RPH. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	**Use is off-label**: Deny, (Medical Appropriateness) Other treatments should be tried as appropriate. **Below the line diagnoses**: Deny, (Not covered by the OHP) **If clinically warranted**: Deny, yesterday's date (Medical Appropriateness) and use clinical judgment to approve for 1 month starting today to allow time for appeal. **MESSAGE**: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

**Documented response means that follow-up and response is noted in client's chart per clinic staff*

DUR Board Action: *2/23/12, 9/20/2007, 11/29/2007*
Revision(s): *1/24/12*
Initiated: *1/1/11*

Hormones - Testosterone (Androgens)

Goal(s):

- Approve androgen therapy for covered diagnoses which are supported by the medical literature

Length of Authorization:

Up to 6 months

Requires PA:

- All topical androgens require prior authorization

Preferred Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the diagnosis include any of the following? • Ovarian failure (256.31, 256.39) • Testicular Hypofunction (257.2) • Hypopituitarism and related disorders (253.2, 253.4, 253.7, 253.8) • AIDS-related cachexia (253.2)	Yes: Go to #3	No: pass to RPh. RPh go to #4
3. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class. Approve for 6 months.	No: Go to #4
4. RPH only All other indications need to be evaluated to see if they are above the line or below the line.	**If above the line** and clinic provides supporting literature: Approve for length of treatment.	**If below the line**: Deny; (Not Covered by the OHP)

DUR Board Action: *2/23/12 (TDW),* 9/16/10 *(KS),2-23-06, 2-21-01, 9-6-00*
Revision(s): *1/24/12,* 1/1/11, 9/1/06

Pulmonary Arterial Hypertension (PAH)

Goal(s):

- Approve therapy for covered diagnoses which are supported by the medical literature
  - Erectile dysfunction is not covered by OHP

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh; Deny (not covered by the OHP)
3. Does the patient have a diagnosis of pulmonary arterial hypertension (PAH)?	Yes: Go to #4	No: Pass to RPh; RPh Go to #8
4. Is this a renewal of current therapy?	Yes: Go to #6	No: Go to #5
5. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class.	No: Go to #6
6. Does the patient have PAH with a World Health Organization (WHO) Functional Class (FC) of II-IV (see table below)?	Yes: Go to #7	No: Deny (Medical Appropriateness)
7. Is the drug being prescribed by a pulmonologist or cardiologist?	Yes: Approve for 12 months.	No: Deny (Medical Appropriateness)
8. RPh Only: Is the diagnosis above the line and has the clinic provided supporting literature for use?	Yes: Approve for length of treatment.	No: Deny (not covered by the OHP)

WHO Functional Classification of Pulmonary Hypertension*	
Class I	• Patients with pulmonary hypertension but without resulting limitation of physical activity. • Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope.
Class II	• Patients with pulmonary hypertension resulting in slight limitation of physical activity. • They are comfortable at rest. • Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or syncope.
Class III	• Patients with pulmonary hypertension resulting in marked limitation of physical activity. • They are comfortable at rest. • Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or syncope.
Class IV	• Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. • These patients manifest signs of right heart failure. • Dyspnea and/or fatigue may even be present at rest. • Discomfort is increased by any physical activity.

*Table adapted from “Classification of Pulmonary Hypertension.” Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Peter Libby et al. 2007.web. 21 Oct 2010**.**

DUR Board Action: 2/23/2012(TDW), 9/16/10 (KS)
Revision(s): 1/24/2012
Initiated: 1/1/11

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Oregon State University College of Pharmacy
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: Neuropathic Pain

I. EXECUTIVE SUMMARY:

Month/Year of Review: February 2012
Last Oregon Review: March 2008 (DERP Systematic Review)

Reason for Review:
The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an updated report for the Neuropathic Pain Drug Class Review which was published in June of 2011[1]. The full report can be found on the Evidence-based Practice Center website: http://derp.ohsu.edu/about/final-document-display.cfm and the final executive summary can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings. This report will be evaluated and summarized for any potential Oregon Health Plan policy decisions. Refer to the full reports for details on methods, search strategy, inclusion criteria, outcomes included, and methods for grading the evidence. In addition, the FDA approved a new once daily formulation of gabapentin ER (GRALISE™) for the treatment of post-herpetic neuralgia and the capsaicin 8% patch (Qutenza) for post-herpetic neuralgia[2, 3]. These drugs were not included in the review by the Oregon EPC.

Key Questions[1]:
- What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch for neuropathic pain?
- What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?
- Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

Summary:
Current strategies for the treatment of neuropathic pain include oral anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRI's), tricyclic antidepressants (TCAs), and topical analgesics[1]. Current OHP management of these drugs includes prior authorization criteria restricting approval of pregabalin only if the client has previously tried or is contraindicated to gabapentin and either a TCA or oral carbamazepine. The DERP update

compared the effectiveness and safety of all these drugs excluding the extended release gabapentin (Gralise) and capsaicin 8% patch (Qutenza). Simple analgesics and opioids were also not included in the review. Overall, the current comparative evidence for neuropathic pain is limited. Of the 128 studies included in the DERP report, only 14 were direct comparisons of drugs and the majority of included studies were small and of a relatively short duration[1]. The DERP review of the available evidence concludes the following regarding comparative effectiveness and harms:

Effectiveness[1]:

The majority of direct evidence was in patients with diabetic neuropathy and postherpetic neuralgia. Based on small studies in these populations, there is moderate-strength evidence that there is no significant difference between gabapentin, pregabalin, and lamotrigine compared with TCA's in the rate of response and low-strength evidence that there is also no significant difference between lidocaine 5% patch and pregabalin. Based only on indirect comparisons, there is low strength evidence that duloxetine, pregabalin, and gabapentin are superior to lacosamide and lamotrigine, and pregabalin appears to be superior to topiramate. There is no direct evidence evaluating treatment with divalproex, oxcarbazepine, and topiramate.

There is very limited comparative evidence evaluating efficacy in patients with other types of neuropathic pain and it was not possible to conduct indirect analyses due to significant differences among study designs and outcomes. There was 1 direct comparative trial each of patients with central post stroke pain, spinal cord injury, polyneuropathy, and cancer.

Harms[1]:

In patients with diabetic neuropathy and postherpetic neuralgia, moderate-strength evidence shows there is no significant difference in withdrawals due to adverse events between gabapentin, pregabalin, and lamotrigine compared with amitriptyline and nortriptyline, but greater with oral pregabalin compared to the 5% lidocaine patch. Using only indirect comparisons, low-strength evidence supports no significant difference with withdrawals due to adverse events between duloxetine, pregabalin, lacosamide, and lamotrigine. There is insufficient direct evidence to evaluate comparative harms in other types of neuropathic pain.

Guidelines

In 2010 The National Institute for Health and Clinical Excellence (NICE) published guidelines for the treatment of neuropathic pain in the non-specialist setting and recommended amitriptyline or pregabalin as first-line treatment and duloxetine or amitriptyline first line in patients with painful diabetic neuropathy[4]. Since those there were significant concerns about the associated costs with pregabalin as a first line agent for adults with neuropathic pain and an updated guideline document is anticipated to be available in 2012. The provisional draft recommendations are currently published and state that oral amitriptyline or gabapentin are recommended as first-line agents for neuropathic conditions due to similar efficacy and an added cost benefit. Pregabalin is recommended as an alternative to gabapentin if patients cannot adhere to the dosing schedules or tolerate adverse events[5]. The American Academy of Neurology recently published evidence-based guidelines for the treatment of painful diabetic neuropathy and concluded that pregabalin is established as effective based on evidence displaying pain relief and venlafaxine, duloxetine, amitriptyline, gabapentin, valproate,

and capsaicin cream are probably effective for treatment of painful diabetic neuropathy[6]. This evidence-based systematic review also found a low strength of evidence that the lidoderm patch is possibly effective.

There is limited data for the effectiveness of carbamazepine and what does exist is very dated. However, current guidelines still recognize that carbamazepine has been the routine treatment for trigeminal neuralgia in clinical practice and due to lack of good-quality evidence for treating trigeminal neuralgia, continue to recommend carbamazepine in treating trigeminal neuralgia.[4, 7]

Additional Available Treatment

The approval of gabapentin ER (Gralise) was based on one short-term placebo-controlled study that showed a statistically significant improvement in mean pain score compared to placebo in patients with postherpetic neuralgia. This is a new preparation of gabapentin with a delivery system allowing for once-daily dosing[3, 8]. There is a lack of data supporting its efficacy, safety, and optimal dosing and no comparative effectiveness data with any other treatments for postherpetic neuralgia.

The capsaicin 8% patch (Qutenza) is the first product to contain prescription strength capsaicin for the management of neuropathic pain associated with postherpetic neuralgia. The capsaicin patch was approved based on two randomized low-dose controlled trials in patients with postherpetic neuralgia that were required to of had at least 6 months of oral treatment.[9] There were significantly more patients taking concomitant drugs for neuropathic pain in the treatment group (50% vs. 38%, p=0.021) in one study. These two studies showed that compared to a low-dose capsaicin (0.04%) control patch, capsaicin 8% had a statistically significant greater percent change of pain score from baseline although the clinical significance of the difference is low (less than a 2 point reduction in patient-reported pain). Due to the potential irritation caused by the high strength capsaicin and administration site reactions, the patch has to be administered by a health care professional and would likely require specialist administration. There is a low quality of evidence demonstrating that capsaicin 0.075% cream is probably effective for the treatment of diabetic neuropathy and is recommended for consideration in the evidence-based guidelines by the American Academy of Neurology and is evaluated in the NICE guidelines.[4, 10]

Conclusions:

Overall there is low to moderate evidence comparing benefits and harms of available drugs for neuropathic pain. The majority of available direct comparative evidence is in patients with either diabetic neuropathy or postherpetic neuralgia and included comparisons between amitriptyline or nortriptline and gabapentin, pregabalin, or lamotrigine. There is insufficient comparative effectiveness evidence in patients with other types of neuropathic pain to assess comparative safety and conclusions for efficacy were largely based from placebo-controlled trials and indirect analyses[1].

In patients with diabetic neuropathy and postherpetic neuralgia, there is moderate evidence that there is not a statistically significant difference in response or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared to tricyclic antidepressants and low strength

evidence that there is no difference between oral pregabalin and the lidocaine patch. Low strength evidence based on indirect comparisons demonstrates that duloxetine, pregabalin, and gabapentin are superior to lacosamide and lamotrigine and there are no differences between pregabalin, duloxetine, and gabapentin or comparisons of lidocaine and amitriptyline or gabapentin[1].

Recommendations:

- Include topical analgesics into current neuropathic pain PA criteria including Lidoderm patch and capsaicin 8% patch to restrict use to patients with postherpetic neuralgia who have failed or cannot tolerate oral therapy with gabapentin and TCA's.
- Designate gabapentin ER as a line extension of currently available gabapentin and as a non-preferred agent due no management demonstrated in evidence-based guidelines and alternative therapy with available comparative effectiveness evidence showing efficacy in neuropathic pain.

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Drug Class Review

Neuropathic Pain

Final Update 1 Report
Executive Summary

June 2011

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Drug class review: Neuropathic Pain", dated June 2011. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Original Report: October 2007

Update 1 Authors
Shelley Selph, MD
Susan Carson, MPH
Rongwei Fu, PhD
Sujata Thakurta, MPA:HA
Allison Low, BA
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

INTRODUCTION

Neuropathic pain is defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" and can occur because of dysfunction or disease of the nervous system at the peripheral and/or central level. Neuropathic pain can be very severe and disabling, with significant functional, psychological, and social consequences. Regardless of the underlying cause of neuropathic pain, common treatment goals are to decrease pain and/or improve function. Neuropathic pain is often classified by etiology or by the presumed site of neurologic involvement (central or peripheral) and is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. Neuropathic pain is also commonly associated with hyperalgesia (increased pain intensity evoked by normally painful stimuli), paresthesia, and dysesthesia. Up to 3% of the general population reports neuropathic pain at some time, and neuropathic pain is most commonly associated with painful diabetic neuropathy, postherpetic neuralgia, or lumbar nerve root compression.

Scope and Key Questions

The goal of this report is to compare the effectiveness and safety of the drugs shown in Table 1 in the treatment of neuropathic pain.

Table 1. Included drugs

Drug	Trade name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain
Anticonvulsants			
Gabapentin	Neurontin®	Postherpetic neuralgia	Start at 300 mg, titrate to 900 mg, increase up to 1800 mg (divided tid)
Pregabalin	Lyrica®	Diabetic neuropathy, Postherpetic neuralgia	Start at 150 mg, increase up to 300 mg (divided tid) Start at 150 mg, increase up to 75 to 150 mg bid Adjust dose for renal dysfunction
Carbamazepine	Equetro®	None	NA
	Carbatrol®[a]	Trigeminal neuralgia	Start with 200 mg daily, increase up to a maximum of 1200 mg daily (divided bid) Most patients are maintained on 400-800 mg daily Attempt to reduce dose to minimum effective level, or discontinue, at least every 3 months
	Tegretol® Tegretol® XR Tegretol® CR[b]	Trigeminal neuralgia	Start at 100 mg bid, increase up to a maximum of 1200 mg daily (divided bid) Most patients are maintained on 400-800 mg daily Attempt to reduce dose to minimum effective level, or discontinue, at least every 3 months
	Epitol®	Trigeminal neuralgia	NA
Topiramate	Topamax®	None	NA
	Topamax Sprinkle®	None	NA
Oxcarbazepine	Trileptal®	None	NA
Lacosamide	Vimpat®	None	NA

Drug	Trade name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain
Lamotrigine	Lamictal® Lamictal CD® Lamictal® ODT™ Lamictal® XR™	None	NA
Phenytoin	Dilantin®	None	NA
Levetiracetam	Keppra® Keppra XR™	None	NA
Valproic acid/divalproex	Depakote®[a] Depakote ER®[a]	None	NA
	Depakene®	None	NA
	Epival ECT®[b]	None	NA
	Depacon®[a]	None	NA
	Stavzor®[a]	None	NA
SNRIs			
Duloxetine	Cymbalta®	Diabetic neuropathy	60 mg daily; lower starting dose and gradual increase in patients with renal impairment
Venlafaxine	Effexor®[a] Effexor XR®	None	NA
Desvenlafaxine	Pristiq®	None	NA
Milnacipran	Savella®	None	NA
Topical analgesic			
Lidocaine	Lidoderm®[a]	Postherpetic neuralgia	Up to 3 patches for up to 12 hours within a 24-hour period
Tricyclic antidepressants			
Amitriptyline	Elavil®[b]	None	NA
Desipramine	Norpramin®	None	NA
Nortriptyline	Aventyl®	None	NA
	Pamelor®[a]	None	NA
Protriptyline	Vivactil®	None	NA
Imipramine	Tofranil®	None	NA
Doxepin	Sinequan®[b]	None	NA
	Silenor™[a]	None	NA

Abbreviations: bid, 2 times daily; CD, chewable dispersible; CR, controlled release; ECT, enteric coated tablet, NA, not applicable; ODT, orally disintegrating tablets; qid, 3 times daily, SNRI, serotonin-norepinephrine reuptake inhibitor; tid, 3 times daily; XR, extended release.
[a] Not available in Canada, available in the United States.
[b] Available in Canada, not available in the United States.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch for neuropathic pain?

2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?

3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

METHODS

We searched Ovid MEDLINE® (1966 to November Week 3 2010), the Cochrane Database of Systematic Reviews® (4th Quarter 2010), the Cochrane Central Register of Controlled Trials® (4th Quarter 2010), and the Database of Abstracts of Reviews of Effects (4th Quarter 2010), using terms for included drugs, indications, and study designs. Electronic database searches were supplemented by hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technology in Health, and the National Institute for Health and Clinical Excellence web sites for medical or statistical reviews and technology assessments. Finally, we searched dossiers of published and unpublished studies submitted by pharmaceutical companies. Dossiers were screened for studies or data not found through other searches.

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good, fair, or poor* based on predefined criteria. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality.

RESULTS

Overview

Overall, 128 studies were included in this report (55 were identified in searches conducted for Update 1). We received dossiers from 5 pharmaceutical manufacturers: Eli Lilly, Endo, OMJUS, Ortho McNeil, and UCB. Twenty studies that were included in the original report were excluded in Update 1 either because they were outdated (8 systematic reviews) or because the inclusion criteria had changed. Of the included studies, 14 were direct comparisons of drugs in this review. The remainder was placebo-controlled, observational, or systematic reviews.

Key Question 1. What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch for neuropathic pain?

In patients with diabetic neuropathy and postherpetic neuralgia, based on very small studies, moderate-strength direct evidence did not support a statistically significant difference between gabapentin, pregabalin, and lamotrigine compared with tricyclic antidepressants in the rate of response, defined as a 50% or more reduction in baseline pain analyzed individually or when pooled (relative risk, 1.0; 95% CI, 0.84 to 1.18). Low-strength evidence indicated that lidocaine 5% medicated patch was not statistically different to oral pregabalin in 50% pain reduction in the short term (relative risk, 1.21; 95% CI, 0.88 to 1.67). Using only adjusted indirect comparisons,

duloxetine, pregabalin, and gabapentin were found to be superior to lacosamide and lamotrigine (low- to moderate-strength evidence), pregabalin was found to be superior to topiramate (low-strength evidence), and differences were not found in other comparisons of pregabalin, duloxetine, gabapentin, and oxcarbazepine or comparisons of 5% lidocaine patch and amitriptyline or gabapentin. Three drugs (divalproex, oxcarbazepine, and topiramate) had no direct comparative evidence and 1 drug (divalproex) had inadequate data to conduct an indirect analysis; all of these drugs were found superior to placebo in short-term trials.

Direct evidence for patients with other types of neuropathic pain found that in patients with cancer-related neuropathic pain, no difference in pain relief was shown with low-dose gabapentin (400 mg or 800 mg) plus opioids compared with low-dose imipramine (10 mg) plus opioids; combination with gabapentin plus imipramine plus opioids was more effective than therapy with either gabapentin plus opioids or imipramine plus opioids. In patients with spinal cord injury, amitriptyline was more effective for pain relief than gabapentin; the difference was significant only in the subgroup of patients with the highest levels of depression. In patients with central poststroke pain, there was no difference between amitriptyline and carbamazepine, and there was no direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain.

Because of differences among studies in populations, study designs, and outcomes, it was not possible to conduct indirect analyses in patients with other types of neuropathic pain.

Key Question 2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?

For patients with diabetic neuropathy and postherpetic neuralgia, moderate evidence showed that there was a lack of difference in withdrawals due to adverse events between gabapentin, pregabalin, and lamotrigine compared with amitriptyline and nortriptyline (relative risk, 0.61; 95% CI, 0.33 to 1.12), there were greater withdrawals due to adverse events of oral pregabalin compared with the 5% lidocaine patch (relative risk, 4.39; 95% CI, 2.25 to 8.69), and that gabapentin or pregabalin (as a group) were less likely to cause dry mouth than tricyclic antidepressants (relative risk, 0.27; 95% CI, 0.14 to 0.56). Low-strength evidence indicated that gabapentin or pregabalin (as a group) were more likely to cause ataxia than tricyclic antidepressants (relative risk, 3.70; 95% CI, 1.18 to 11.65), and using only adjusted indirect comparisons, low-strength evidence supported a lack of difference in withdrawals due to adverse events between duloxetine, pregabalin, lacosamide, and lamotrigine (with a range of relative risks from 0.82 [95% CI, 0.42 to 1.61] for gabapentin compared with lacosamide to 1.78 [95% CI, 0.91 to 3.48] for duloxetine compared with gabapentin). Low-strength evidence indicated that gabapentin and lamotrigine cause fewer withdrawals due to adverse events than topiramate or oxcarbazepine (with a range of relative risks from 0.44 [95% CI, 0.21 to 0.90] for gabapentin compared with oxcarbazepine to 0.60 [95% CI, 0.37, 0.97] for lamotrigine compared with topiramate.

For patients with other types of neuropathic pain, direct evidence was insufficient to evaluate comparative harms. Among 3 head-to-head trials, 1 reported no withdrawals due to adverse events with either amitriptyline or carbamazepine, and the others reported similar proportions of patients withdrawing due to adverse events for amitriptyline or imipramine compared with gabapentin.

Key Question 3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

No evidence was found that assessed differences in effectiveness or harms based on demographics, socioeconomic status, comorbidities, or cointerventions. Post hoc analyses have not found older age to have an impact on response or treatment-emergent adverse events with duloxetine, but older patients withdrew from studies more often than younger patients due to adverse events, regardless of assigned treatment (duloxetine or placebo). Only low-strength evidence suggested that combinations of duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine had a potential benefit compared to monotherapy therapy, but that there was a risk of increased adverse events – although if lower doses of the combined drugs are used, benefits may be seen in both efficacy and harms.

SUMMARY

The main findings of this review are summarized in Table 2. Based on the scope of this review the evidence presented and synthesized here is applicable to a somewhat limited group of patients. Patients in direct comparison trials included in this review were most often from Europe or Asia, female (53%), 60 years old, and had diabetes or postherpetic neuralgia for 7 years (mean range 4-13 years). Only 1 trial was based in the United States; this trial consisted of 26 United States military veterans who included 25 males and 23 Caucasians. Therefore, it is difficult to know whether the results presented here apply equally well to African Americans, Hispanics, or to Caucasians in the United States. The selection of drugs included in this review was influenced by the specific programmatic interests of the organizations participating in the Drug Effectiveness Review Project and were not meant to be read as a usage guideline. Of the drugs studied, trials differed with respect to dosing regimens limiting any conclusions about optimal dose. While evidence on how the drugs compared directly was the goal, the evidence with direct comparison is limited; much of the evidence consisted of placebo-controlled trials. Given that neuropathic pain is a chronic condition, the applicability of results from short-term trials such as those included in this report may be limited. Outcomes studied were primarily measures of pain, with multiple methods used to assess pain response. Neuropathic pain may impact a patient's life in other ways as well, such as causing fatigue, depression, lack of ability to have full employment, or reduced quality of life. These outcomes were not well studied, and the evidence does not provide insight here.

Table 2. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
Key Question 1. What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?		
Diabetic neuropathy and postherpetic neuralgia	Gabapentin, pregabalin, lamotrigine vs. tricyclic antidepressants: Moderate	No difference in rate of response defined as ≥50% reduction in baseline pain
	5% lidocaine patch vs. oral pregabalin: Low	No difference in ≥50% reduction in baseline pain
	Duloxetine, pregabalin, gabapentin vs. lacosamide, lamotrigine: Low-moderate	Duloxetine, pregabalin, gabapentin superior to lacosamide, lamotrigine in providing pain relief in adjusted, indirect comparisons
	Pregabalin vs. topiramate: Low	Pregabalin superior to topiramate in pain relief
Other neuropathic pain	Low	Cancer-related neuropathic pain: no difference in pain relief with low-dose gabapentin (400 mg or 800 mg) plus opioids compared with low-dose imipramine (10 mg) plus opioids Combination with gabapentin + imipramine + opioids was more effective than therapy with either gabapentin + opioids or imipramine + opioids
	Low	Spinal cord injury: amitriptyline was more effective for pain relief than gabapentin The difference was significant only in the subgroup of patients with the highest levels of depression
	Low	Central poststroke pain: no difference between amitriptyline and carbamazepine
	Insufficient	No direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain
Key Question 2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?		
Diabetic neuropathy and postherpetic neuralgia	Gabapentin, pregabalin, lamotrigine vs. tricyclic antidepressants: Moderate	No difference in withdrawals due to adverse events
	Pregabalin vs. 5% lidocaine patch: Moderate	Significantly more withdrawals in the oral pregabalin group than the lidocaine patch group
	Gabapentin/pregabalin vs. tricyclic antidepressants: Moderate	Gabapentin/pregabalin cause less dry mouth than the tricyclic antidepressants
	Gabapentin/pregabalin vs. tricyclic antidepressants: Low	Gabapentin/pregabalin combined cause more ataxia than the tricyclic antidepressants

Key question	Strength of evidence	Conclusion
	Duloxetine vs. pregabalin vs. lacosamide vs. lamotrigine: Low	No difference in withdrawals due to adverse events using adjusted indirect comparisons
	Gabapentin, lamotrigine vs. topiramate, oxcarbazepine: Low	Fewer withdrawals due to adverse events in gabapentin and lamotrigine when compared to either topiramate or oxcarbazepine
Other types of neuropathic pain	Insufficient	Among 3 head-to-head trials, 1 reported no withdrawals due to adverse events with either amitriptyline or carbamazepine, and the others reported similar proportions of patients withdrawing due to adverse events for amitriptyline or imipramine compared to gabapentin
Key Question 3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?		
	Low	*Age:* Post hoc analyses have not found older age to have an impact on response or treatment emergent adverse events with duloxetine *Combination therapy*: Combinations of duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine have a potential benefit compared to monotherapy, but increased adverse events occurred *Demographics, socioeconomic status, comorbidities or cointerventions*: no evidence

CONCLUSION

Overall, the strength of evidence evaluating the comparative benefits or harms of these drugs to treat neuropathic pain was low to moderate. Based on a small number of short-term trials directly comparing the drugs in patients with painful diabetic neuropathy and postherpetic neuralgia, the evidence did not support a statistically significant difference in response (50% reduction in pain) or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared with tricyclic antidepressants. Oral pregabalin was similar to lidocaine 5% medicated patch in rate of response, but resulted in more patients withdrawing due to an adverse event. Adjusted indirect comparisons of placebo-controlled trials suggested that duloxetine, pregabalin, and gabapentin were superior to lacosamide and lamotrigine, but no difference in withdrawal from study due to adverse events was found. In these analyses, differences were not found between pregabalin, duloxetine, and gabapentin or comparisons of 5% lidocaine patch and amitriptyline or gabapentin. Tricyclic antidepressants caused more dry mouth than pregabalin or gabapentin while gabapentin and pregabalin resulted in higher rates of ataxia.

In patients with cancer-related neuropathic pain who were taking opioids, there was no difference in pain relief with low-dose gabapentin compared with low-dose imipramine. Monotherapy with either drug was insufficient for pain relief. In patients with spinal cord injury, gabapentin was more effective for pain relief than amitriptyline. The difference was significant only in the subgroup of patients with the highest levels of depression. In patients with central poststroke pain, there was no difference between amitriptyline and carbamazepine. There was no direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain. Evidence for comparative effectiveness in patients with types of neuropathic pain other than diabetic or postherpetic was insufficient to assess comparative safety.

Post hoc analyses have not found older age to have an impact on response or treatment-emergent adverse events with duloxetine. Combination therapy with duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine may have had a potential benefit compared with monotherapy, but there was an increased risk of adverse events.

Oregon State University College of Pharmacy
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

Abbreviated Class Review: Chronic Obstructive Pulmonary Disease (COPD)

Executive summary:

Month/Year of Review: February 2012

New Product for review:	**Manufacturer:**	**Dossier received:**
Indacaterol (Arcapta®)	Novartis Pharmaceuticals	No
Roflumilast (Daliresp®)	Forest Pharmaceuticals	Yes

Available Alternatives

Current Preferred Agents:		**Requires PA***
Pulmonary Anticholinergic Inhalers	**Long-acting Controllers**	Advair (fluticasone/salmeterol)
Ipratropium (Atrovent HFA®)	Flunisolide (Aerobid®)	Symbicort (budesonide/formoterol)
Ipratropium/Albuterol AER (Combivent®)	Mometasone (Asmanex®)	Dulera (mometasone/formoterol)
Ipratropium Bromide Solution	Fluticasone (Flovent Diskus®)	
Ipratropium-Albuterol AMPUL-NEB	Fluticasone (Flovent HFA®)	
Tiotropium (Spiriva®)	Formoterol (Foradil®)	
	Budesonide (Pulmicort Flexhaler®)	
	Beclomethasone (Qvar®)	
	Salmeterol (Serevent Diskus®)	

*Requires fail of combination of short acting and long-acting inhaled bronchodilators (Appendix 1)

Previous Conclusions:

Beta$_2$Agonists (HRC 2007):

1. There is no significant difference between salmeterol and formoterol in COPD patients in efficacy or effectiveness for respiratory symptoms in the outpatient setting.

2. There is no evidence of comparative difference in efficacy or effectiveness among the short-acting inhaled beta$_2$-agonists in the outpatient setting
3. There is insufficient evidence to determine comparative differences in safety or rates of adverse events among inhaled long acting beta$_2$-agonists, when used in COPD patients in the outpatient setting.

Inhaled Corticosteroids (HRC 2006):

1. There is insufficient evidence to evaluate difference among ICSs for comparative effectiveness.
2. There is consistent evidence that ICSs do not reduce mortality or improve quality of life in COPD.

Inhaled Anticholinergics: (Provider Synergies 2010)

1. Both agents in this class (ipratropium and tiotropium) have been shown to improve bronchodilation, dyspnea, exacerbation rates, and health-related quality of life
2. Adverse effects are limited primarily to dry mouth that appears to resolve with continued use.

Reason for Review:

Two new FDA approved medications indicated for the treatment of COPD are now available. Indacaterol (Arcapta®) is the first LABA available that is dosed once daily.[1] It is available as a single drug inhaled product and is indicated for COPD only. Roflumilast (Daliresp®) is the first oral phosphodiesterase-4 (PDE4) inhibitor made available in the U.S.[2] It has a novel mechanism of action and is indicated for a very narrow COPD population to help reduce the risk of exacerbations. Refer to individual drug reviews for efficacy and safety evaluations which can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings.

Additionally, there has been several new or revised COPD treatment guidelines published. The National Institute for Clinical Excellence in the United Kingdom (NICE) and the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) updated their respective guidelines in 2010. An international collective of physician groups: the American College of Physicians (ACA), the American College of Chest Physicians (ACCA), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) also published COPD treatment recommendations in 2011.[3, 4, 5]

Several high quality systematic reviews have been published in the interim as well. The Canadian Agency for Drugs and Technologies in Health (CADTH) evaluated the effectiveness of triple therapy (ICS + LABA + LAMA) compared with dual (ICS + LABA) or monotherapy (LAMA) for moderate-to-severe COPD in 2010.[6] The Cochrane group has numerous reviews on COPD treatment that have become available in 2010 and 2011. These systematic reviews compared the effectiveness of the various COPD classes, many looking at whether combination therapy has benefits over monotherapy.[7, 8, 9, 10, 11]

Issues:

- Is there new comparative evidence that there is a meaningful difference in LABAs, LAMAs, and ICSs or combinations thereof in long term clinical outcomes or safety that could justify changes in current PDL management?
- Is there any evidence that indacaterol or roflumilast are more effective or safer than currently available medications?

Summary:

Three organizations recently updated their evidence based treatment guidelines for management of stable COPD.[2,3,4] These include starting treatment with a long-acting bronchodilator in patients with moderate stage COPD (FEV_1>50%) experiencing dyspnea symptoms. Addition of an ICS is not recommended until more severe disease (stage $\geq$ 3; repeated exacerbations) presents. All guidelines treat progressing COPD disease in the same stepwise fashion: short-acting bronchodilator, long-acting bronchodilator, additional long-acting product(s)-LABA, LAMA, or ICS, and finally long-term O_2 therapy. None of the current guidelines can conclude that there is a meaningful difference or favor individual products within each class.[2, 3, 4]

The guidelines differ in where they put emphasis on one long-acting class over another. NICE favors LAMA over LABA for monotherapy in more severe disease. Both GOLD and the joint CHEST guidelines consider LABA and LAMA as therapeutically equivalent. NICE and GOLD favor ICS products for patients with more severe disease, while the joint CHEST guideline offers a weak recommendation for ICS products in this population.[2,3,4]

The role of combination therapy is not yet entirely established. In the last two years, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Cochrane Collaboration have published systematic reviews attempting to clarify the issue of what combination might be the most efficacious. Two Cochrane reviews updated in 2010 compared combination dual ICS + LABA therapy with ICS or LABA monotherapy. One concluded adding an ICS to LABA monotherapy decreased exacerbation but increased pneumonia rates, while LABA therapy alone showed modest improvements in lung function.[7] The other 2010 Cochrane review examined LABA/ICS combination therapy versus ICS monotherapy and found all outcomes, including mortality, exacerbations, and hospitalizations, improved with combination therapy.[8]

Several other reviews looked at triple therapy (LAMA + LABA + ICS) versus LAMA monotherapy or dual therapy with either an ICS + LABA or LAMA + LABA combination.[6, 9, 10] There was some evidence for improvement in lung function and quality of life measures with triple therapy; however, no conclusions as to whether triple therapy improved mortality or hospitalizations could be made. These reviews are severely limited by the lack of clinical trials examining triple therapy. Inadequate data also hampered a Cochrane review looking at LAMA monotherapy compared with ICS/LABA combination therapy; the authors drew no conclusions due to insufficient evidence.[11] In the recent clinical trial POET-COPD, LAMA monotherapy was shown to be superior to LABA monotherapy; decreasing total annual exacerbation rate by 11% (0.64 vs. 0.72, RR 0.89 95% CI 0.83 to 0.96). Although more evidence is needed, LAMA monotherapy may be more effective at improving symptoms and decreasing exacerbations than LABA monotherapy in patients initiating treatment, especially with more severe disease. [12]

Entering the COPD landscape are two new medications. The first, indacaterol (Arcapta®), is a new LABA. Unlike the currently available LABAs, indacaterol is dosed one daily and is not available in combination with an ICS entity. In clinical trials, indacaterol was shown to improve lung function and improve symptom control compared with placebo.[13, 14, 15, 16, 17] The approved dose, however, was not compared with available LABAs or LAMAs, making it difficult to establish clinical efficacy. The second is roflumilast (Daliresp®), a selective phosphodiesterase-4 inhibitor. Roflumilast is not used to control symptoms; it is indicated to decrease the risk of exacerbations in patients with severe COPD who have chronic bronchitis and a history of exacerbations. In clinical trials when compared to placebo, it decreased exacerbation rates only in the specific indicated population. Several adverse events not seen with other COPD medications (weight loss, suicide ideation, depression) were significantly higher in roflumilast versus placebo groups.[18, 19, 20]

Conclusions:

Guideline recommendations are similar although not uniform. GOLD, NICE and CHEST guidelines agree in treating COPD patients in a stepwise fashion, starting with long-acting bronchodilator monotherapy and adding agents with disease progression. GOLD and CHEST make no differentiation between the long-acting bronchodilator classes LABA and LAMA, while NICE recommends initiating with LAMA therapy in COPD patients with more severe symptoms. All three guidelines recommend adding an ICS only when warranted by symptoms and disease severity (stage 3; exacerbations). None of the guidelines make recommendations regarding triple therapy use.

The CADTH and Cochrane systematic review conclusions confirm the guideline recommendations. A LABA product is recommended in COPD patients with less severe symptoms as an initial agent, while a LAMA product may be a better first line choice for a patient with more severe disease. Addition of an ICS is recommended for patients still experiencing symptoms and persistent exacerbations with monotherapy. There is limited evidence for the advantage of triple therapy in outcomes important to COPD: exacerbation, pneumonia, hospitalization and mortality rates. More evidence is needed to establish if triple therapy brings any additional benefit.

Remaining Issues:

There is still little comparative evidence for long-term benefits or harms of LABAs, LAMAs, and ICSs. The debate as to which class, or combination of classes, is best remains unresolved. More comparative effectiveness research for triple therapy versus dual therapy is needed.

Further comparative studies are needed to evaluate:

- Comparisons of triple therapy with various combinations of dual and monotherapy
- Outcomes over several years to compare pneumonia, hospitalization and mortality rates

Recommendations:

1. No significant comparative effectiveness evidence exists since last OHA class review necessitating PDL changes. Recommend comparing costs of agents for any further additions or eliminations to preferred products.
2. Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommended making indacaterol a nonpreferred LABA.
3. Recommend maintaining roflumilast as a non-preferred agent and include the following clinical criteria necessary for approval to ensure it is only used in the appropriate patient population:
    a. Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation.
    b. Patient has documented failure with an ICS or ICS combination product or tiotropium
    c. Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Background/Current Landscape

COPD is the fourth leading cause of morbidity and mortality in the United States. More than 13 million US adults have COPD and in 2010, the cost to the nation for COPD was over 45 billion.[21] COPD is a condition characterized by limitation of airflow that is not fully reversible. Airflow limitation is usually progressive and associated with abnormal inflammatory response. It is caused by a mixture of small airway disease (chronic bronchitis) and parenchymal destruction (emphysema). Risk factors can include non-modifiable and modifiable causes. The leading predictor of COPD is a history of long term cigarette smoking. [3, 4, 5]

Current guidelines consider spirometry the gold standard in diagnosing COPD. [3, 4, 5] Spirometry is described as the most reproducible, standardized, and objective way of measuring airflow limitation.[22] Airflow limitation that is not fully reversible is defined as present when the post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is below 0.70. [3, 4, 5] All patients with COPD, regardless of disease severity, have an FEV_1/FVC ratio of <0.70. Disease severity, however, is evaluated by the patient's FEV_1 measured against a population standard. Using spirometry, COPD patients are classified into four stages: Stage I (mild): $FEV_1 \geq 80$ % predicted, Stage II (moderate): 80 % > FEV_1 > 50 % predicted, Stage III (Severe): 50 % > FEV_1 > 30 % predicted, and Stage IV (Very severe): $FEV_1 < 30$ % predicted. Exacerbations and symptoms (i.e. SOB, cough, and sputum production) tend to increase with disease progression. [3, 4, 5]

Long-acting bronchodilators are used to improve breathing in adults with airflow obstruction due to COPD including chronic bronchitis and emphysema. Two types of bronchodilators, long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA), are indicated as maintenance therapy for COPD patients stage 2 or higher. LABAs are considered a mainstay of COPD therapy, and are often the starting maintenance

medication for a patient. Current treatment guidelines recommend LABAs as a central therapy for the alleviation of symptoms and are recommended for treatment of COPD. [3, 4, 5] However, recent evidence suggests initiating a LAMA instead of a LABA in patients with more severe symptoms may improve outcomes such as hospitalizations and mortality.[12] Inhaled corticosteroids (ICS) are not used as an initial therapy but added in patients with more severe symptomatic COPD (stage 3; exacerbations).[3, 4, 5]

None of the existing COPD classes have been shown to modify long term decline in lung function[4] and reduction of therapy once symptoms are controlled is not always possible. Further deterioration of lung function frequently entails the progressive introduction of more medications. All three classes are used frequently in combinations of dual and triple therapy; and combination products of LABAs and ICS are available and intended to facilitate adherence to medication. When to use combination therapy instead of monotherapy has not clearly been established. Triple therapy is not uncommon and is even more controversial. At this time, there is insufficient evidence to show triple therapy improves exacerbation, hospitalization or mortality rates.[6, 9, 10]

National/International Guidelines

1. Diagnosis and management of stable COPD : a clinical practice guideline update[3]

Developer:
American College of Physicians, American Thoracic Society,
European Respiratory Society, American College of Chest Physicians

Published:
CHEST, August 2011

Recommendations:

1. There is moderate-quality evidence that asymptomatic COPD patients staged moderate or better (stages 1 &2; >50% FEV) should receive no treatment.
2. Based on a weak recommendation and low-quality evidence, symptomatic patients with an FEV_1 between 60-80% may begin treatment with inhaled bronchodilator (LABA or LAMA).
3. There is moderate-quality evidence that symptomatic patients with an FEV_1<60% should begin treatment with an inhaled bronchodilator (LABA or LAMA).
4. There is moderate-quality evidence that monotherapy can begin with either a LABA or LAMA. Evidence shows no significant difference in outcomes among various monotherapies.

5. There is moderate-quality evidence and a weak recommendation that combination therapy may be utilized for symptomatic patients with an $FEV_1 < 60\%$. The evidence is still insufficient to support a strong recommendation for the broad use of combination therapy.

Critique:
These evidence based guidelines utilized strong methods performed by the Minnesota Evidence-based Practice Center including a literature search, internal peer review, and individual quality assessment of trials included. It was intended for physician use and focused on clinically important outcomes of exacerbations, mortality, hospitalizations, and quality of life. This guideline is funded by the American College of Physicians, a professional organization dedicated to the practice of internal medicine[24].

2. **Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease[4]**

Developer:
Global Initiaitve for COPD
National, Heart, Lung, and Blood Institute
World Health Organization

Published:
2010 (revision)

Recommendations:
1. There is high-quality evidence that patients with moderate COPD ($FEV_1 \geq 50\%$) who experience dyspnea should start treatment with a long acting inhaled bronchodilator. There is insufficient evidence to favor one long-acting bronchodilator over others.
2. There is moderate-quality evidence that in patients with severe ($FEV_1 < 50\%$) to very severe COPD who experience repeated exacerbations, the addition of an ICS reduces the frequency of exacerbations and improves health status.

Critique:
Global Initiative from Chronic Lung Disease (GOLD) guideline for COPD provides a more detailed overview than most other guidelines and includes aspects outside of management and treatment of stable COPD including acute, emergency and preventive care, as well as treatment of co-morbidities common in the COPD population. The target audiences for this guideline are healthcare providers in the primary care setting. A detailed search strategy was conducted, and a defined rating scheme for rating the strength of the evidence is also used. Evidence is ranked as "A, B, C or D" on the basis of the source of the data.
GOLD is funded by a mixture of private non-profit and for-profit companies. Numerous pharmaceutical companies are contributors including AstraZeneca (Pulmicort™), Novartis (Foradil™), GlaxoSmithKline (Advair™), and Pfizer (Spiriva™).

3. **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care**[5]

Developer:
National Institute for Health and Clinical Excellence

Published:
2010 (updated)

Recommendations:

1. There is moderate-quality evidence that patients experiencing "exacerbations and persistent breathlessness" and have an $FEV_1 \geq 50\%$ should be treated with a long-acting beta-2 agonist (LABA) or a long-acting muscarinic agonist (LAMA) monotherapy.
2. There is moderate-quality evidence that patients experiencing "exacerbations and persistent breathlessness" and have an $FEV_1 < 50\%$, should be treated with a LAMA as monotherapy or with dual therapy of an inhaled corticosteroid (ICS) & LABA or LABA-LAMA combination.
3. There is low-to-moderate-quality evidence that patients with persistent exacerbations should be treated with dual or triple therapy: an ICS-LABA or ICS-LABA-LAMA combination.

Critique:
Unlike the two previous guidelines, the NICE COPD guideline is aimed at a much larger target audience and is broader in scope.
Search criteria are given in broad descriptions, but with direction to appendices with more detailed information. Internal and external peer reviews were conducted to validate the guideline. A hierarchy of Evidence Rating system was used to assess the quality and strength of the evidence
This guideline is funded by the Government of the United Kingdom.

Systematic reviews:

Triple Therapy for Moderate to Severe Chronic COPD[6]
CADTH

Published in December 2010
This systematic review evaluated the clinical efficacy of single, dual (ICS + LABA) and triple (ICS + LABA + LAMA) therapy in patients with COPD. Clinical outcomes of interest were lung function, hospitalizations, exacerbations, and quality of life. CADTH also assessed cost-effectiveness and impact on Canadian Health systems. The review included only tiotropium as the monotherapy comparator. Studies included were not designed to analyze efficacy in triple versus dual therapy. The evidence is extremely limited in this review and based on only four studies evaluating triple therapy and can only be generalized to patients with moderate-to-severe COPD with a history of exacerbations and smoking.

Conclusions:

- There is limited evidence of moderate quality that triple therapy, dual therapy, and combination therapy decreased the number of COPD hospitalizations, improved lung function, and quality of life in patients with moderate to severe COPD in comparison with tiotropium monotherapy.
- There is insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination therapy.

***Cochrane Collaboration**:*

1. "Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease"[9]

Published 2011
The main objective was to examine the efficacy of triple therapy (LABA + tiotropium + ICS) versus LAMA monotherapy or dual therapy (LABA + ICS). Clinical outcomes of interest included lung function, hospitalizations, mortality, and quality of life. Only three trials met the inclusion criteria for the review, limiting the external validity of the review.

Conclusions:
- There is weak evidence that triple therapy improved lung function and quality of life in patients COPD in comparison with dual therapy.
- There is insufficient evidence as to whether triple therapy has additional benefits in decreasing mortality, hospitalizations, exacerbations and pneumonia.

2. "Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease"[11]

Published 2011
This systematic review looked at the relative effects of LAMA monotherapy versus LABA +ICS combination therapy. Clinical outcomes of interest included exacerbations, hospitalizations, and mortality. Again only three trials met the review's inclusion criteria. In the largest study included, there were serious issues surrounding withdrawals calling into question the validity of the study.

Conclusions:
- There is insufficient evidence to compare efficacy and safety of LAMA monotherapy with LABA+ICS dual therapy

3. "The effect of adding inhaled corticosteroids to tiotropium and long-acting beta2-agonists for chronic obstructive pulmonary disease"[10]

Published 2011
This systematic review examined if there is additional efficacy in adding an ICS to LABA + LAMA dual therapy with dual LABA+LAMA therapy alone. Only one trial met the review's inclusion process and that study had some high, uneven rates of attrition.

Conclusions:

- There is insufficient evidence to conclude if triple combination therapy has greater efficacy over LABA/LAMA dual therapy.

4. "Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease"[8]

Published 2010
This systematic review examined whether combination LABA/ICS therapy provided any additional benefit over ICS monotherapy. Clinical outcomes of interest included lung function, exacerbations, hospitalizations, mortality, and quality of life. This review included seven studies with a fairly homogenous population of severe COPD patients. The review also looked at differences between the two combination products available for COPD: salmeterol/fluticasone and formoterol/budesonide.

Conclusions:

- There is strong evidence combination LABA/ICS therapy reduces mortality compared with ICS monotherapy.
- There is strong evidence combination therapy reduces hospitalizations and exacerbations compared with ICS monotherapy.
- There is strong evidence of greater improvements in lung function and quality of life measures with combination therapy versus ICS monotherapy.
- There is strong evidence that adverse events are similar between combination and monotherapy populations.
- There is insufficient evidence to determine if one combination product is superior to the other.

5. "Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease"[7]

Published 2010
The objective of this systematic review is to assess the effectiveness of combination LABA/ICS therapy compared with LABA therapy alone. Clinical outcomes of interest were exacerbations, mortality, and pneumonia. Ten studies were included in this review. The majority of studies used salmeterol/fluticasone as the combination product.

Conclusions:

- There is strong quality evidence that combination dual therapy (LABA+ICS) reduces exacerbations compared with LABA monotherapy.
- There is insufficient evidence combination therapy reduces mortality or hospitalizations compared with LABA monotherapy.
- There is strong evidence of greater risk of developing pneumonia with combination therapy versus LABA monotherapy.

Appendix 1
Current PA Criteria

LABA/ICS Inhalers

Goal(s):

- *Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication)*
- *LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).*
- *Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#oregon*

Iniative: LABA/ICS Step Therapy

Length of Authorization: 6 months - 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Step Therapy Required prior to coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),

COPD: short and long-acting beta-agonist inhalers, anticholinergics (Atrovent, Combivent), inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml), and theophylline DO NOT require prior authorization.

Requires PA: Advair diskus and Advair HFA (fluticasone/salmeterol) HICL= 19963, Symbicort (budesonide/formoterol) HICL= 21993, Dulera (mometasone/formoterol) HICL = 37050

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to **2**	**No:** Go to **3**
2. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Is there documentation of step 3 or 4 asthma OR • Is there a hospital admission or ER visit related to asthma or reactive airway	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record	**No**: **PASS TO RPH** **DENY (Medical Appropriateness).** *Oregon Asthma guidelines*

disease within last 60 days?	Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	*recommend combination inhaled corticosteroids plus LABA after failure of low or medium dose ICS.* *http://www.oregon.gov/DHS/ph/asthma/pubs.shtml#Oregon_Guiding_Documents_for_Asthma*
3. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.)?	**Yes:** Go to **4**	**NO: PASS TO RPH DENY (Medical Appropriateness).** *Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.*
4. Has patient failed a combination of **short acting** (ipratroprium or ipratroprium/albuterol) **and long-acting** (salmeterol, formoterol and/or tioptropium) inhaled bronchodilators?	**Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications in the PA record**.** Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	(**No:** Pass to RPH; Deny, (Medical Appropriateness). *Gold guidelines recommend addition of inhaled corticosteroid if disease severity persistent despite use of combination of short acting and long-acting bronchodilators.* *http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf*

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Oregon State University College of Pharmacy
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

Month/Year of Review: February 2012
Generic Name: roflumilast
PDL Class: No current PDL class
Preferred COPD medications: formoterol, ipratropium, ipratropim/albuterol, salmeterol, tiotropium
Non-preferred: ICS/LABA combination products, and indacaterol (pending)

End date of literature search: November 2011
Brand Name (Manufacturer): Daliresp (Forest Pharmaceuticals)
Comparator Therapies: salmeterol, tiotropium, formoterol
Dossier received: Yes

EXECUTIVE SUMMARY:

FDA Approved Indications:
Roflumilast is indicated as a treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations[1]

Background: Current standard of care for COPD patients is usually stepwise and generally guided by disease severity. Several guidelines advocate the use of long-acting bronchodilators beta-2 alpha adrenergic antagonists (LABA) or muscarinic antagonists (LAMA) for initial maintenance of symptom control. With more severe symptoms (i.e. patients with exacerbations) an inhaled corticosteroid (ICS) may be added.[2, 3, 4] Unfortunately, COPD is a progressive disease and often more medications are added with different mechanisms of action in order to control symptoms and improve patient quality of life. Eventually, most patients are on a combination of LABA, LAMA, and ICS as dual or triple therapy. Roflumilast is the first approved phosphodiesterase type-4 inhibitor. It is most closely related mechanistically to the phosphodiesterase inhibitor theophylline, but roflumilast has a more targeted site of action and narrow indication for use.[5] Roflumilast is approved to help reduce exacerbations. It is not intended to improve lung function.

Issues:
Key questions:

1. Is roflumilast more effective than currently preferred agents in the treatment of COPD to decrease exacerbations and mortality?
2. Is roflumilast better tolerated than current agents including formoterol, ipratropium, ipratropim/albuterol, salmeterol, or tiotropium?
3. Are there specific populations for which roflumilast is better tolerated or more effective?

Efficacy: Outcomes of interest when evaluating drugs for COPD include mortality, hospitalizations, pneumonia, exacerbations, quality of life and symptom control. The primary efficacy outcome reported in the roflumilast studies was improvement in pre-bronchodilator forced expiratory volume in one second (FEV_1). FEV_1 is an important measurement in diagnosing and staging COPD. It is also commonly used in COPD clinical trials because it is an objective, reproducible measurement of lung function. It is not, however, an ideal outcome measure for roflumilast as it doesn't provide any information about risk of exacerbation.

FDA approval of roflumilast relied on two good quality, randomized control trials (RCT), M2-124 and M2-125.[5] The trials had identical design and included only patients with severe or very severe COPD, with chronic bronchitis and a history of exacerbations. The primary study outcomes were change in pre-bronchodilator FEV_1 and rate of COPD exacerbations per patient per year. These trials demonstrated that roflumilast 500 mg once daily produced an improvement in pre-bronchodilator FEV_1 (roflumilast = 40ml vs. placebo = -9 ml, $P < 0.0001$). It was associated with fewer patients with severe exacerbations (roflumilast: 157 [10.2%] vs. placebo: 198 [12.7%], RR: 0.80 95% CI 0.66 –0.98), fewer patients with moderate exacerbations (roflumilast: 624 [40.6%] vs. placebo: 723 [46.5%], RR: 0.87 95% CI 0.80 – 0.95).[6] There was no difference in mortality.

There were four additional RCTs conducted in pairs: M2-111, M2-112 and M2-127, M2-128. These studies evaluated the efficacy and safety of roflumilast versus placebo in patients over 40 years old with moderate to severe COPD.[7, 8] All but M2-111, were published and of good quality.[6, 7, 8] M2-112[7] demonstrated that roflumilast 500 mg once daily produced an improvement in pre-bronchodilator FEV_1 (roflumilast: 9ml vs. placebo: -27ml, $P< 0.002$). There was no difference in rates of moderate to severe exacerbations or death from any cause.

Studies M2-127 and M2-128 evaluated lung function and exacerbations when roflumilast was used as add-on therapy.[8] Study M2-127 compared roflumilast plus salmeterol versus placebo plus salmeterol and study M2-128 compared roflumilast plus tiotropium versus placebo plus tiotropium. Both trials showed significant improvement in FEV_1 (both trials: $p<0.001$). The proportion of patients on roflumilast with moderate to severe exacerbations was fewer that those on placebo in both studies. M2-127 reported roflumilast: 51 (10.9%) vs. placebo: 83 (17.8%), RR: 0.62 95% CI: 0.45 – 0.85, P=0.0015 and M2-128 reported roflumilast: 42 (11.3%) vs. placebo: 58 (15.6%) RR: 0.72 95% CI: 0.50 – 1.05, P=0.0867. Death was not reported. These studies used different definitions of exacerbation and inclusion criteria than the prior studies.[5]

Safety: Rates of attrition were fairly high among studies but were comparable for treatment and placebo arms. Loss to follow-up was generally low and similar. But, the reason for withdrawal varied. More patients on roflumilast withdrew for adverse events whereas more patients on placebo withdrew for exacerbations. The most common adverse side effects were diarrhea, nausea and weight loss. Weight loss was moderate (5-10% of body weight) to severe (> 10% of body weight); and patients with more severe disease or those with lower baseline body weights experienced a higher occurrence of weight loss.[5, 6, 7, 8]

More serious adverse events documented through the trials were psychiatric in nature. Anxiety, insomnia and suicide ideation rates were increased in the roflumilast subjects compared with placebo. One patient committed suicide and two others attempted suicide in the roflumilast treatment arms during clinical trials. There were no attempts of suicide in the placebo groups, although one patient experienced suicide ideation.[5] These side effects could be an area of concern in populations with high rates of psychiatric co-morbidities, such as Medicaid patients. Roflumilast caused an increase in cancer in animal studies. In clinical trials, although cancer rates were higher in intervention subjects compared with placebo, the overall incidence was low and statistically insignificant.[5]

The data presented for adverse events was not always complete or easy to track. Weight loss was not followed consistently through all studies[7] and patient psychiatric adverse events were not always transparent. For example, the safety information available in FDA summary review documents was not in published studies.[5]

Conclusions: There is high level evidence roflumilast is superior to placebo in improving FEV_1 in patients with severe COPD, although the clinical significance of this is unclear. There is low to moderate level evidence that roflumilast modestly reduces the proportion of patients experiencing a moderate to severe exacerbation. There is insufficient evidence to determine comparative efficacy or safety with other medications indicated for the reduction of COPD exacerbations. Evidence for the approved indication is based on two placebo-controlled studies with very specific inclusion criteria (severe COPD, history of exacerbations, current bronchitis symptoms), limiting the applicability of the data for the population at large.[5, 6, 7, 8]

Overall, the studies were of short term duration and have not been shown to decrease mortality. Withdrawal due to adverse events was statistically higher for roflumilast with most due to diarrhea, nausea and weight loss. Unresolved safety concerns include suicide risk, which is not seen with other COPD medications.

Although roflumilast is the first in its class and in the future may be a valuable addition to COPD treatment, it has not been shown to be superior to other available treatments for COPD. Additional evidence and clinical experience will be helpful in the future to determine the appropriate place in therapy for roflumilast.

Recommendations:
Recommend maintaining roflumilast as non-preferred agent and include the following clinical criteria necessary for approval to ensure it is only used in the appropriate population:

- Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation.
- Patient has documented failure with an ICS or ICS combination product or tiotropium
- Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

BACKGROUND/CURRENT LANDSCAPE

Medication management is based on severity of disease and degree of symptoms. There are clear shared recommendations through guidelines from the Global Initiative for COPD (GOLD) within the World Health Organization, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom and collaborating organizations the American College of Physicians, the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society (CHEST). Patients with moderate stage COPD (FEV_1>50%) experiencing dyspnea symptoms are recommended a long-acting bronchodilator (LABA or LAMA). Patients with more severe disease (stage $\geq$ 3; repeated exacerbations) can add an ICS. NICE and GOLD guidelines recommend a short acting bronchodilator throughout all stages of disease (barring contraindications) to manage immediate symptoms. None of the existing COPD classes have been shown to modify long term decline in lung function[5] and reduction of therapy once symptoms are controlled is not always possible. Further deterioration of lung function frequently requires the progressive introduction of more medications. All guidelines treat progressing COPD disease in the same stepwise fashion: short-acting bronchodilator, long-acting bronchodilator, additional long-acting product(s)-LABA, LAMA, or ICS, and finally long-term O_2 therapy. No guideline favors an individual product; all products within a class are considered equivalent.[2, 3, 4]

CLINICAL PHARMACOLOGY [1, 9]

Roflumilast is most closely mechanistically related to theophylline, a non-specific phosphodiesterase inhibitor. Roflumilast differs from theophylline in that, it is a selective inhibitor of phosphodiesterase 4 (PDE 4). Phosphodiesterases, including PDE4, are enzymes that break down cyclic '3,'5-adenosine monophosphate (cyclic AMP). The specific mechanism of action of roflumilast in COPD is unknown. However, PDE4 works primarily in the lung tissue. By inhibiting PDE4, roflumilast and its active metabolite (roflumilast N-oxide) are believed to cause an accumulation of intracellular cyclic AMP in lung cells. Roflumilast also reduces the recruitment of inflammatory cells such as neutrophils, macrophages into the bronchi.

PHARMACOKINETICS[1, 9]

Table 4

Parameter	Result
Oral Bioavailability	80%
Protein Binding	99%
Elimination	70% urine
Half-Life	roflumilast 17 hours roflumilast N-oxide 30 hours
Metabolism	Extensively metabolized by phase I (CYP 1A2 & 3A4) and Phase II (conjugation) reactions. N-oxide is major metabolite*

*The N-oxide metabolite is active but is less potent than roflumilast

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Mortality
2) Severe Exacerbation (resulting in hospitalization or death)
3) Moderate Exacerbation (requiring corticosteroid rescue)
4) Withdrawals due to adverse events

Primary Study Endpoint:
1) Mean change in pre-bronchodilator FEV_1
2) Moderate to Severe Exacerbations per patient per year

Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[b]	ARR / NNT	Safety Results (CI, p-values)	ARI / NNH	Quality Rating[d]; Comments
M2-124 & M125[6]									
Calverley et. al. PC, RCT, DB, PG	R: Roflumilast 500µg QD P: Placebo QD	Patients with severe to very severe COPD Mean Age:64 yrs Male: 75% White: 84% Current smokers: 41% Inclusion: COPD w/$FEV_1 \leq 50\%$,Smoking history ≥ 20 pack year, ≥ 40 yo, hx of bronchitis and exacerbation Exclusion: Asthma or other lung disease; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; history of GI bleeds within last year; part of another clinical trial within 30 days; current part in within 3 months of the run-in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 1537 P: 1554	Outcomes assessed at 52 weeks	Death any cause R: 42(2.7%) P: 42 (2.7%) RR: 1.01 95% CI 0.66 – 1.54 (NS) Severe Exacerbations R: 157 (10.2%) P: 198 (12.7%) RR: 0.80 95% CI 0.66 –0.98 Moderate Exacerbations R: 624 (40.6%) P: 723 (46.5%) RR: 0.87 95% CI 0.80 – 0.95 Mean change in pre-bronchodilator FEV1 (mL): R: 40 mL P: -9 ml Difference: 48 ml 95% CI: 35 – 62 P <0.0001	ARR: 0% NNT: NS ARR:2.5% NNT: 40 ARR: 5.9% NNT: 17 ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 220 (14.3%) P: 161 (10.4%) RR: 1.38 95% CI 1.14 – 1.67	ARI: 3.95% NNH: 25	Good; Total attrition rates: R: 510 (33.2%) P: 482 (31.0%) Overall attrition rate: 32.4% Attrition is >20% but loss to follow-up was the same in both groups. There were differential rates in withdrawals due to adverse events and for COPD exacerbation. Adherence to treatment was similar in all groups with a mean compliance of 93% (R) and 95% (P). ICS and LAMA use prohibited; LABA and SAMA use allowed at stable doses. 4-week placebo run-in used to select patients with severe disease. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-112[7]									Good
Calverley et. al. Phase III, RCT, DB, PC, PG	R: Roflumilast 500µg QD P: Placebo QD X52 weeks; mean:	Patients with severe to very severe COPD Mean Age: 65 yrs Male: 76% Current smokers: 37% Inclusion: COPD w/FEV_1≤ 50%,Smoking history ≥ 10 pack year, ≥ 40 yo Exclusion: Asthma hx or other relevant lung dx (lung CA, bronchiectasis) long term O2, or other clinically significant cardio-pulmonary co-morbidity	R: 760 P: 753	Outcomes reported for 52 weeks.	<u>Death from any cause:</u> R: 12 (1.6%) P: 20 (2.7%) RR: 0.59 95% CI 0.29 – 1.21 (NS) <u>Overall moderate or severe exacerbations (rate/patient/yr):</u> R: 0.857 P: 0.918 RR: 0.9 P=0.451 <u>Change in Pre-bronchodilator FEV1 versus from baseline (mL):</u> R: 9ml P: -27ml P< 0.002	ARR: 1.0% NNT: NS ARR: NA NNT: NA ARR: NA NNT: NA	<u>Withdrawals due to Adverse events:</u> R: 103 (14.6%) P: 56 (7.4%) RR: 1.82 95% CI (1.34 – 2.48)	ARI: 6.1% NNH: 16	Total attrition rates: R: 217 (29%) P: 163 (22%) Overall: 25% Attrition rate >20% but there was no reported loss to follow-up. Differential rate due to withdrawals for adverse events. Withdrawals due to exacerbations were similar. Adherence rates not reported by authors. LABA and LAMA use prohibited; ICS use allowed. 4-week placebo run-in used to select patient with severe disease. Change in pre-bronchodilator reported as secondary outcome. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-127[8]									Good;
Fabbri et. al. RCT, DB, PG	R: Roflumilast 500μg QD + salmeterol P: Placebo QD + salmeterol X24 weeks	Patients with Moderate to Severe COPD Mean Age: 65 yrs Male: 66% Current smoker: 39% Inclusion: COPD w/FEV_1< 70%,Smoking history > 10 pack year, > 40 yo Exclusion: Asthma or other lung disease; lower respiratory tract infection in last 4 weeks; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; part of another clinical trial within 30 days; curren part in within 3 months of the run in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 466 P: 467	Outcomes assessed Every 4 weeks up t week 12, and every 6 weeks thereafter until week 24.	Moderate or Severe Exacerbation: R: 51 (10.9%) P: 83 (17.8%) RR: 0.62 95% CI: 0.45 – 0.85 P=0.0015 Mean change in pre-bronchodilator FEV_1 relativ to placebo: R: 39ml P: -10ml 95% CI: 27 – 71 P=<0.0001	ARR:6.8% NNT 15 ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 77 (16.5%) P: 45 (9.6%) RR: 1.71 95% CI: 1.21 – 2.42 P=0.0019	ARI: 6.9% NNH: 15	Total attrition rates: R: 33 (7.1%) P: 20 (4.3%) Overall: 5.7% Rates of attrition were acceptable. Differential rates due to adverse events. COPD exacerbation withdrawals also varied (R: 16, P: 27). Adherence to treatment was similar in all groups with a mean compliance between 94% and 97%. 4-week placebo run-in period to select moderate to severe patients. Chronic bronchitis was not an inclusion criterion. ICS use prohibited. Shorter duration. Outcomes assessed at each visit; unclear when outcomes that were reported were assessed. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

M2-128[8]									Good;
Fabbri et. al. RCT, DB, PG	R: Roflumilast 500μg QD + tiotropium P: Placebo QD + tiotropium X24 weeks	Patients with Moderate to Severe COPD Mean Age: 64 yrs Male: 80% Current smoker: 40% Inclusion: COPD w/FEV_1≤ 50%,Smoking history ≥ 20 pack year, ≥ 40 yo, hx of bronchitis, pretreatment with tiotropium for ≥ 3months Exclusion: Asthma or other lung disease; lower respiratory tract infection in last 4 weeks; cardiopulmonary abnormalities; abnormal labs; pregnant/ planned pregnancy /breast feeding /females of child-bearing age not using contraception; part of another clinical trial within 30 days; curren part in within 3 months of the run in period of a pulmonary rehab program; immunosuppressive meds within 4 weeks; Alpha-1-antitrypsin deficiency; HIV infection; active hepatitis; any cancer (other than basal cell) within 5 years; abnormal ECG results; alcohol or drug abuse; hypersensitivity to study med	R: 371 P: 372	Outcomes assessed Every 4 weeks up t week 12, and every 6weeks thereafter until week 24.	Moderate or Severe Exacerbation: R: 42 (11.3%) P: 58 (15.6%) RR: 0.72 95% CI: 0.50 – 1.05 (NS) P=0.0867 Mean change in prebronchodilator FEV_1 relative to placebo: R: 65ml P: -16 ml 95% CI: 51 – 110 P=<0.0001	ARR: 4.3% NNT: NS ARR: NA NNT: NA	Withdrawals due to Adverse events: R: 33 (8.9%) P: 20 (5.4%) P=0.0864	ARI: 3.5% NNH: 29	Total attrition rates: R: 62 (16.7%) P: 39 (10.5%) Overall: 13.6% Rates of attrition were acceptable. No difference in loss to follow-up. Differential rates due to adverse events. COPD exacerbation withdrawals also varied (R: 4, P 8). Adherence to treatment was similar in all groups with a mean compliance between 94% and 97%. ICS use prohibited. Moderate exacerbation defined as a patient receiving any dose of oral or parenteral steroids to control symptoms. Severe exacerbation defined as any stay in hospital for symptoms or death.

[a]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group.
[b]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI=absolute risk increase NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, NS = Not Significant, NA = Not Applicable
Other abbreviations: COPD = chronic obstructive pulmonary disease, R = roflumilast, P=placebo

CLINICAL EFFICACY

FDA approval was based upon six phase III efficacy trials submitted by Forest Pharmaceuticals. All studies showed some degree of improvement in lung function compared with placebo, measured by forced expiratory volume in one second (FEV_1). Measurement of FEV_1 is important in the diagnosis and staging of COPD. Demonstrating change in FEV_1 is also frequently used in clinical trials as a primary outcome as it is an objective and reproducible measurement that correlates to

lung function. Improving lung function in COPD, however, is usually transitory, and promising gains seen at the beginning of treatment frequently disappear with long-term therapy.[10] It is also difficult to translate change in FEV_1 to improvement in other outcomes relevant to COPD management: mortality, hospitalizations, and symptoms (especially exacerbations).[2]

Population inclusion/exclusion criteria, study outcomes, and design evolved with the roflumilast clinical program. Quality of life outcomes (i.e. St George Respiratory Questionnaire score) used in prior safety and efficacy trials were not emphasized. Change in FEV_1 and rate of exacerbation versus placebo were the endpoints examined for the six pivotal trials. Secondary outcomes varied per trial. [5, 6, 7, 8]

All six trials showed a significant improvement compared with placebo in change in FEV_1. [5, 6, 7, 8] Roflumilast is not a bronchodilator or indicated for symptom maintenance; it is approved to decrease risk of exacerbation. The FEV_1 measurement does not provide any clinical efficacy information for roflumilast. Only one pair of studies (M2-124 & M2-125) showed statistical improvement in rate of exacerbations per patient per year with roflumilast versus placebo.[6]

The trials M2-124 and M2-125 were fundamental to FDA approval. For these trials, inclusion criteria were more specific and patients without a history of exacerbation and chronic bronchitis were excluded. Both trials demonstrated a significant decrease in moderate or severe exacerbations per patient per year (M2-124: 1.08 vs. 1.27, P = 0.0278; M2-125: 1.21 vs. 1.49, P = 0.0035). Moderate exacerbation was defined as a patient receiving any dose of oral or parenteral steroids to control symptoms; severe was defined as any stay in hospital for symptoms or death.[6]

None of the four supporting trials were significant compared with placebo in exacerbation reduction. One of these trials (M2-111) was not published and is unavailable for further evaluation.[5] Two of the trials, M2-127 and M2-128, were designed to examine what extent the concurrent use of a long-acting bronchodilator added to roflumilast. In M2-127, patients received either roflumilast plus salmeterol, or placebo plus salmeterol. In M2-128, patients received roflumilast plus tiotropium, or placebo plus tiotropium. These studies used a different definition of exacerbation and inclusion criteria as the prior studies.[5] In both trials, mild, moderate and severe exacerbations rates were included together and roflumilast was not significantly different than the placebo arms.[8] However, in the FDA statistical study when mild exacerbations were omitted, the rate for the roflumilast group in trial 127 was significantly improved (37% reduction, RR 0.63, P=0.032), although this was not true for M2-128. In the pooled analysis, there was no difference in exacerbation rates.[5]

In general, sensitivity analysis showed the finding for primary endpoints to be robust with regard to missing data and dropouts. In the five published trials, the internal validity was good. Blinding and allocation concealment were not consistently explicit, but inclusion/exclusion criteria and randomization were uniformly transparent. Baseline populations were evenly matched. All trials had a high attrition rate, and it is not clear if any sensitivity analysis were done to account for this. However, rates were similar between groups, and the COPD population recruited was those with the most severe disease. [5, 6, 7, 8]

The main limitation of these studies was in testing efficacy against a placebo control. Additionally, patients were allowed use of a concurrent long-acting COPD medication in all six trials, making it difficult to establish the efficacy of roflumilast as a monotherapy agent or to compare its effectiveness against other standard therapy. Another limitation is the use of FEV_1 as a primary outcome. Examination of more relevant outcomes (mortality, hospitalizations) would require studies of longer duration.

There have been no head-to-head trials of roflumilast and comparator therapy. Until roflumilast is actively compared with other COPD medications used to decrease exacerbations (ICS), no judgment can be made on its place in therapy.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Roflumilast is not a bronchodilator and should not be used to treat acute bronchospasm. Roflumilast is contraindicated in patients with moderate to severe liver impairment (Child-Pugh score B or C). Recommend precaution in patients with mild liver impairment, a history of depression or a history of suicide ideation.[1] Mortality rates were low, and rates were similar between placebo and roflumilast groups.[6, 7, 8]

Weight Loss

Weight loss was a common side effect reported throughout the roflumilast clinical program. This side effect was seen in studies for indications other than COPD which may suggest this effect is not disease specific.[1] In the M2-124 and M2-125 trials, 62.4% subjects in the roflumilast group versus 37.7% placebo patients lost some weight from their baseline.[5] In these studies' pooled data, 20% and 7% of roflumilast subjects experienced moderate (5-10%of total body weight) and severe (>10% body weight) respectively, compared with 7% and 2% of placebo subjects.[1] Patients with more severe disease lost more weight than those with less severe COPD.[5]

Psychiatric Adverse Events

Psychiatric adverse events were more common in the roflumilast treatment groups than in the placebo groups during the clinical program. The most common events were insomnia (3.0% roflumilast vs. 1.1% placebo), anxiety (1.4% vs. 0.8%), and depression (1.4% vs. 0.8%).[5] In subjects enrolled in the clinical program and receiving treatment, there were three suicide adverse events. One patient committed suicide and two attempted suicide in the roflumilast groups. There was one report of suicide ideation but no attempts in the placebo population.[1] Two other suicides were reported in patients who had discontinued roflumilast at least 21 days prior. None of the three completed suicides had a history of depression; the two attempted suicides, however, did.[5]

For FDA approval, Forest Laboratories performed analyses to calculate the possible suicide-related adverse events (PSRAE) risk. In this analysis, the two suicides which occurred after discontinuation of roflumilast were excluded due to lack of evidence of causation. Forest pooled all the patients included in any controlled parallel group study including indications beyond COPD. From 36 studies, the pool comprised of 21,263 patients; 11,848 received roflumilast. No new cases of suicide-related adverse effects were found beyond the three cases in the roflumilast group and one in the placebo groups reported above. The risk rate per 1000 patient years for a PSRAE when taking roflumilast was 0.793 versus 0.284 for placebo.[5]

Cancer risk

Animal studies with hamsters and mice saw a statistically significant increase roflumilast treated animals developing nasal epithelium carcinomas. The carcinogenicity appeared dose-related and was attributed primarily to the active metabolite roflumilast N-oxide.[1] In clinical trials, the rate of development of tumors of any kind was comparable between roflumilast and placebo treated patients (1.6% vs.1.5%). However, rates of new diagnoses of several specific cancers were higher in roflumilast groups compared with those on placebo: lung cancer 0.5% vs. 0.3%, prostate cancer 0.2% vs. 0.09%, and colorectal cancer 0.15% vs. 0.04%. Some of these cancers may have been present but undiagnosed prior to initiation of treatment. A conclusive association between human use of roflumilast and cancer cannot be proven.[5]

Adverse Effects

The most common side effects experienced by patients receiving roflumilast were diarrhea, nausea and weight loss.

Table 1 summarizes the adverse reactions from eight COPD controlled trials. Events recorded were reported by ≥ 2% of patients in the roflumilast population and were greater than the event recorded in the placebo population.[1]

Table 1: Adverse reactions reported by ≥ 2% of patients treated with roflumilast 500 mcg daily and greater than placebo treatment event rate[1]

Adverse Reactions	Roflumilast N=4438 (%)	Placebo N=4192 (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Tolerability (Drop-out rates, management strategies):[6, 7, 8]

Attrition rates were similar in the placebo and intervention populations in all published studies.

Pregnancy/Lactation rating:[1, 9]

Roflumilast is rated Pregnancy Category C. Roflumilast was not found to be teratogenic during animal studies. Dosing hasn't been studied in pregnant women and it should only be given if the potential benefit outweighs the risk to the mother and fetus. Roflumilast was shown to be secreted into milk when studied in rats. Its use should be avoided by nursing mothers.

Unanswered safety questions:

The safety of taking roflumilast long term is unknown. There is some concern with use in populations prone to depression and in populations under-weight; both conditions are seen in patients with COPD. In addition, the possible increase in cancer risk warrants more investigation. Prospective surveillance for adverse events related to roflumilast is ongoing and may help better understand the risk-benefit profile especially for patients with history of psychiatric disorder.[1]

Dose Index (efficacy/toxic):[1, 9]

Patients should take the recommended dose of one 500 mcg tablet per day without regard to food.

No reports of overdose have been reported with roflumilast. During dose-ranging trials, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

Monitoring:[1]

Patients with history of depression or suicidal thoughts should be monitored closely when receiving roflumilast.

Patient weight should be monitored regularly while on roflumilast.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources, the following drug names may cause LASA confusion:

Table 2

NME Drug Name	Lexi-Comp	USP Online	MicroMedex	ISMP	Clinical Judgment
LA/SA for roflumilast (generic)	None	None	None	None	None
LA/SA for Daliresp (brand)	None	None	None	None	None

DOSE & AVAILABILITY[1, 9]

Table 3

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Roflumilast 500 mcg	Tablet	Oral	Once daily	No dosage adjustment necessary	Use with caution in mild hepatic impairment Avoid use in moderate or severe hepatic impairment	N/A	No dosage adjustment necessary	-Very narrow indication; not a maintenance medication to improve symptoms or lung function -Use with caution in patients with low baseline weight -Use with caution in patients with history of depression - May be given with or without food

ALLERGIES/INTERACTIONS[1, 9]

Drug-Drug:
Roflumilast is a substrate for CYP 1A2 and 3A4. CYP 450 inducers such as rifampin, phenobarbital, phenytoin, and carbamazepine resulted in reduction in exposure and decrease in therapeutic effectiveness of roflumilast (79% reduction in AUC for roflumilast). Increased plasma concentrations of roflumilast can occur with concomitant administration of CYP inhibitors such as fluvoxamine, enoxacin, cimetidine, erythromycin ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan. The co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects.

Food-Drug:
No food-drug interactions have been reported. Bioavailability is not affected by food, but delays T_{max} by 1 hour and reduces C_{max} by 40 %.

Allergy/Cross Reactive Substances:
Not established

CONCLUSIONS AND RECOMMENDATIONS

There is high level evidence roflumilast is superior to placebo in improving FEV_1 in patients with moderate to severe COPD, although the clinical significance of this is uncertain. There is low to moderate level evidence that roflumilast modestly reduces the proportion of patients experiencing a moderate to severe exacerbations. There is insufficient evidence to determine comparative efficacy or safety with other medications indicated for the reduction of COPD exacerbations. Evidence for the approved indication is based on two placebo-controlled studies with very specific inclusion criteria (severe COPD, history of exacerbations, current bronchitis symptoms), limiting the applicability of the data for the population at large.[5, 6, 7, 8]

Serious safety concerns remain concerning roflumilast that are not seen with other COPD medications. Some weight loss from baseline was seen in the majority of patients in the M2-124 and M2-125 trials. Patients with more severe disease tended to have greater loss than those less ill. This could be a potentially serious adverse event in patients who are underweight or near underweight; weight should be monitored throughout treatment with roflumilast.

A more serious side effect which was uncovered during clinical trials was development of suicidal ideation. In clinical trials, one patient taking roflumilast committed suicide while two others who discontinued roflumilast three weeks prior also committed suicide. Another two patients in a roflumilast group attempted suicide but did not succeed. In all trials, one placebo patient exhibited signs of suicidal ideation. Rates of psychiatric adverse events (insomnia, anxiety or depression) were higher in roflumilast than in the placebo groups. Although total incidence of suicide ideation and psychiatric events were very low overall, further safety evaluation is needed.

Roflumilast is the first in its class and in the future may be a valuable addition to COPD treatment, but it has not been shown to be superior to other available treatments for COPD. Additional evidence and clinical experience will be helpful in the future to determine the appropriate place in therapy for roflumilast.
It is recommended roflumilast be a non-preferred agent in the COPD PDL class and use clinical prior authorization criteria to limit use to severe or very severe COPD patients.

APPENDIX:
Suggested PA Criteria

Roflumilast

Goal(s):

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

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient failed an inhaled corticosteroid (ICS) or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

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Oregon State University College of Pharmacy
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

Month/Year of Review: February 2012
End date of literature search: November 2011
Generic Name: Indacaterol
Manufacturer: Novartis
Brand Name: Arcapta™
Dossier received: No
Medication Class: Long acting beta-2 agonist (LABA)
Comparator Therapies: tiotropium, formoterol, salmeterol
Preferred: salmeterol, formoterol
Non-Preferred: Inhaled LABA/corticosteroid combination products (see appendix for complete list of preferred products and PA criteria)

Executive Summary:

FDA Approved Indications: Indacaterol maleate is indicated for the long term maintenance bronchodilator treatment of airflow obstructions in adults with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.[1] It is not indicated for the treatment of asthma.

Background: Current standard of care for COPD patients is usually stepwise and generally guided by disease severity. Several guidelines advocate the use of long-acting bronchodilators beta-2 alpha adrenergic antagonists (LABA) or muscarinic antagonists (LAMA) for initial maintenance of symptom control. With more severe symptoms (i.e. exacerbations), an inhaled corticosteroid (ICS) may be added.[2,3,4] Unfortunately, COPD is a progressive disease and often more medications are added with different mechanisms of action in order to control symptoms and improve patient quality of life. Eventually, most patients are on a combination of LABA, LAMA, and ICS as dual or triple therapy. Indacaterol is the first approved LABA that can be administered once daily.

Issues:
Key questions:

1. Is indacaterol more effective than currently available preferred agents in the treatment of COPD to decrease exacerbations and mortality?
2. Is indacaterol safer or better tolerated than current agents such as salmeterol, formoterol, or tiotropium?
3. Are there specific populations where indacaterol is better tolerated or more effective?

Efficacy: FDA approval of indacaterol was based on six phase III, randomized, double-blind trials. Inclusion criteria were similar through each trial; patients were over 40 years old with moderate to severe COPD and at least a 10 pack-year smoking history. Short-acting beta-agonist (SABA) rescue meds and ICS monotherapy were permitted throughout all trials.[5, 6, 7, 8, 9]

The primary efficacy outcome reported in all six studies was the difference in least square mean forced expiratory volume in one second (FEV_1) trough at 24 hours after 12 weeks of treatment. FEV_1 is an important measurement in diagnosing and staging COPD. It is also commonly used in COPD clinical trials because

it is an objective, reproducible measurement of lung function. The secondary outcome of interest was the change from baseline in the St George Respiratory Questionnaire (SGRQ) score. This instrument is universally administered COPD studies to measure improvement in patient quality of life.[5, 6, 7, 8, 9]

The FDA based approval on those two outcomes only.[9] Outcomes of interest in clinical practice for management of COPD patients include mortality, hospitalizations, pneumonia, symptoms (especially exacerbations) and medication tolerability. Mortality and pneumonia were not primary outcomes included in the indacaterol trials. Data was reported but the study power was not sufficient to detect differences. Because the FDA and Novartis Pharmaceuticals could not reach an agreement on the definition of "exacerbation", this important outcome was not involved in the FDA approval process and was not reported in two of the four published trials. [5, 7, 9] Data was available from FDA documents and no differences were detected.[10]

There is low level evidence that indacaterol is superior to formoterol and there is insufficient evidence that it is superior to salmeterol or tiotropium with regard to trough FEV_1. There also insufficient evidence for superiority for quality of life improvement. All six studies showed indacaterol to be significantly better than placebo at improving post-dose trough FEV_1, as were the three comparator medications. [5, 6, 7, 8, 9] The outcome of FEV_1 can be difficult to translate to clinical improvements in patients. Although FEV_1 is nominally a measurement of lung function, because COPD is a progressively worsening disease improvement in lung function tends to be transitory and not always indicative of symptom improvement.[2]

Furthermore, only two unpublished trials of brief duration were conducted with the approved 75 mcg dose. The majority of trials used indacaterol in doses of two to eight times the final FDA approved dose. The two unpublished studies with the 75 mcg indacaterol dose were placebo-controlled only. The difference in mean FEV_1 compared to placebo in these two studies is significantly lower than that of indacaterol in the majority of the published trials. Although one 75 mcg study showed a difference exceeding the minimum clinical difference, the other only equaled it. [5, 6, 7, 8, 9]

The four of the indacaterol trials have been published and are fair quality studies. Randomization, blinding and allocation concealment were not uniformly apparent through all trials, although baseline traits and attrition rates were similar between groups. [5, 6, 7, 8] One study excluded a significant number of randomized patients from the analysis for "poor clinical practice".

There is insufficient evidence to make a conclusion as to whether indacaterol can improve COPD patients' quality of life. For the secondary outcome, three of the six trials had an indacaterol treatment arm that met the minimum clinical difference from baseline in St George Respiratory Questionnaire score.[6, 7, 8] There was, however, no apparent correlation between dose and improvement. Two arms of 150 mcg and one of 600 mcg indacaterol had a change in SGRQ score greater than or equal to $\pm$ 4, while arms of 75 mcg, 150 mcg and 300 mcg did not. Of the three comparators studied, only salmeterol met or exceeded the prespecified difference.[8]

Safety: In general, rates of adverse events were low throughout all six trials. Cough, nasopharyngitis and respiratory infections were the most commonly reported side effects with rates greater in the treatment arms than in the placebo groups. Attrition rate was moderate throughout all six trials. [5, 6, 7, 8, 9] Total attrition ranged from a low of 9% to a high 26%; total withdrawals were highest in the placebo arm in all studies. There were few deaths during the studies. Pooling participants from safety and efficacy trials, 7 out 4764 patients died who received any dose of indacaterol while 23 out 4677 patients died in the placebo groups.[1]

Conclusions: There is insufficient evidence demonstrating that indacaterol 75mcg is as, or more, effective than current treatment options in long term clinical outcomes of interest, including mortality, hospitalizations, pneumonia, symptoms (especially exacerbations), and medication tolerability. Although there is moderate quality evidence that indacaterol is superior to placebo in improving trough FEV_1, there is insufficient evidence to determine comparative efficacy or safety with other LABAs indicated for the management of COPD. Evidence for the approved dose is based on two unpublished 12-week, placebo-controlled studies in which the indacaterol arm did not show improvements in SGRQ and met or barely exceeded the minimum clinical difference for FEV_1.

Future comparative evidence and clinical experience will be helpful to determine the appropriate place in therapy of the 75mcg dose of indacaterol.

Recommendations:

- Due to limited comparative effectiveness evidence compared to alternative available medications, recommend maintaining indacaterol as a non-preferred LABA and evaluating cost comparisons of agents.
- Recommend considering the following PA criteria for indacaterol: documented previous trials of formoterol and salmeterol.

BACKGROUND/CURRENT LANDSCAPE

Long-acting bronchodilators are used to improve breathing in adults with airflow obstruction due to COPD including chronic bronchitis and emphysema. Two types of bronchodilators, long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA), are indicated as maintenance therapy for COPD patients stage 2 or higher. LABAs are considered a mainstay of COPD therapy, and are often the starting maintenance medication for a patient. Organizations such as GOLD, NICE and CHEST have published guidelines on COPD management stating LABAs are a central therapy for the alleviation of symptoms and are recommended in the treatment of COPD.[2, 3, 4]

Currently there are two twice daily LABA medications approved for use in the U.S.: formoterol (Foradil™) and salmeterol (Serevent™). COPD guidelines consider both LABA agents therapeutically equivalent; both products have shown to increase lung function (FEV_1), and improve symptoms (SGRQ) compared with placebo.[11, 12] Salmeterol has also been shown to decrease exacerbations and increase mortality compared with placebo.[13] Tiotropium (Spiriva™), the sole LAMA approved for use in the U.S., is dosed once daily and is often used interchangeably with salmeterol and formoterol as first line for symptom control.[2, 3, 4] A recent clinical trial comparing salmeterol and tiotropium concludes, however, that although both improve lung function (FEV_1), tiotropium may be more effective at decreasing exacerbations; suggesting tiotropium may be a better initial choice for patients with more severe disease.[14]

A third class of medication, inhaled corticosteroids (ICS), is indicated for more severe symptomatic COPD (stage 3 or higher; history of exacerbations). All three classes are used frequently in combinations of dual and triple therapy. A recent Cochrane systematic review compared the efficacy of inhaled corticosteroids versus long-acting beta agonists on clinical outcomes including exacerbations, hospitalizations due to exacerbations, pneumonia, and death. They found that the two therapies provide similar benefits across the majority of outcomes including frequency of exacerbations and mortality. They also concluded that LABAs may have a small benefit in terms of improvements in lung function.[15]

Salmeterol and formoterol are both available in combination with an ICS. Indacaterol is approved by the FDA as a once daily COPD maintenance therapy.[1] Unlike salmeterol and formoterol, it is currently not approved in a combination formulation with an ICS.

CLINICAL PHARMACOLOGY[1]

Indacaterol is an inhaled long-acting beta-2-adrenergic agonist. Effects of beta-2 receptor agonists are thought to be attributed to the increased conversion of adenosine triphosphate (ATP) to cyclic-3', 5' adenosine monophosphate (cyclic AMP). Cyclic AMP causes smooth muscle relaxation; in the lungs, the local effect is bronchodilation.

PHARMACOKINETICS[1, 16]

Parameter	Result
Bioavailability	~44% (43-45%)
Protein Binding	95.1-96.2%
Elimination	2-6% urine, 77% feces
Half-Life	40-56 hours
Metabolism	Hydroxylation and phenolic O-glucuronidation via CYP3A4 and UGT1A1

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of Exacerbations
3) St. George's Respiratory Questionnaire (SGRQ) - Clinically relevant improvement defined as > or = 4 points on total score
4) Withdrawals due to adverse events
5) Pneumonia or Lower Respiratory Tract Infection

Primary Study Endpoint:

1) Difference in FEV_1 trough after 24 hours at week 12

Reference/ Study Design[a]	Drug Regimens	N	Patient Population	Duration	Efficacy Results[b]	ARR / NNT	Safety Results	ARI / NNH	Quality Rating[c]; Comments
Donohue et al.[5] Phase II/III RCT, DB, PC, AC, MC, OL-(Tio arm)	Indacaterol 150 mcg QD Indacaterol 300 mcg QD Tiotropium 18 mcg QD Placebo	416 416 415 418	62.8% male Mean age 63.3 yo Stage2-3 COPD Inclusion: >40 yo History of ≥ 20 pack-years Exclusion: Asthma patients	Phase III for 26 weeks (primar endpoint at 12 wks)	Mortality In 150 mcg: 2 (0.5%) In 300 mcg: 0 (0) Tio: 1 (0.2%) Placebo: 0 (0%) Difference in least square mean FEV_1 trough @24 hr at wk 12 vs. placebo: *0.12 L prespecified as clinically relevant In 150 mcg: **0.18 L** (95% CI 0.14-0.22); p<0.001 In 300 mcg: **0.18 L** (95% CI 0.14-0.22); p<0.001 Tio 18 mcg: **0.14 L** (95% CI 0.10-0.18); p<0.001 vs. tiotropium: *0.055 L prespecified as clinically relevant difference In 150mcg and 300mcg: 0.04 L P≤0.01 for superiority Rate of exacerbation per year Rate Ratio vs placebo Placebo 1.33 In 150 mcg: 0.95 Rate Ratio 0.71 p=0.185 In 300 mcg:0.86 Rate Ratio 0.65 p=0.108 Tio 18 mcg: 0.93 Rate Ratio 0.69 p=0.157 SGRQ - Least Squares Mean reported : Odds ratio of likelihood of achieving a difference vs. placebo In 150 mcg: OR 1.4 (95% CI1.0-1.9); p=0.033 In 300 mcg: OR 1.32 NS Tio 18 mcg: OR 1.07 NS	ARR: -0.5% ARR: 0ARR:-0.2% NS NA NA ARR: 0.38 NS ARR: 0.47 NS ARR:0.4 NS NA	Withdrawals due to adverse events RR vs. placebo P: 45 (10.8%) In 150: 30 (7.2%) RR: 0.67 95% CI 0.43 – 1.04 In 300: 24 (5.8%) RR: 0.54 95% CI 0.33 – 0.86 Tio: 17 (4.1%) RR: 0.38 95% CI 0.22 – 0.65 Pneumonia: RR vs placebo P : 4 (1%) In 150: 2(0.5%) RR: 0.50 95% CI 0.09 – 2.7 In 350: 3 (0.7%) RR: 0.75 95% CI 0.17 – 3.35 Tio: 4 (1%) RR: 1.01 95% CI 0.25 – 4.0	ARI: -3.6% NNH: NS ARI:-5.0% NNH: 20 ARI: -6.7% NNH:15 ARI: -0.5% NNH:NS ARI:-0.3% NNH:NS ARI: 0% NNH:NS	Study quality: Fair Primary and secondary outcomes do not reflect clinically relevant endpoints for COPD management. Attrition rates fairly high although similar across treatment arms. There was a higher rate of withdrawal in the placebo arm for adverse events. In 150 mcg: 23% In 300 mcg: 18% Tio 18 mcg: 21% P: 31% Doses for indacaterol used are 2 to 4 times higher than the FDA approved dose of 75 mcg. Patients allowed to continue ICS monotherapy and use of a short acting bronchodilator Two week safety run-in established trial doses of indacaterol. Trial to establish efficacy continued until 26 weeks. Population sizes for the initial seven arms not provided in published paper. All arms discontinued except for indacaterol 150 & 300 mcg, tiotropium 18 mcg and placebo. Unclear if patients from the other arms were randomized into continuing arms, more patients were recruited for the efficacy trial. Tiotropium arm was open-label Missing values at Week 12 were replaced with previous value (Week 2 or greater). Exacerbations per year data was imputed for patients discontinuing prematurely. All treatment arms met clinical threshold of Δ FEV_1 > 0.12 L from placebo at 12 & 26 weeks Neither dose of indacaterol reached the study-imposed clinical threshold difference (.55 L) for superiority No active treatment arm exceeded the clinical threshold for SGRQ (>4-point difference from baseline)

Feldman et al.[6] Phase III, RCT, MC, DB, PC	Indacaterol 150 mcg QD Placebo	211 205	52.4% male W: 92.5% Mean age 63.3 yo Stage2-3 COPD >40yo Hx of ≥ 20 pack-years Excluded: Hx of asthma, RTI or COPD hospitalization in last six weeks any pulmonary disease or cardiovascular disorder	12 weeks	Mortality: In 150mcg: 0 (0.0%) Placebo: 1 (0.5%) Difference in least square mean FEV_1 trough @24 hr at wk 12 vs placebo: *0.12 L prespecified as clinically relevant In 150 mcg: **0.13 L** P<0.001 Rate of exacerbation per year[10] In 150 mcg: 0.37 Placebo:0.58 SGRQ - Least Squares Mean) :[10] Odds ratio of likelihood of achieving a difference vs. placebo In 150 mcg: OR 2.1 (95% CI 1.4-3.3); p<0.001	ARR: 0.5 NNT:NS NA ARR: 0.21 NNT: NS NA	Withdrawals due to adverse events: In 150: 6 (2.8%) P: 3 (1.5%) RR: 1.94 95% CI 0.49 – 7.67	ARI: 1.3% NS	Study quality: Fair Total attrition rate 12.5% In 150 mcg: 25 (11.8%) P: 27 (13.2%) Primary and secondary outcomes do not reflect clinically relevant endpoints for COPD management. Doses for indacaterol are 2 times higher than the FDA approved dose of 75 mcg. Both a pre-screening period and 2-week screening/run-in period Results were imputed with last observation carried forward. Patients allowed to continue ICS monotherapy and use of a short acting bronchodilator Indacaterol met clinical threshold of Δ FEV_1 > 0.12 L from placebo at 12 weeks Indacaterol met clinical threshold of >4-point difference for SGRQ SGRQ, exacerbation rate from FDA, not reported in published trial Adverse events categorized by organ system (i.e. musculoskeletal, respiratory); individual side effects pneumonia, etc. not reported

Dahl et al.[7]	Indacaterol	437	79.7% male	52 weeks	Mortality:		Withdrawals due to		Study quality: Fair
Phase III,	300 mcg QD			(primary	RR vs placebo		adverse events:		
RCT, DB,			Mean age 63.5	endpoint at	P: 5 (1.2%)		RR vs placebo		Total attrition rate 26%
PC, AC, MC	Indacaterol	425	yo	12 wks)			P: 35 (8.1%)		In 300 mcg: 23% In 600 mcg: 24%
	600 mcg QD				300 mcg: 1 (0.2%)	ARR:			For 12 mcg: 26% P: 32%
			Stage2-3 COPD		RR: 0.20	1.0%	In 300 mcg: 35	ARI: -	
	Formoterol	434	>40 yo		95% CI 0.2 – 1.69	NS	(8.0%)	0.1%	Primary and secondary outcomes do not reflect clinically
	12 mcg BID		Hx of ≥ 20 pack-years				RR: 0.99	NS	relevant endpoints for COPD management.
					600mcg: 1 (0.2%)		95% CI 0.63 – 1.56		
	Placebo	432			RR:0.20				Doses for indacaterol are 4 to 8 times higher than the FDA
			Excluded:		95% CI 0.24 – 1.73	ARR:	In 600 mcg: 24	ARI: -	approved dose of 75 mcg.
			Hx of asthma,			1.0%	(5.6%)	2.5%	
			RTI or		For: 5 (1.2%)	NS	RR: 0.69	NS	Patients allowed to continue ICS monotherapy and use of a
			hospitalization		RR: 0.99		95% CI 0.42 – 1.14		short acting bronchodilator
			in last six weeks		95% CI 0.29 – 3.41	ARR:0.0			
			oral steroid use			%	For: 40 (9.2%)	ARI:	Last observation carried forward used for missing data in
			or Δ in ICS w/in		Difference in least square mean FEV_1	NS	RR: 1.14	1.2%	analysis of FEV_1 @ 12 & 52 weeks, SGRQ & TDI scores,
			last month		trough @24 hr at wk 12 vs. placebo:		95% CI 0.74 – 1.75	NS	exacerbation rate and in # of days w/o rescue inhaler
					*0.12 L prespecified as clinically		Lower Respiratory		
					relevant In 300 mcg: In 300 mcg: **0.17 L**		Tract Infection:		SGRQ data from FDA statistical summary
					(95% CI 0.13-0.20) p<0.001		RR vs placebo		
						NA	P: 22 (5.1%)		129 patients d/c'd from study due to "poor clinical
					In 600 mcg: **0.17 L**				practice"; This affected treatment arms equally but was
					(95% CI 0.13-0.20) p<0.001	NA	In 300 mcg: 27		~7% of randomized sample. The ITT modified to exclude
							(6.2%)		these patients for efficacy but not safety analysis.
					For 12 mcg: 0.07 L		RR: 1.21	ARI:	
					(95% CI 0.04-0.10) p<0.001	NA	95% CI 0.70 – 2.10	1.1%	LS mean trough FEV_1difference from placebo @52 weeks
								NS	statistically significant for each intervention
					vs. formoterol:		In 600 mcg: 23		However, all treatment arms saw a decrease in FEV_1 at 52
					*0.055 L prespecified as clinically		(5.4%)		compared w/ values at 12 wks
					relevant difference	NA	RR: 1.06	ARI:	
					In 300mcg and 600mcg: 0.10 L		95% CI 0.60 – 1.88	0.3%	All treatment arms met clinical threshold of Δ FEV_1 > 0.12 L
					P≤0.01 for superiority			NS	from placebo at 12 weeks
							For: 22 (5.2%)		
					Rate of exacerbation per year		RR: 1.02		No active treatment arm exceeded the clinical threshold fo
					Rate Ratio vs placebo		95% CI 0.57 – 1.81	ARI:0.1%	SGRQ (>4-point difference from baseline)
					Placebo 0.74			NS	
									Non-inferiority to formoterol not listed as outcome
					In 300 mcg: 0.60				
					Rate Ratio 0.82 NS				Only indacaterol 600 mcg met clinical threshold (>± 4) for
						ARR:0.1			SGRQ
					In 600 mcg: 0.57				
					Rate Ratio 0.74 (95% CI 0.56-0.97)				Rates of exacerbation similar across all arms
					p<0.05	ARR:0.1			
					For 12 mcg: 0.56				
					Rate Ratio 0.75 (95% CI 0.58-0.99)	ARR:			
					p<0.05	0.18			
					SGRQ : Least Squares Mean) :[10]				
					Odds ratio of likelihood of achieving				
					a difference vs. placebo				
					In 300mcg: OR 1.6				
					(95% CI 1.2-2.2); p=0.003				
					In 600mcg: OR 1.8				
					(95% CI 1.3-2.4); p<0.001				
					For 12 mcg: OR 1.6 NS				
					(95% CI 1.2-2.2); p=0.004				

Kornmann et al.[8] Phase III, RCT, DB, PC, AC, MC B2336[d]	Indacaterol 150 mcg qd Salmeterol 50mcg bid Placebo	330 333 335	74.7% male Mean age 63.3 yo Stage2-3 COPD >40 yo Hx of ≥ 20 pack-years Hx of asthma excluded	26 weeks (primary endpoint at 12 wks)	Mortality: RR vs. placebo P: 3 (0.9%) In 150 mcg: 1 (0.3%) RR: 0.34 95% CI 0.4 – 3.21 Sal: 0 (0%) RR: 0.00 Difference in least square mean FEV_1 trough @24 hr at wk 12 vs. placebo: *0.12 L prespecified as clinically relevant In 150 mcg: **0.17 L** P<0.001 Sal 50 mcg**: 0.11 L** P<0.001 vs. salmeterol: *0.055 L prespecified as clinically relevant difference Difference from salmeterol:**0.06 L** P<0.001 Rate of exacerbation per year [10] In 150 mcg: 0.47 Sal 50 mcg: 0.40 Placebo:0.62 SGRQ : Least Squares Mean:[10] Odds ratio of likelihood of achieving a difference vs. placebo In 150 mcg: OR 2.4 (95% CI 1.7-3.4); p<0.001 Sal 50 mcg: OR 1.5 (95% CI 1.0-2.2); p=0.027	ARR: 0.6% NS ARR: 0.9% NS NA NS NA	Withdrawals due to adverse events: RR vs placebo P: 13 (3.9%) In: 18 (5.4%) RR: 1.39 95% CI 0.69 – 2.80 Sal:16 (4.8%) RR: 1.23 95% CI 0.60 – 2.53 Lower Respiratory Tract Infection: RR vs placebo P: 8 (2.4%) In 150mcg: 9 (2.7%) RR: 1.13 95% CI 0.44 – 2.90 Sal: 13 (3.9%) RR: 1.63 95% CI 0.68 – 3.88	ARI: 1.5% NS ARI: 0.9% NS ARI: 0.3% NS ARI : 1.5% NS	Study quality: Fair Primary and secondary outcomes do not reflect clinically relevant endpoints for COPD management. Total attrition rate 16% In 150 mcg: 13.2% Sal 50 mcg: 15% P:20.9% (most due to lack of effect) 2-week run in and screening period Dose for indacaterol are 2 times higher than the FDA approved dose of 75 mcg. Patients allowed to continue ICS monotherapy and use of a short acting bronchodilator Only indacaterol met clinical threshold of Δ FEV_1 > 0.12 L from placebo at 12 weeks Non-inferiority to salmeterol not listed as an outcome Both treatment arms exceeded the clinical threshold for SGRQ (>4-point difference from baseline) Number of exacerbations not reported Exacerbation rate, SGRQ data from FDA statistical summary Per FDA "days of poor control' was to be the key secondary outcome, but was switched to SGRQ prior to unblinding[9] Last observation carried forward used in data analysis[9]

B2354[9 d] Unpublished Phase III, RCT, MC, DB, PC	Indacaterol 75 mcg QD Placebo	163 160	40-90 years old Stage2-3 COPD Hx of ≥ 10 pack-years	12 weeks	Difference in least square mean FEV_1 trough @24 hr at wk 12 vs. placebo: *0.12 L prespecified as clinically relevant In 75 mcg: **0.12 L** (95% CI 0.08-0.15) P<0.001 Rate of exacerbation per year [10] In 75 mcg: 0.54 Placebo: 0.37 Quality of Life (SGRQ : Least Squares Mean) :[10] Odds ratio of likelihood of achieving a difference vs. placebo In 75mcg: OR 1.8 (95% CI 1.1-3.0) p=0.025	N/A NS N/A			Unable to assess quality Attrition 15.2%, Primary and secondary outcomes do not reflect clinically relevant endpoints for COPD management. Trial is unpublished but considered pivotal to FDA approval as it is one of two studies with final market strength and dosage form. Patients allowed to continue ICS monotherapy and use of a short acting bronchodilator Indacaterol met clinical threshold of Δ FEV_1 > 0.12 L from placebo at 12 weeks Indacaterol arm did not meet the clinical threshold for SGRQ (>4-point difference from baseline) Exacerbation rate, SGRQ data from FDA statistical summary Last observation carried forward used in data analysis
B2355[9 d] Unpublished Phase III, RCT, MC, DB, PC	Indacaterol 75 mcg QD Placebo	159 159	40-86 years old Stage2-3 COPD Hx of ≥ 10 pack-years	12 weeks	Difference in least square mean FEV_1 trough @24 hr at wk 12 vs. placebo: *0.12 L prespecified as clinically relevant In 75 mcg: **0.14 L** (95% CI 0.10-0.18) P<0.001 Rate of exacerbation per year [10] In 75 mcg: 0.40 Placebo: 0.40 Quality of Life (SGRQ : Least Squares Mean) :[10] Odds ratio of likelihood of achieving a difference vs. placebo In 75mcg: OR 1.7 (95% CI 1.1-2.8) p=0.028	N/A NS N/A			Unable to assess quality Attrition 8.8% Primary and secondary outcomes do not reflect clinically relevant endpoints for COPD management. Trial is unpublished but considered pivotal to FDA approval as it is one of two studies with final market strength and dosage form. Patients allowed to continue ICS monotherapy and use of a short acting bronchodilator Indacaterol met clinical threshold of Δ FEV_1 > 0.12 L from placebo at 12 weeks Indacaterol arm did not meet the clinical threshold for SGRQ (>4-point difference from baseline) Exacerbation rate, SGRQ data from FDA statistical summary Last observation carried forward used in data analysis

[a] **Study design abbreviations:** DB = double-blind, RCT = randomized trial, AC = active comparator, PC = placebo-controlled, MC = multi-center, OL = open label.
[b] **Results abbreviations**: RR =relative risk, OR = Odds Ratio, ARR = absolute risk reduction, ARI = absolute risk increase, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, SGRQ = St George respiratory Questionnaire, LS mean FEV_1 = least square mean forced expiratory volume in one second, NA = not applicable, NS = not significant, In = indacaterol, For= formoterol, P = placebo, Sal = salmeterol, Tio = tiotropium, QD = once daily, BID = twice daily, yo = years old, COPD = Chronic Obstructive Pulmonary Disease, RTI = respiratory tract infection, FDA = Food and Drug Administration, ICS = inhaled corticosteroid, hx = history, Δ = change, wks = weeks, hr = hour
[c] **Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
[d] **FDA trial identifiers**

Clinical Efficacy

Indacaterol was approved on the basis of six pivotal trials establishing efficacy, as well as several safety and dosing studies.[9] In the original NDA submitted, Novartis proposed two dose strengths 150 and 300 mcg based on evidence from three efficacy trials.[5, 6, 7] The FDA rejected the NDA on the basis there was not enough evidence to show an increase in effectiveness with the escalating doses, as well as concern with the safety of higher dose LABAs in general.[9] Novartis then resubmitted their NDA with three new studies for approval of the doses 75 and 150 mcg.[8, 9] On the basis of all six studies, the FDA approved indacaterol for the 75 mcg dose for maintenance of symptomatic relief in COPD patients. The 150 mcg dose was not approved due to a lack of evidence of increased efficacy with dose escalation.[9]

Only two studies conducted used the final approved 75 mcg dose. Both were 12-week placebo-controlled trials. Neither was published. Unfortunately, no study compared the 75 mcg dose to higher doses of indacaterol or any active comparator.[9] Three earlier trials with higher doses of indacaterol had an active comparator: salmeterol, formoterol or tiotropium.[5, 6, 8] All six trials included an outcome for percent or rate of COPD exacerbations, but not all reported the results in their published papers.[6, 8]

FDA approval was based on two measures: the primary outcome (change in FEV_1 at 12 weeks) and change in SGRQ score from baseline.[9] Measurement of FEV_1 is important in the diagnosis and staging of COPD. Demonstrating change in FEV_1 is also frequently used in clinical trials as a primary outcome as it is an objective and reproducible measurement that correlates to lung function. Improving lung function in COPD, however, is usually transitory, and promising gains seen at the beginning of treatment frequently disappear with long-term therapy.[13] It is also difficult to translate change in FEV_1 to improvement in other outcomes relevant to COPD management: mortality, hospitalizations, and symptoms (especially exacerbations).[2] The St George Respiratory Questionnaire (SGRQ) is often used to show symptom improvement and is a subjective, patient-measured outcome. This instrument is very commonly used in COPD clinical trials. The SGRQ is helpful in measuring patient quality of life issues such as breathlessness, exercise capacity, and general well-being.

At week twelve, indacaterol demonstrated some improvement in lung function in all trials; a prespecified difference from placebo of 120 mL was considered the minimum change needed in FEV_1 for clinical relevance. However, there is no evidence that indacaterol is superior to comparative treatments of salmeterol, formoterol, or tiotropium with regard to FEV_1. All six studies showed indacaterol to be significantly better than placebo at improving post-dose trough FEV_1, as were the three comparator medications. The difference in mean FEV_1 compared to placebo in the two 75 mcg studies just met or barely exceeded the minimum clinical difference.[5, 6, 7, 8, 9]

For the quality of life measure, a change in SGRQ score of $\pm$ 4 points from baseline was established as the minimum clinically important difference. Indacaterol met this benchmark in less than 50% of the studied doses and for the approved dose, both 75 mcg trials of indacaterol failed. There was no apparent correlation between dose and score improvement. Salmeterol was the only comparator therapy with a score greater than four.[8] No conclusion can be made from this evidence as to whether indacaterol can improve COPD patients' quality of life.

The FDA and Novartis could not agree on the definition of "exacerbation", and therefore this important measure was not included in the FDA approval process.[10] Of the two trials which published exacerbation data only one out four indacaterol doses studied showed a significant improvement over placebo.[5] Although exacerbation rates were numerically reduced, in most cases the effect was not statistically significant. Both comparators (formoterol and tiotropium) included in the two trials were also non-significant compared with placebo.[5, 7] These studies were not designed to measure exacerbations as a primary outcome.

Trials with longer duration are needed to assess the effect of indacaterol on clinically relevant COPD outcomes such as mortality, hospitalizations, and rate of exacerbations.

DRUG SAFETY[1, 16]

In general, rates of adverse events were low throughout all six trials. Cough, nasopharyngitis and respiratory infections were the most commonly reported side effects with rates greater in the treatment arms than in the placebo groups.[5, 6, 7, 8] There were few deaths during the studies. Hospitalization rates were not reported. Only one trial published data on pneumonia incidence.[5] Pooling participants from safety and efficacy trials, 7 out 4764 patients died who received any dose of indacaterol while 23 out 4677 patients died in the placebo groups.

Serious (REMS, Black Box Warnings, and Contraindications): Black Box Warning – Long-acting beta-2-adrenergic agonists increase the risk of asthma-related death. All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. Indacaterol is not indicated to treat asthma.

Do not initiate in acutely decompensated COPD patients. Not for relief of acute symptoms. Do not exceed recommended dosage; excessive usage or concurrent usage with other LABA agents, may result in clinically significant CV effects, including death. Life threatening paradoxical bronchospasm can occur; discontinue use immediately if this occurs. Use with caution in patients with CV or convulsive disorders, thyrotoxicosis, or sensitivity to sympathomimetic drugs

Tolerability: Total attrition ranged from a low of 9% to a high 26%; total withdrawals were highest in the placebo arm in all six studies.[5, 6, 7, 8, 9]

Pregnancy/Lactation rating: Category C. There were no adequate, well controlled studies in pregnant women. Indacaterol was not found to be teratogenic in rats and rabbits at doses approximately 130 and 260 times, respectively, the 75 mcg dose.
Indacaterol has not been studied in nursing mothers. It is unknown whether it is excreted in human breast milk, however in animal studies, indacaterol has been found in the milk of lactating rats.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from three data sources (Lexi-Comp, USP Online LASA Finder, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	ISMP	Clinical Judgment
LA/SA for indacterol (generic)	None	None	None	Inderal™, Adderall™, Aldactone™
LA/SA for Arcapta™(brand)	None	None	None	None

ADVERSE REACTIONS[1]

Adverse Drug Events	Indacaterol	Placebo
	n=449	n=445
Respiratory, thoracic, and mediastinal disorders		
Cough	6.5%	4.5%
Oropharyngeal pain	2.2%	0.7%
Infections and infestations		
Nasopharyngitis	5.3%	2.7%
Nervous system disorders		
Headache	5.1%	2.5%
Gastrointestinal disorders		
Nausea	2.4%	0.9%
Cardiovascular disorders*		
	2.5%	1.6%

Adverse events pooled from trials conducted with the approved 75 mcg dose of indacaterol.

*Cardiovascular adverse events reported as a comment, not originally included in table. Specific CV events and rates not included.

DOSE & AVAILABILITY[16]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose
75 mg	Capsule*	Inhalation	75 mg daily	No adjustment.	No adjustment needed in mild to moderate hepatic disease. Not studied in those with severe disease.	Not studied.	No adjustment.

*Indacaterol capsules are used with the Neohaler™ inhaler devise; they will not be as effective if swallowed.

ALLERGIES/INTERACTIONS

Drug-Drug: Concurrent use of beta-blockers (atenolol, propranolol, metoprolol, labetolol, etc) and indacaterol may cause a decrease in the effectiveness of both medications. Concurrent use of tri-cyclic anti-depressants (nortriptyline, amytriptyline, desipramine, doxepin, etc) and indacaterol may cause an increased risk of QT prolongation. Concurrent use of monoamine oxidase inhibitors (selegiline, rasagiline, tranylcypromine, etc) and indacaterol may result in an increased risk for tachycardia, agitation or hypomania.[1, 16]

Food-Drug: No food-drug interactions have been reported.[1]

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Oregon State University College of Pharmacy
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

Month/Year of Review: February 2012
PDL Class: Anti-Parkinson's Agents

Date of Last Review: September 2010
Source Document: Provider Synergies (PS)

Current Preferred Agents:

Anticholinergics:
Benztropine
Trihexyphenidyl HCL

Dopaminergic Agents:
Carbidopa/Levodopa

Dopamine Agonists:
Pramipexole DI-HCL

Combination Product:
Carbidopa/Levodopa/Entacapone

MAO- B Inhibitors:
Selegiline

COMT Inhibitors:
Tolcapone (Tamsar®)

Current Non-Preferred Agents:

Dopaminergic Agents:
Carbidopa/Levodopa ER

MAO-B Inhibitors:
Rasagaline (Azilect®)

COMT Inhibitors:
Entacapone (Comtan®)

Dopamine Agonists*:
Ropinirole (Requip®)
Bromocriptine (Parlodel®)

Abbreviations used:
MAO-B: Monoamine oxidase B, COMT: Catechol-O-methyl transferase
**Amantadine included in antiviral class

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one agent from each category with prior authorization (PA) criteria for comparable products

Special Considerations:

- Consider stage of Parkinson's Disease (PD)
- Pramipexole and ropinirole are two drugs specifically approved for restless leg syndrome.

PA Criteria: All non-preferred agents require prior authorization to first try preferred products when feasible for covered diagnosis. Pramipexole and ropinirole require an OHP covered diagnosis for coverage.

Methods

A MEDLINE OVID search was conducted using all treatments for PD and limited to randomized controlled trials and meta-analysis, English language, and conducted in humans since the date of the literature search conducted for the previous PS review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:
A total of 79 citations resulted from initial literature search. After inclusion for further review, 18 were evaluated further and five potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (Appendix 1). These trials are briefly described in table 1.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Poewe[1], 2011	Pramipexole ER vs. pramipexole IR	Early PD; monotherapy	Unified Parkinson's Disease Rating Scale	Adjusted mean 33-week UPDRS II+III change: ER -8.2 (-9.5 to -6.9) IR -8.7 (-10.1 to -7.4) Placebo -1.2 (-3.1 to 0.6) • Showing ER was noninferior to IR • Tolerability and safety did not differ between the formulations.
Schapira[2], 2011	Pramipexole ER vs. pramipexole IR	Advanced PD; on levodopa.	Unified Parkinson's Disease Rating Scale	Adjusted mean 18-week UPDRS II+III change: ER -11 (-9.5 to -6.9) IR -12.8 (-10.1 to -7.4) Placebo -6.1 (-3.1 to 0.6)
Stocci[3], 2011	Ropinirole PR vs. ropinirole IR	Advanced PD; adjunctive therapy	Number of patients maintaining a >20% reduction in "off" time	Proportion of patients maintaining 20% reduction in ''off'' time at week 24: PR 66% IR 51% OR 1.82 (95% CI 1.16-2.86) P=0.009 • More withdrawals due to AE in the PR group than IR (12% vs 9%)
Hauser[4], 2010	Pramipexole ER vs. pramipexole IR	Early PD	Unified Parkinson's Disease Rating Scale	Change from baseline to week 18 in UPDRS: ER -8.1 IR -8.4 Placebo -5.1 • Discontinuations due to AE (10.4% ER, 7.8% IR, 4% placebo)
Stocci[5], 2010 STRIDE-PD	Levodopa/carbidopa (Sinemet) vs. levodopa/carbidopa/entacapone (Stalevo)	PD; requiring levodopa initiation	Time to onset of dyskinesia	Discontinuations due to AE: Levo/carb/entacapone: 38 (10.2%) Levo/carb: 24 (6.5%) • Those on levodopa/carbidopa/entacapone had a shorter time to onset and increased frequency of dyskinesia

The STRIDE-PD study evaluated 747 patients with PD over a period of 134 weeks comparing the risk of developing dyskinesia.[5] In this double-blind trial, patients were randomized to levodopa/carbidopa or levodopa/carbidopa/ entacapone (Stalevo®). The primary endpoint was time to onset of dyskinesia. The study found that patients taking levodopa/carbidopa/entacapone had a shorter time to onset of dyskinesia (hazard ratio, 1.29; p=0.04) and increased frequency at week 134 (42% vs. 32%; p=0.02). While not significantly different, time to wearing off and motor scores did trend in favor of the levodopa/carbidopa/ entacapone group. Initiating therapy with added entacapone failed to delay the time of onset or reduce the frequency of dyskinesia compared to levodopa/carbidopa therapy alone.

New drugs:
None

New FDA Indications:
None

New FDA safety alerts:

In August 2010, the FDA notified healthcare professionals about concerns that the use of levodopa/carbidopa/entacapone may be associated with an increased risk of cardiovascular events, including heart attack, stroke, and cardiovascular death, when compared to the use of carbidopa/levodopa.[6] This safety communication is based on findings from the Stalevo Reduction in Dyskinesia Evaluation – Parkinson's disease (STRIDE-PD) trial,[5] which reported an imbalance in the number of myocardial infarctions in patients treated with levodopa/carbidopa/entacapone compared to those receiving only carbidopa/levodopa. At this time, the FDA is reviewing data from a meta-analysis to evaluate the potential cardiovascular risk. In this meta-analysis, of 15 clinical trials comparing Stalevo to carbidopa/levodopa, a small increased risk of cardiovascular events was found in the Stalevo group compared to the carbidopa/levodopa group (27 events versus 10 events, RR 2.46; 95% CI: 1.19-5.09). However, the FDA noted that several factors make these findings difficult to interpret. The clinical trials were not designed to evaluate cardiovascular safety, the majority of patients had preexisting risk factors for cardiovascular disease, and many of the events occurred in one single trial (STRIDE-PD). The FDA continues to assess the results of the STRIDE-PD trial and recommends regularly evaluating the cardiovascular status of patients taking Stalevo, especially if they have a history of cardiovascular disease.

New Systematic Reviews:

Two meta-analyses were identified and were both reviewed by the Centre for Reviews and Dissemination (CRD) and included in the Cochrane database of abstracts of reviews of effects (Appendix 2).[7,8] Both of these relied greatly on indirect comparisons and were recommended by the CRD reviewer to use caution in interpreting the conclusions. A meta-analysis was reported by the Movement Disorder Society and evaluated the comparative benefits and risks of medications used as adjunctive treatment with levodopa in patients with later PD.[8] This review conducted indirect analysis to conclude that dopamine agonist may be more effective than COMT inhibitors or MAO inhibitors when used as adjunctive treatment with levodopa. However, the unknown quality of the trials, lack of information about the studies and the use of indirect comparisons means the authors' conclusions may not be reliable and should be interpreted with some caution.

Evidence-based Clinical Guidelines:

Recommendations based on systematic reviews of best available evidence were published from the Scottish Intercollegiate Guideline Network (SIGN) on the diagnosis and drug management of Parkinson's disease.[9] These have a grade A recommendation to initiate treatment with an agent from the following classes: Dopamine agonists (a non-ergot agonist is preferred to ergot derived agonists), Levodopa with a dopa-

decarboxylase inhibitor, or a monamine oxidase B inhibitor. There is also a grade B recommendation to not use anticholinergic drugs as first line treatment due to the high risk of adverse effects. For treatment advanced disease with motor complications, they recommend adjunct treatment with COMT inhibitors, MAO-B inhibitors, or dopamine agonists to manage motor complications (Grade A). Their recommendation grading scheme relates directly to the strength of the evidence, not the clinical importance of the recommendation.

Rare cases of fatal hepatotoxicity have been reported with use of tolcapone and have led to recommendations of more stringent liver function monitoring. Guidelines from the National Institute for Health and Clinical Excellence (NICE)[10] recommend only using tolcapone after patients have failed therapy with entacapone due to lack of efficacy or side effects. Recommendations from the American Academy of Neurology[11] conclude that entacapone is established as effective in reducing off time, while tolcapone is probably effective and should be used with caution.

Recommendations:

1) Replace tolcapone with entacapone due to reported liver toxicity with tolcapone.
2) Correct PDL to include amantadine as preferred.
3) No further research or review needed.

Appendix 1: Clinical Trial Abstracts:

1. Poewe W, Rascol O, BaroneP, et al. Extended-release pramipexole in early Parkinson disease: a 33-week randomized controlled trial. *Neurology.* Aug 23;77(8):759-66. Epub 2011 Aug 10.

   Objective: To assess the clinical efficacy of a novel once-daily extended-release (ER) formulation of the dopamine agonist pramipexole as monotherapy in patients with early Parkinson disease (PD) and establish its noninferiority vs. standard immediate-release (IR) pramipexole.
   Methods: This was a multicenter, double-blind, parallel study of patients with early PD not receiving levodopa or dopamine agonists, randomly assigned to pramipexole IR, pramipexole ER, or placebo. Seven-week flexible titration was followed by 26-week maintenance, with levodopa permitted as rescue medication. The primary analysis was to test pramipexole ER noninferiority to pramipexole IR based on a change in the Unified Parkinson's Disease Rating Scale (UPDRS) part II+III score at 33 weeks, with noninferiority predefined as a treatment group difference for which the lower bound of the 95% confidence interval (CI) did not exceed -3 points.
   Results: Among 213 ER and 207 IR recipients, the adjusted mean 33-week UPDRS II+III change (excluding levodopa rescue effects) was -8.2 for ER and -8.7 for IR, a difference of -0.5 with a 95% CI of -2.3 to 1.3. Compared with placebo (n = 103), pramipexole ER and pramipexole IR were significantly superior on UPDRS II+III score, all key secondary outcomes, and almost all other endpoints. On the 39-item Parkinson Disease Questionnaire, superiority of pramipexole ER failed to reach statistical significance. Both formulations were equally safe and well-tolerated.
   Conclusion: As monotherapy for early PD, pramipexole ER was noninferior to pramipexole IR and significantly more effective than placebo. Tolerability and safety did not differ between the formulations.

2. Schapira AH, Barone P, Hauser Ra, et al. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. *Neurology.* 2011 Aug 23;77(8):767-74. Epub 2011 Aug 10.

   Background: In advanced Parkinson disease (PD), immediate-release pramipexole, taken 3 times daily, improves symptoms and quality of life. A once-daily extended-release formulation may be an effective and simple alternative therapy.
   Methods: For a multicenter randomized, double-blind, parallel trial of extended- and immediate-release pramipexole vs. placebo, patients experiencing motor fluctuations while taking levodopa underwent flexible study drug titration and then maintenance at optimized dosage (0.375-4.5 mg/day). The primary endpoint was a change in the Unified Parkinson's Disease Rating Scale (UPDRS) part II+III score at 18 weeks, with further assessments at 33 weeks in a subset of patients. Adverse events were recorded throughout.
   Results: Among 507 patients in the 18-week analyses, UPDRS II+III scores decreased (from baseline means of 40.0-41.7) by an adjusted mean of -11.0 for extended-release pramipexole and -12.8 for immediate-release pramipexole vs. -6.1 for placebo ($p = 0.0001$ and $p < 0.0001$) and off-time decreased (from baseline means of 5.8-6.0 hours/day) by an adjusted mean of -2.1 and -2.5 vs. -1.4 hours/day ($p = 0.0199$ and $p < 0.0001$). Other outcomes were largely corroborative, including a significant improvement in early morning off symptoms. Among 249 pramipexole patients completing 33 weeks, UPDRS II+III and off-time findings showed ≤10.1% change from 18-week values. Both formulations were well-tolerated.
   Conclusion: Extended-release pramipexole significantly improved UPDRS score and off-time compared with placebo, with similar efficacy, tolerability, and safety of immediate-release pramipexole compared with placebo.

3. Stocci F, Giorgi L, Hunter B, Schapira AH. PREPARED: Comparison of prolonged and immediate release ropinirole in advanced Parkinson's disease. *Mov Disord.* 2011 Jun;26(7):1259-65. doi: 10.1002/mds.23498. Epub 2011 Apr 5.

Background: PREPARED was a randomized, parallel-group, double-blind, multicenter study to evaluate the efficacy of adjunctive ropinirole prolonged release (PR) versus immediate release (IR) in patients with advanced Parkinson's disease (PD).
Methods: Patients received once-daily PR (2-24 mg/d; n = 177) or three-times-daily IR (0.75-24 mg/d; n = 173) for 24 weeks. The primary endpoint was the proportion of patients maintaining ≥ 20% reduction from baseline in "off" time over two consecutive visits at Week 24 last observation carried forward (LOCF
Results: At Week 24 LOCF, PR significantly increased the proportion of patients maintaining ≥ 20% reduction in "off" time versus IR (adjusted odds ratio: 1.82; 95% CI: 1.16, 2.86; P = 0.009). Mean (SD) doses at Week 24 LOCF were: PR, 18.6 (6.5) mg/d; IR, 10.4 (6.4) mg/d; mean (SD) reductions from baseline in levodopa (L-dopa) dose were -162 (226) mg and -113 (138) mg, respectively. Adverse events (AEs) were reported by 72% of patients in the PR group and 61% in the IR group; 12% and 9% of patients, respectively, withdrew from the study due to an AE, and 6% and 5%, respectively, reported serious AEs.
Conclusion: Adjunctive PR provided a significantly greater improvement in symptom control in terms of the odds of achieving ≥ 20% maintained reduction in time spent "off" compared with IR. Interpretation may be confounded by the higher doses of PR versus IR that were achieved, in combination with lower doses of L-dopa by the study end. Despite dosing differences, the PR titration regimen was generally well tolerated, with an AE profile similar to that of IR.

4. Hauser RA, Schapira AH, Rascol O, et al. Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. *Mov Disord.* 2010 Nov 15;25(15):2542-9.

Background: The objective of this study was to evaluate the efficacy and safety of pramipexole extended release (ER) administered once daily in early Parkinson's disease (PD). Pramipexole immediate release (IR) administered three times daily (TID) is an efficacious and generally well-tolerated treatment for PD. A pramipexole ER formulation is now available.
Methods: We performed a randomized, double-blind, placebo and active comparator-controlled trial in subjects with early PD. The primary efficacy and safety evaluation of pramipexole ER compared with placebo took place at week 18. Two hundred fifty-nine subjects were randomized 2:2:1 to treatment with pramipexole ER once daily, pramipexole IR TID, or placebo.
Results: Levodopa rescue was required by 7 subjects in the placebo group (14%), 3 subjects in the pramipexole ER group (2.9%, P = 0.0160), and 1 subject in the pramipexole IR group (1.0%, P = 0.0017). Adjusted mean [standard error (SE)] change in Unified Parkinson Disease Rating Scale (UPDRS) II [activities of daily living (ADL)] + III (motor) scores from baseline to week 18, including post-levodopa rescue evaluations, was -5.1 (1.3) in the placebo group, -8.1 (1.1) in the pramipexole ER group (P = 0.0282), and -8.4 (1.1) in the pramipexole IR group (P = 0.0153). Adjusted mean (SE) change in UPDRS ADL + motor scores, censoring post-levodopa rescue data, was -2.7 (1.3) in the placebo group, -7.4 (1.1) in the pramipexole ER group (P = 0.0010), and -7.5 (1.1) in the pramipexole IR group (P = 0.0006). Adverse events more common with pramipexole ER than placebo included somnolence, nausea, constipation, and fatigue.
Conclusion: Pramipexole ER administered once daily was demonstrated to be efficacious compared with placebo and provided similar efficacy and tolerability as pramipexole IR administered TID.

5. Stocchi F, Rascol O, Kieburtz K, et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol*. 2010 Jul;68(1):18-27.

Background: L-dopa is the most widely used and most effective therapy for Parkinson disease (PD), but chronic treatment is associated with motor complications in the majority of patients. It has been hypothesized that providing more continuous delivery of L-dopa to the brain would reduce the risk of motor complications, and that this might be accomplished by combining L-dopa with entacapone, an inhibitor of catechol-O-methyltransferase, to extend its elimination half-life.

Methods: We performed a prospective 134-week double-blind trial comparing the risk of developing dyskinesia in 747 PD patients randomized to initiate L-dopa therapy with L-dopa/carbidopa (LC) or L-dopa/carbidopa/entacapone (LCE), administered 4x daily at 3.5-hour intervals. The primary endpoint was time to onset of dyskinesia.
Results: In comparison to LC, patients receiving LCE had a shorter time to onset of dyskinesia (hazard ratio, 1.29; $p = 0.04$) and increased frequency at week 134 (42% vs. 32%; $p = 0.02$). These effects were more pronounced in patients receiving dopamine agonists at baseline. Time to wearing off and motor scores were not significantly different, but trended in favor of LCE treatment. Patients in the LCE group received greater L-dopa dose equivalents than LC-treated patients ($p < 0.001$).
Conclusion: Initiating L-dopa therapy with LCE failed to delay the time of onset or reduce the frequency of dyskinesia compared to LC. In fact, LCE was associated with a shorter time to onset and increased frequency of dyskinesia compared to LC. These results may reflect that the treatment protocol employed did not provide continuous L-dopa availability and the higher L-dopa dose equivalents in the LCE group.

Appendix 2 : New Systematic Reviews

1. Stowe R, Ives N, Clarke CE, Handley K, Furmston A, et al. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. *Mov Disord*. 2011 Mar;26(4):587-98. doi: 10.1002/mds.23517. Epub 2011 Mar 2.

   Background: Levodopa initially provides good symptomatic control of the symptoms of Parkinson's disease, but motor complications often develop after long-term use. Other classes of antiparkinsonian drugs including dopamine agonists, catechol-O-methyl transferase inhibitors, or monoamine oxidase type B inhibitors are then added as adjuvant therapy. It is unclear whether one class of drug is more effective than another. This meta-analysis evaluates the comparative benefits and risks of these agents as adjuvant treatment in Parkinson's disease patients with motor complications.
   Methods: A systematic review of the literature from 1966 to the end of June 2010 was conducted to identify randomized trials involving a dopamine agonist, catechol-O-methyl transferase inhibitor, or monoamine oxidase type B inhibitor versus placebo, as adjuvant to levodopa therapy.
   Results: Forty-five trials involving nearly 9,000 participants were included. The meta-analysis confirms reports from individual trials that compared with placebo, adjuvant therapy significantly reduces patient off-time and levodopa dose, with improved symptom severity scores (e.g., Unified Parkinson's Disease Rating Scale). However, dyskinesia and numerous other side effects are increased with adjuvant therapy. Few randomized comparisons between drugs have been undertaken, but indirect comparisons suggest that dopamine agonist therapy may be more effective than catechol-O-methyl transferase inhibitor and monoamine oxidase type B inhibitor therapy, which have comparable efficacy. No differences between drugs within each class were observed other than the catechol-O-methyl transferase inhibitor tolcapone appearing more efficacious than entacapone.
   Discussion: This meta-analysis highlights the need for direct head-to-head randomized trials to assess the impact of adjuvant therapy on patient-rated quality of life and health economic outcomes.

2. Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials.

   Background : Dopamine agonists have a well established role in the treatment of Parkinson's disease. The choice of a particular dopamine agonist requires assessing the benefit-risk balance of each available medication.
   Objective: The present study evaluated the tolerability and safety of ropinirole against those of other dopamine agonists (bromocriptine, cabergoline, pramipexole, rotigotine, pergolide) and placebo in monotherapy and adjuvant therapy with levodopa in the treatment of Parkinson's disease, as reported in the peer reviewed medical literature.
   Methods: A systematic review of the medical literature was carried out for relevant English language articles in the MEDLINE database and Cochrane Library from January 1975 to November 2008. The searches were limited to either double-blind clinical trials or randomized clinical trials that included both patients with early Parkinson's disease receiving dopamine agonist monotherapy, and patients at a later stage on combined treatment with levodopa. The Cochrane Collaboration guidelines were followed and the following data were extracted from each study: identifier (title and bibliographical reference), classification of the quality of the evidence (Jadad criteria), type and design of the study, number of patients, patient demographics (average age, sex), Parkinson's disease stage (Hoehn and Yahr Scale), treatment (monotherapy or adjuvant to levodopa), drugs used (including dosage and duration), study objective (safety or tolerability), method of evaluation of results, randomization and blinding, and description of all the adverse events in all treatment groups. A meta-analysis was performed, calculating relative risks (RRs) and confidence intervals for the 12 most relevant adverse events. On the basis of incidence and clinical importance criteria, the final selection of 12 adverse events was made by consensus between the investigators.
   Results: Forty randomized clinical trials were included. Direct comparison of ropinirole with bromocriptine showed a lower RR of constipation for ropinirole (0.55 [95% CI 0.35, 0.89]), while the direct comparison with levodopa showed a lower RR of dyskinesia for ropinirole (0.25 [95% CI 0.09, 0.71]); no significant differences for either dyskinesia or constipation were found when a direct comparison of ropinirole and rotigotine was made. For nausea, ropinirole,

pergolide and rotigotine versus placebo all demonstrated similar RRs (2.25 [95% CI 1.85, 2.74]; 2.28 [95% CI 1.54, 3.37]; and 2.08 [95% CI 1.30, 3.34], respectively). On indirect comparison of ropinirole with pramipexole, ropinirole showed a higher RR for nausea (2.25 [95% CI 1.85, 2.74] vs 1.48 [95% CI 1.24, 1.76]), dizziness (1.87 [95% CI 1.48, 2.37] vs 1.20 [95% CI 1.01, 1.43]), somnolence (2.45 [95% CI 1.30, 4.61] vs 1.68 [95% CI 1.25, 2.25]), and dyskinesia (2.71 [95% CI 1.74, 4.21] vs 2.27 [95% CI 1.58, 3.27]). Pramipexole (3.36 [95% CI 2.41, 4.68], pergolide (4.80 [95% CI 2.24, 10.29]), ropinirole (2.84 [95% CI 1.34, 5.99]), and rotigotine (4.02 [95% CI 1.23, 13.11]) all had a higher RR of hallucinations compared with placebo. Pramipexole also showed a higher RR of confusion (2.64 [95% CI 1.18, 5.91]) and constipation (2.23 [95% CI 1.53, 3.25]) compared with placebo.

Conclusions: In all the included studies, dopamine agonists, including ropinirole, exhibited a higher incidence of adverse events than placebo. Ropinirole showed an adverse event profile similar to other dopamine agonists. Consideration of the clinical characteristics of each patient and the differences in the incidence of adverse events related to each dopamine agonist, may help to optimize the dopamine agonist therapy.

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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

Month/Year of Review: January 2012 **Date of Last Review:** February 2007
PDL Class: Analgesics: NSAIDS **Source Document:** HRC Report

Current Preferred Agents:

Diclofenac	Meloxicam
Diclofenac DR	Nabumetone
Etodolac	Naproxen
Flurbiprofen	Naproxen DR
Ibuprofen	Oxaprozin
Indomethacin	Salsalate
Ketoprofen	Sulindac
Ketorolac tromethamine*	

*with quantity limit

Current Non-Preferred Agents:

Celecoxib (Celebrex®)
Piroxicam
Mefenamic acid
Tolmetin
Fenoprofen
Diflunisal
Meclofenamate

Topical Agents
Diclofenac topical (Flector patch®)
Diclofenac topical (Voltaren®, Voltaren gel®)

Combination Agents:
Diclofenac/misoprostol (Arthrotec®)

Previous Recommendations:

- There is no evidence to demonstrate a significant difference in efficacy amongst NSAIDs including celecoxib.
- There are concerns about adverse cardiac events of celecoxib as compared to naproxen, but data is inconclusive at the present time to draw definitive conclusions.
- There is no evidence that celecoxib is superior to other NSAIDs in preventing ulcer complications.
- There is raised concern that for patients taking aspirin the benefit of celecoxib in preventing serious gastrointestinal events was obviated.
- Caution should be used in treating patients with recent GI bleeding with all NSAIDS because of the high risk for re-bleeding.
- In patients with hypertension there is a risk of further elevation of blood pressure with all NSAIDs

PA Criteria/QL:

PA: Non-preferred NSAIDS require a PA to ensure use is for covered diagnoses
Quantity Limit: Restricts ketorolac to short-term use (5 days every 60 days) per the FDA black boxed warning

New Systematic Reviews:

The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an updated report on the Drug Class Review of Nonsteroidal Antiinflammatory Drugs (NSAIDS) in November 2010.[1] The full report can be found on the Evidence-based Practice Center website:

http://derp.ohsu.edu/about/final-document-display.cfm and the final executive summary can be found on the Oregon Pharmacy and Therapeutics website: http://pharmacy.oregonstate.edu/drug_policy/meetings. It compared the effectiveness and harms of oral and topical NSAIDs in the treatment of chronic pain from five diagnoses: osteoarthritis (OA), rheumatoid arthritis (RA), soft tissue pain, anklylosing spondylitis, and back pain.

Key Questions:

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from OA, RA, soft-tissue pain, back pain, or anklylosing spondylitis?
2. Are there clinically important differences in short-term harms between NSAIDs?
3. Are there clinically important differences in long-term harms (≥6 months) between NSAIDs?
4. Are there subgroups of patients based on demographics, other medications, socio-economic conditions, co-morbidities for which one medication is more effective or associated with fewer harms?

Conclusions:

1. There was high-strength evidence that there are no significant differences between oral NSAIDs for efficacy, including celecoxib.
2. No significant differences were found between oral NSAIDS, topical NSAIDs, or between oral and topical NSAIDs for short-term (less than 6 months) pain relief.
3. There is high-strength evidence that celecoxib seems to offer a short-term advantage over nonselective NSAIDs in regard to gastrointestinal adverse events but there is insufficient long-term evidence.
4. Celecoxib does not appear to have a higher risk of cardiovascular events compared to nonselective NSAIDs, but evidence is primarily from short-term studies.
5. There is moderate strength evidence that all non-selective NSAIDs, except naproxen, are associated with increased risks of CV events similar to that seen with COX-2 inhibitors. Naproxen appears to be risk-neutral.
6. There is high-strength evidence that all non-selective oral NSAIDS have similar risk of short-term and long-term gastrointestinal complications, but the partially selective NSAID nabumetone appears to be gastroprotective.
7. For comparisons among different topical diclofenac products, only low-strength, indirect evidence was available indicating that diclofenac 1.5% topical solution and 1.0% topical gel had similar significant improvements in pain, functional outcome measures, and response rate
8. Compared with oral NSAIDs, high-strength evidence showed that diclofenac 1.5% solution resulted in similar improvements in efficacy but with significantly improved gastrointestinal tolerability.
9. There is low-strength evidence that suggests there may be lower risks of serious gastrointestinal, cardiovascular, and renal adverse events in elderly patients with celecoxib compared to diclofenac or ibuprofen.

Limitations:

- Majority of trials are short term duration and little evidence exists on the comparative effectiveness of NSAIDs that is truly effectiveness
- No trials that directly compared the effectiveness or efficacy between different topical NSAIDs were found
- Insufficient evidence was available to evaluate any differences in effects based on ethnicity/race, gender, or socioeconomic status.

Methods:

Search Strategy

An Ovid MEDLINE search was conducted since the literature search performed for the DERP report and used the following search terms:

NSAIDS; anti-inflammatory agents, non-steroidal; diclofenac; etodolac; flurbiprofen; ibuprofen; ketoprofen; ketorolac tromethamine; meloxicam; nabumetone; naproxen; oxaprozin; salsalate; sulindac; arthritis; osteoarthritis; osteoarthritis, hip; osteoarthritis, spine; osteoarthritis, knee; arthritis, rheumatoid; ankylosing spondylitis; back pain; soft tissue pain. The search was limited to controlled trials conducted with humans in English language publications from 2010 to present.

Results:

The MEDLINE search retrieved 80 full citations. After a full review of citations and abstracts, no new head-to-head using FDA approved agents were identified. The majority of the RCTs identified compared available NSAIDS with opiates, DMARDs, dietary supplements, herbal agents and NSAIDS not approved for use in the U.S. Other exclusions were for wrong study type (observational, case study), or for the wrong endpoint (C-reactive protein levels, cartilage turnover).

New FDA-approved drugs:

No new molecular entities were approved but two fixed-dose combination products were FDA approved and one new formulation/delivery system of ketorolac was approved in May 2010.

1. **Sprix®** (ketorolac tromethamine) is a new nasal spray formulation indicated for short-term (5 days or less) management of moderate to moderately severe pain. It carries the same black box warning as the oral and IV formulations. Ketorolac nasal spray was approved based on two randomized placebo-controlled trial of adults treated post-operatively from elective abdominal or orthopedic surgery for 48 hours. The primary efficacy outcome was summed pain intensity difference over 6 hours. Patients in both studies were also treated with morphine PCA on an as-needed basis. These studies only demonstrated efficacy compared to placebo in the inpatient setting for postoperative pain and therefore it is difficult to extrapolate to use in the outpatient setting

Treatment Group	N	Single-dose summed pain intensity difference score (mean score)	P-Value	Mean morphine use (mg) during hours 0-48	P-Value[#]
Brown, et al.[2]	300				
Intranasal ketorolac 30mg	199	83.3 ± 10.6	< 0.007	51.4 ± 2.75	<0.001
Placebo	101	37.2 ± 12.9	--	77.4 ± 5.28	
Singla, et al.[3]	321				
Intranasal ketorolac 30mg	214	117.4 ± 7.7	<0.032	23	=0.041
Placebo	107	89.9 ± 10.6		31	
				--	

2. **Vimovo®** (naproxen/esomeprazole) is a new oral combination product indicated for pain relief in patients with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis and to decrease the risk of stomach ulcers in patients at risk of developing a NSAID induced gastric ulcer. Approval was based on four randomized, double-blind, placebo-controlled studies. Two of these were 12-week studies to determine efficacy of naproxen/esomperazole in treating the signs and symptoms of OA of the knee compared to placebo and celecoxib.[4] Patients receiving naproxen/esomeprazole had significantly better results compared to placebo as measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale and a Patient Global Assessment score. The study results did not find naproxen/esomeprazole to be noninferior to celecoxib but did compared to placebo.
   There were also two randomized, double-blind studies performed comparing the incidence of gastric ulcer formation compared to placebo and naproxen EC 500mg BID.[5] The incidence of cumulative gastric ulcers at 6 months was significantly lower for the naproxen/esomperazole group vs. naproxen EC (Study 301: 4.1% vs. 23.1%, $p<0.001$; Study 302: 7.1% vs. 24.3%, $p<0.001$).

3. **Duexis ®** (ibuprofen/famotidine) is a new oral combination product indicated for the relief of signs and symptoms of RA and OA and to decrease the risk of developing gastric ulcers. Ibuprofen/famotidine was evaluated in two phase III, randomized, double-blind trials of 24 weeks in duration comparing ibuprofen/famotidine three times daily to ibuprofen 800mg three times daily.[6, 7] The primary outcome was the incidence of endoscopic gastroduodenal ulcers. The incidence of endoscopic gastroduodenal ulcers with Duexis was 11%, compared to 21.9% with ibuprofen alone. These trials were not published and they therefore cannot be assessed for quality or risk of bias.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Guidelines:
None identified.

Recommendations:
1. No further research or review needed.
2. Consider Sprix nasal spray for PDL placement pending price comparison and restrict to a 5-day quantity limit.
3. Add new combination products to Proton Pump Inhibitor clinical pa similar to PrevPac.

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Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Final Update 4 Report
Executive Summary

November 2010

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Nonsteroidal Antiinflammatory Drugs", dated November 2010. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 3: November 2006
Update 2: May 2004
Update 1: September 2003
Original Report: May 2002
The literature on this topic is scanned periodically

Kim Peterson, MS
Marian McDonagh, PharmD
Sujata Thakurta, MPA: HA
Tracy Dana, MLS
Carol Roberts, BS
Roger Chou, MD
Mark Helfand, MD, MPH

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

INTRODUCTION

Compared with placebo, nonsteroidal antiinflammatory drugs (commonly called NSAIDs) reduce pain significantly in patients with arthritis, low back pain, and soft tissue pain. However, NSAIDs have important adverse effects, including gastrointestinal bleeding, peptic ulcer disease, hypertension, edema, and renal disease. More recently, some NSAIDs have also been associated with an increased risk of myocardial infarction. NSAIDs reduce pain and inflammation by blocking cyclo-oxygenases (COX), enzymes that are needed to produce prostaglandins. Most NSAIDs block 2 different cyclo-oxygenases, COX-1 and COX-2. COX-2, found in joints and muscle, contributes to pain and inflammation. NSAIDs cause bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the United States, complications from NSAIDs are estimated to cause about 6 deaths per 100 000, a higher death rate than that for cervical cancer or malignant melanoma. A risk analysis based on a retrospective case-control survey of emergency admissions for upper gastrointestinal disease in 2 United Kingdom general hospitals provided useful estimates of the frequency of serious gastrointestinal complications from NSAIDs. In people taking NSAIDs, the 1-year risk of serious gastrointestinal bleeding ranges from 1 in 2100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12 353 to 1 in 647.

Scope and Key Questions

The goal of this report is to compare the effectiveness and harms of nonsteroidal antiinflammatory drugs (NSAIDs) in the treatment of chronic pain from osteoarthritis, rheumatoid arthritis, soft tissue pain, back pain, and ankylosing spondylitis. Included drugs are shown in Table 1.

Table 1. Included NSAIDs

Generic name	Trade name(s)	Dosage forms
Oral drugs		
Celecoxib	Celebrex®	Capsule
Diclofenac sodium	Voltaren [a]	Tablet, suppository
	Voltaren SR [a]	Tablet, ER
	Voltaren® XR [b]	Tablet, ER
Diclofenac potassium	Cataflam® [b]	Tablet
	Voltaren Rapide® [a]	Tablet
	Zipsor® [b]	Capsule
Diflunisal	*Generic only*	Tablet
Etodolac	Ultradol [a]	
Fenoprofen [b]	Nalfon® [b]	Capsule
Flurbiprofen	Ansaid®	Tablet
Ibuprofen	Advil® [c]	Tablet, caplet, gel caplet
	Motrin® IB [c]	Tablet, caplet
Indomethacin	Indocin® [b]	Suspension
	Indocin® SR [b]	Capsule, ER
	Generic only [a]	Capsule; suppository
Ketoprofen	Nexcede® [b, c]	Film
	Generic only [a]	Capsule, EC tablet, suppository
Ketoprofen SR [a]	*Generic only*	
Ketorolac tromethamine	Toradol® [a]	Tablet
Meclofenamate [b]	*Generic only* [b]	Capsule
Mefenamic acid	Ponstel® [b]	Capsule
	Ponstan® [a]	Capsule
Meloxicam	Mobic® [b]	Tablet, suspension
	Mobicox® [a]	Tablet
Nabumetone	*Generic only*	Tablet
Naproxen	Aleve® [c]	Tablet
	Naprosyn® [b]	Tablet, suspension
	EC-Naprosyn® [b]	EC Tablet, DR
	Naprosyn E [a]	EC Tablet
Naproxen SR [a]	Naprosyn® SR [a]	Tablet
Naproxen sodium	Anaprox®, Anaprox® DS	Tablet
	Naprelan®	Tablet, ER
Oxaprozin	Daypro®	Tablet
Piroxicam	Feldene® [b]	Capsule
	Generic only [a]	Capsule, suppository
Sulindac	Clinoril® [b]	Tablet
	Generic only [a]	Tablet
Tenoxicam [a]	*Generic only* [a]	Tablet
Tiaprofenic Acid [a]	*Generic only* [a]	Tablet
Tolmetin [b]	Tolectin® [b], Tolectin® 600 [b]	Tablet
	Tolectin® DS [b]	Capsule
Topical drugs		
Diclofenac epolamine [b]	Flector®	Topical patch 1.3%
Diclofenac sodium	Voltaren® [b]	Topical gel 1%
	Pennsaid®	Topical solution 1.5%
	Solaraze®	Topical gel 3%
Diclofenac diethylamine [a]	Voltaren® Emulgen™ [a]	Topical gel 1.16%

Abbreviations: DR, delayed release; EC, Enteric coated; ER, extended release; SR, sustained release; XR, extended release.

[a] Available in Canada, *not* available in the United States (generic products may be available in the United States).

[b] Not available in Canada, available in the United States.

[c] Miscellaneous over-the-counter brand names; prescription-only products available as generic products.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
2. Are there clinically important differences in short-term harms (< 6 months) between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
3. Are there clinically important differences in long-term harms (≥ 6 months) between NSAIDs, with or without antiulcer medication, when used chronically in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?
    a. How do oral drugs compare to one another?
    b. How do topical drugs compare to one another?
    c. How do oral drugs compare to topical drugs?
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one medication is more effective or associated with fewer harms?

METHODS

We searched Ovid MEDLINE® (1996 to June week 2, 2010), the Cochrane Database of Systematic Reviews® (2005 to May 2010), the Cochrane Central Register of Controlled Trials® (2nd Quarter 2010), and Database of Abstracts of Reviews of Effects (2nd Quarter 2010) using included drugs, indications, and study designs as search terms. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review.

We assessed the internal validity (quality) of included studies as *good, fair, or poor* based on predefined criteria. We graded the overall strength of a body of evidence pertaining to a particular key question or outcome based on the approach proposed in the Evidence-based Practice Center Methods Guide. This approach considers the risk of bias of the studies (based on quality and study designs), consistency of results, directness of evidence, and precision of pooled estimates resulting from the set of studies relevant to the question. Strength of evidence was graded as High, Moderate, Low, and Insufficient.

RESULTS

Overview

A total of 2941 (1139 from update 4) records were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comments. By applying the eligibility and exclusion criteria, we ultimately included 159 publications (33 for Update 4). Of these, 68 were trials (23 for Update 4), 47 were observational studies (4 for Update 4), 32 were systematic reviews (4 for Update 4), and 12 were pooled analyses and post-hoc analyses (2 for Update 4).

Key Question 1

Among oral drugs, celecoxib 200 mg daily to 800 mg daily and nonselective NSAIDs have been associated with similar pain reduction effects in primarily short-term randomized controlled trials of patients with osteoarthritis, rheumatoid arthritis, soft tissue pain, and ankylosing spondylitis. Compared with nonselective NSAIDS, partially selective NSAIDs (meloxicam, nabumetone, and etodolac) were associated with similar pain reduction effects in short-term randomized controlled trials. Good-quality Cochrane reviews and more recent trials found no clear differences among nonselective NSAIDs in efficacy for treating osteoarthritis of the knee or hip or for low-back pain. Evidence on the comparative efficacy of salsalate was limited to 2 randomized controlled trials that found no significant difference as compared with indomethacin. Based on findings from a good-quality systematic review of 18 randomized controlled trials, improvement in pain with tenoxicam was significantly greater as compared with piroxicam, but was similar to that of diclofenac and indomethacin. Randomized controlled trials have also found the pain reduction effects of tiaprofenic acid to be comparable to those of diclofenac, ibuprofen, indomethacin, naproxen, piroxicam, and sulindac in the treatment of rheumatoid arthritis and osteoarthritis.

We found no trials that directly compared the effectiveness or efficacy between different topical NSAIDs. Both diclofenac 1.5% topical solution and 1.0% topical gel had significantly greater mean changes in pain subscale scores than the placebo groups.

Comparison between diclofenac 1.5% topical solution and oral diclofenac found no significant differences on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function variables in 2 head-to-head trials.

Key Questions 2 and 3

Celecoxib

Among oral drugs, celecoxib may offer a short-term advantage over nonselective NSAIDs with regard to upper gastrointestinal adverse events, but this has not been conclusively demonstrated in longer-term (>6 months) studies. In high-risk patients, 3 short-term randomized controlled trials found rates of ulcer complications to be similar with celecoxib and nonselective NSAIDs when a proton pump inhibitor is given concomitantly with the nonselective NSAID. In contrast, the short-term risk of clinically significant upper and lower gastrointestinal events (combined) was lower with celecoxib than diclofenac slow release plus omeprazole in a good-quality trial of

4484 patients (CONDOR). However, the findings from the CONDOR trial should be interpreted with caution as celecoxib's advantage on the primary composite outcome was mostly due to its advantage on the individual outcome of anemia, which was only presumed to be of lower gastrointestinal tract origin.

The strategy of adding esomeprazole 20 mg to celecoxib 200 mg in patients at very high risk, with a recent upper gastrointestinal bleed, resulted in lower risk of 13-month cumulative incidence of recurrent ulcer bleeding compared with celecoxib 200 mg alone in a good-quality randomized controlled trial.

Based on findings from 3 meta-analyses of randomized controlled trials that were primarily 12 weeks in duration, as well as in 1 large case-control study, risk of myocardial infarction for celecoxib was not significantly different compared with NSAIDs and no significant increase in risk of other cardiovascular events or cerebrovascular events was found for celecoxib as compared with nonselective NSAIDs in 6 meta-analyses of randomized controlled trials and 5 observational studies. With regard to cardiorenal harms, results from the longest-term CLASS trial and meta-analyses of shorter-term trials found no increased risk of hypertension or heart failure with celecoxib compared with nonselective NSAIDs. Celecoxib was also not associated with an increased fracture risk in a fair-quality, large-scale, Danish population-based cohort study.

Partially selective NSAIDs

Among oral partially selective NSAIDs, meloxicam has not been conclusively demonstrated to offer an advantage over nonselective NSAIDs with regard to gastrointestinal adverse events and limited evidence from observational studies has not suggested any increased risk for meloxicam in myocardial infarction, hepatotoxicity, or fracture. Compared with nonselective NSAIDs, nabumetone had a lower short-term risk of gastrointestinal perforation, symptomatic ulcer, or bleeding events, but long-term comparative risks are unknown, and nabumetone was not associated with an increased fracture risk in a fair-quality, large-scale, Danish population-based cohort study. Comparative short-term and long-term gastrointestinal risk for etodolac relative to nonselective NSAIDs has not been evaluated. But, a small increase in risk of fracture was found to be associated with recent use of etodolac (within 1 year) in a fair-quality, large-scale, Danish population-based study (adjusted relative risk, 1.14; 95% CI, 1.06 to 1.22).

Nonselective NSAIDs

There was strong evidence from numerous randomized controlled trials and observational studies that all oral nonselective NSAIDs are associated with relatively similar risks of serious gastrointestinal events relative to nonuse. All nonselective NSAIDs except naproxen were associated with similar risks of clinically important cardiovascular events (primarily myocardial infarction) compared with COX-2 inhibitors (data primarily on high-dose ibuprofen and diclofenac), whereas naproxen was associated with a lower risk of myocardial infarction compared with COX-2 inhibitors (relative risk, 2.04; 95% CI, 1.41 to 2.96; P=0.0002). In a systematic review of published and unpublished short-term randomized controlled trials, diclofenac was associated with the highest rates of aminotransferase elevations >3 times the upper limit of normal (3.55%; 95% CI, 3.12 to 4.03) compared with ibuprofen (0.43%; 95% CI, 0.26 to 0.70), and the only evidence available for diclofenac regarding longer-term risk of

hepatotoxicity was noncomparative, but similar rates of aminotransferase elevations >3 times the upper limit of normal (3.1%) were found. In a large, fair-quality population-based study, the nonselective NSAID that had the highest overall risk of fracture was ibuprofen (adjusted relative risk, 1.76; 95% CI, 1.72 to 1.81) and an observed inverse dose-response relationship did not clearly suggest a direct correlation with the COX system.

Evidence on serious gastrointestinal and cardiovascular harms was limited for salsalate, tenoxicam and tiaprofenic acid. For salsalate, the best evidence comes from a single observational study that found the rates of gastrointestinal-related hospitalizations after 14 months similar for salsalate and other NSAIDs. Whereas, for tenoxicam or tiaprofenic acid, no specific data was found on the comparative risks of serious cardiovascular or serious gastrointestinal effects. However, 3 observational studies reported cases of potentially serious cystitis in patients using tiaprofenic acid, particularly in patients >70 years old.

Topical NSAIDs

Evaluation of comparative harms among topical NSAIDs was limited to indirect evidence based on 1 placebo-controlled trial of diclofenac 1.5% topical solution and 2 of diclofenac 1.0% topical gel. Compared with placebo, withdrawals due to adverse events were significantly greater with diclofenac 1.5% topical solution, but not for diclofenac 1% topical gel. Dry skin at the application site was significantly greater for diclofenac 1.5% topical solution compared with placebo solution, but rates of overall application site reactions were not significantly different for diclofenac 1.0% topical gel compared with placebo gel. There was no significant difference between diclofenac 1.5% topical solution and placebo solution or between 1.0% topical gel and placebo gel in gastrointestinal adverse events.

Comparative harms between topical and oral NSAIDs were evaluated in 2 trials that directly compared diclofenac 1.5% topical solution to oral diclofenac. Incidence of dry skin at the application site was significantly greater for topical diclofenac and incidence of gastrointestinal adverse events was significantly greater for oral diclofenac. However, withdrawals due to adverse events were similar in the topical and oral diclofenac treatment groups.

Key Question 4

Concerning differential effects in specific patient subgroups of interest, the strongest evidence was available for comparison among oral drugs specifically in high-risk patients with a history of ulcer bleeding and for patients using low-dose aspirin concomitantly.

In patients with a history of ulcer bleeding, the 13-month cumulative incidence of recurrent ulcer bleeding was significantly lower for celecoxib plus esomeprazole compared with celecoxib alone in a good-quality trial and two shorter-term trials found no statistically significant differences in recurrent ulcer bleeding between celecoxib and treatment with a nonselective NSAID plus a proton pump inhibitor.

For patients taking an NSAID and low-dose aspirin (325 mg or less), similar rates of endoscopically confirmed gastroduodenal ulcers were found with celecoxib alone compared with treatment with naproxen plus lansoprazole based on a single randomized controlled trial. Findings were consistent in prior subgroup analyses according to the use of low-dose aspirin,

which also indicated no significant differences between celecoxib and nonselective NSAIDs in endoscopic ulcer rates.

Evidence remains unclear as to whether concomitant NSAID use could interfere with the cardioprotective effects of aspirin in patients with preexisting cardiovascular disease. While limited evidence from 1 case-control study suggested that concomitant NSAID use could interfere with the cardioprotective effects of aspirin in patients with preexisting cardiovascular disease, 2 other observational studies in more broadly defined populations found no increased risk of myocardial infarction.

Regarding subgroups of patients based on demographics, although evidence from randomized controlled trials of elderly populations consistently found no significant differences in efficacy outcomes between celecoxib and either naproxen or diclofenac, results from primarily retrospective cohort studies suggested that celecoxib may be associated with fewer selected serious adverse events than some nonselective NSAIDs when used in elderly populations. There were significantly fewer gastrointestinal hospitalizations when a proton pump inhibitor was added to celecoxib compared with celecoxib alone when age was above 75 years, but not when age was 66 to 74 years. Additionally, in high-risk elderly patients with a recent admission for heart failure, compared with nonselective NSAIDs, rates of death and recurrent congestive heart failure were lower for celecoxib. One randomized controlled trial found no significant differences between celecoxib and diclofenac on pain when used concomitantly with angiotensin-converting enzyme inhibitors in a small study of all black or Hispanic patients.

Regarding subgroups of patients taking other concomitant medications, a single, small crossover trial examining the effects of using NSAIDs in patients taking anticoagulants found no significant changes in the mean international normalized ratio values after 5 weeks of either celecoxib or codeine. Comparative evidence of the safety of celecoxib relative to NSAIDs when used concomitantly with anticoagulants was limited to 2 small observational studies and was inconclusive due to flaws in design.

No evidence was found regarding the comparative effectiveness and harms of topical diclofenac products or between oral and topical NSAIDs in patient subgroups.

SUMMARY

The main findings of this review are summarized in Table 2. Little evidence on the comparative effectiveness of NSAIDs was truly effectiveness or "real world" – while some trials evaluated longer-term (>6-12 months) and real life (symptoms, clinical ulcers, functional status, myocardial infarctions, pain relief) outcomes, none were conducted in primary care or office-based setting or used broad enrollment criteria.

Table 2. Summary of the evidence by key question

Key Question	Strength of evidence	Conclusion
1. Are there differences in effectiveness between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?		
1a. How do oral drugs compare to one another?		
Celecoxib	High. Evidence is available from many published trials.	No clear differences in pain reduction.
Meloxicam	High. Consistent evidence from many published trials	No consistent differences.
Nabumetone	Moderate. Fewer	No consistent differences.

Key Question	Strength of evidence	Conclusion
	RCTs/systematic review	
Etodolac	High. Consistent evidence from many published trials	No consistent differences.
Nonselectives	High. Consistent evidence from many published trials and several good-quality systematic reviews	No consistent differences.
Salsalate	Moderate. Limited evidence from few RCTs	No consistent differences.
Tenoxicam	High. Many published RCTs, meta-analysis	No consistent differences.
Tiaprofenic acid	High. Several RCTs and 1 fair-quality review	No consistent differences.
1b. How do topical drugs compare to one another?		
Diclofenac 1.5% topical solution and 1.0% topical gel	Low. Indirect evidence from placebo-controlled trials.	Both topical drugs had significantly greater mean changes in pain subscale scores than placebo.
Other topical drugs	Insufficient	No trials met inclusion criteria.
1c. How do oral drugs compare to topical drugs?		
Diclofenac 1.5% topical solution	High. 2 head-to-head trials	Compared with oral diclofenac, diclofenac 1.5% topical solution produced similar improvement in WOMAC pain and physical function variables.
2 and 3. Are there clinically important differences in short-term (< 6 months) or long-term (≥ 6 months) harms between NSAIDs, with or without antiulcer medication, when used in adults with chronic pain from osteoarthritis, rheumatoid arthritis, soft-tissue pain, back pain, or ankylosing spondylitis?		
2a and 3a. How do oral drugs compare to one another?		
Celecoxib	High. Evidence from many published trials and systematic reviews	*GI Harms:* Lower risk for celecoxib than nonselective NSAIDs in the short-term, but longer-term evidence is inconclusive. *CV Harms:* No significant difference in risk of MI for celecoxib compared with nonselective NSAIDs, but evidence is primarily from short-term studies. *Other serious adverse events:* No consistent differences.
Meloxicam	Moderate for GI harms; low for others	*Short-term and long-term GI harms:* No consistent differences. *Long-term CV harms:* No conclusive evidence of increased risk relative to nonselectives. *Hepatotoxicity:* No evidence of increased risk relative to placebo. *Other serious adverse events:* No evidence.
Nabumetone	Moderate for short-term GI safety; low for others	*Short-term GI harms:* Decreased risk relative to nonselectives. *Other serious adverse events:* No evidence.
Etodolac	Low for perforation, symptomatic ulcer, or bleeding, insufficient for others	*Perforation, symptomatic ulcer, or bleeding rates (duration unknown):* No increased risk relative to nonuse. *Other serious adverse events:* No evidence.
Nonselectives	High for GI safety; moderate for CV safety; low for other serious adverse events	*Short-term/long-term GI safety:* All nonselectives are associated with similar increased risks relative to nonuse.

Key Question	Strength of evidence	Conclusion
		Short-term/long-term CV safety: Nonselective NSAIDs other than naproxen are associated with increased risks of CV events similar to that seen with COX-2 inhibitors (most data on high-dose ibuprofen and diclofenac). Naproxen appears to be risk-neutral with regard to cardiovascular events. *Hepatotoxicity:* In short-term trials, diclofenac associated with highest rates of aminotransferase elevations >3 times upper limits of normal. Noncomparative evidence suggests similar rates in the longer term. *Fracture risk:* Preliminary evidence from 1 case-control study suggestive of higher risk with ibuprofen compared with other nonselective NSAIDs. *All-cause mortality/blood pressure/ CHF/edema/renal function/hepatotoxicity:* No consistent difference.
Nonselective+antiulcer medications	Low for GI events; moderate for endoscopic ulcers	*Clinical GI events:* Misoprostol only antiulcer medication proven to reduce rates, but at expense of reduced GI tolerability. *Endoscopic ulcers:* All proven to reduce rates.
Salsalate	Low for short-term overall toxicity and long-term GI harms, insufficient for others	*Short-term overall toxicity:* Significantly lower rates. *Long-term GI harms:* No differences. *Other serious adverse events:* No evidence.
Tenoxicam	Insufficient	No evidence found for specific GI and CV adverse events; reporting of AEs and dropouts slightly lower with tenoxicam compared with indomethacin and piroxicam respectively.
Tiaprofenic acid	Moderate for cystitis, insufficient for others	Observational studies report serious cases of cystitis.
2b and 3b. How do topical drugs compare to one another?		
Diclofenac 1.5% topical solution and 1.0% topical gel	Low. Indirect evidence from placebo-controlled trials.	Withdrawals due to adverse events: Significantly greater for diclofenac 1.5% topical solution, but not for 1.0% topical gel. Short-term GI harms: Compared with placebo, neither topical product resulted in significant increased incidence. Application site reactions: Only diclofenac 1.5% topical solution resulted in significantly greater skin dryness.
2c and 3c. How do oral drugs compare to topical drugs?		
Diclofenac 1.5% topical solution	High. 2 head-to-head trials	Topical diclofenac resulted in significantly lower incidence of GI adverse events, but higher incidence of application site skin dryness. Withdrawals due to adverse events were similar for oral and topical diclofenac.
4. Are there subgroups of patients based on demographics, other medications (e.g., aspirin), socio-economic conditions, co-morbidities (e.g., gastrointestinal disease) for which one medication is more effective or associated with fewer harms?		

Key Question	Strength of evidence	Conclusion
4a. How do oral drugs compare to one another?		
All	Moderate for concomitant use of low-dose aspirin and for NSAID use in high-risk patients with recent GI bleed. Low for others.	*Demographics*: No differences in efficacy, but risk of certain serious harms may be lower for celecoxib than some NSAIDs in elderly patients. *History of ulcer bleeding:* Recurrent ulcer bleeding significant lower for celecoxib plus esomeprazole compared with celecoxib alone. No significant difference for celecoxib alone compared with a nonselective NSAID plus a PPI. *Cardiac/renal comorbidities:* Celecoxib possibly associated with decreased risk of death and recurrent heart failure compared with nonselective NSAIDs in elderly patients with a recent admission for heart failure. *Concomitant use of anticoagulants*: Comparative evidence from observational studies was inconclusive. Noncomparative evidence suggested no significant increase in INR after 5 weeks of celecoxib. *Concomitant use of low-dose aspirin:* Similar rates of endoscopic ulcers for celecoxib compared with naproxen plus lansoprazole in prospective RCT. Subgroup analyses also found similar endoscopic ulcer rates for celecoxib and nonselective NSAIDs.
4b. How do topical drugs compare to one another?		
All	Insufficient	No evidence
4c. How do oral drugs compare to topical drugs?		
All	Insufficient	No evidence

Abbreviations: AE, adverse event; COX, cyclo-oxygenase; CV, cardiovascular; GI, gastrointestinal; INR, international normalized ratio; MI, myocardial infarction; NSAID, nonsteroidal antiinflammatory drug; OARSI, Osteoarthritis Research Society International; PPI, proton pump inhibitor; RCT, randomized controlled trial; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

CONCLUSION

For pain relief, no significant short-term (< 6 months) differences were found among oral NSAIDs, topical NSAIDs, or between oral and topical NSAIDs. For serious harms, celecoxib did not appear to be associated with higher risk of cardiovascular events and is gastroprotective in the short term compared with nonselective NSAIDs. These findings vary by subgroup, depending on age, recent history of gastrointestinal bleeding, and concomitant use of antiulcer medication. Nonselective NSAIDs were associated with similar increased risks of serious gastrointestinal events, and all but naproxen were associated with similar increased risk of serious cardiovascular events, but the partially selective NSAID nabumetone was gastroprotective compared with nonselective NSAIDs. Compared with oral NSAIDs, topical diclofenac was gastroprotective but had higher risk of application site dryness. Compared with placebo, application site reactions and withdrawals due to adverse events were higher with diclofenac 1.5% topical solution, but not with diclofenac 1.0% topical gel.

Oregon State University College of Pharmacy
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

Month/Year of Review: February 2012
PDL Class: Analgesics for Gout

Date of Last Review: Sept 2010
Source Document: Provider Synergies (PS)

Current Preferred Agents:
Allopurinol
Colchicine/probenecid

Current Non-Preferred Agents:
Colcyrs® (colchicine)
Probenecid
Uloric® (febuxostat)

Previous Recommendations:

1. There is moderate-quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
2. Colchicine is the only agent for gout and Famalial Mediterranean Fever.
3. Febuxostat reduces serum urate below 6mg/dl in a significantly greater proportion of patients with gout and hyperuricemia compared to patients receiving allopurinol but with no difference in gout flares.
4. Recommend inclusion of each chemical entity.
5. Consider PA for febuxostat for intolerance or ineffectiveness of allopurinol.

PA Criteria/QL: Patient must have a covered ICD9 diagnosis.

Background:

Treatment of gout is managed in three stages. Acute gout can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS), and intra-articular corticosteroid injections. After treatment of an initial gout attack, uricosuric drugs (probenecid) or xanthine oxidase inhibitors (allopurinol and febuxostat) can be used to lower uric acid to a goal of <6mg/dl. Febuxostat has not been studied in patients with secondary hyperuricemia and has not been shown to improve outcomes. It can be an alternative to allopurinol for patients who fail to achieve serum urate less than 6mg/dl after three months or are intolerant of allopurinol treatment. Pegloticase (Krystexxa), a pegylated uric acid specific enzyme, is the latest FDA approved agent and is indicated only for the management of refractory gout and administered intravenously. In clinical trials, pegloticase 8 mg administered intravenously every two weeks was shown to lower serum uric acid level and significantly improve a course of gout in patients with very severe and refractory disease. Due to the risk of anaphylaxis and infusion reactions, pegloticase should be administered intravenously under the supervision of a healthcare professional and should be billed under the Medical benefit. Its use should be restricted to patients who are refractory to conventional therapies such as oral allopurinol, probenecid and Uloric.

Methods:
A MEDLINE OVID search was conducted using all treatments for acute and chronic gout limited to randomized controlled trials and meta-analysis, English language, and conducted in humans since the literature search conducted for the previous PS review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:
A total of 41 citations resulted and after review for inclusions, three potentially relevant clinical trials were identified (Appendix 1). A randomized, double-blind study compared low-dose colchicine (1.2mg followed by 0.6mg one hour later) and high-dose colchicines (4.8 mg total over 6 hours) with placebo in gout flares, demonstrating superior safety of low-dose colchicine, without loss of efficacy, compared to high-dose.[1] Rates of response was defined by target joint pain score 24 hours after the first dose were similar for the recommended low-dose treatment group and the non-recommended high-dose group (high-dose vs. placebo, OR 2.64, 95% CI1.06-6.62, p=0.034; low-dose vs. placebo, OR 3.31 95% CI 4.41-7.77, p=0.005).[1] Patients in the high-dose group reported significantly more diarrhea, vomiting, and other adverse events (76.9% diarrhea, 19.2% severe diarrhea, OR 21.3, 95%CI 7.9-56) compared with the low-dose (23% diarrhea, no severe diarrhea, OR 1.9, 95% CI 0.8-4.8) and placebo groups. Another identified trial published the two randomized controlled trials which assessed the efficacy and safety of pegloticase (Krystexxa), the newest medication for treatment of gout.[2]

New drugs:

Pegloticase (Krystexxa) IV-
- Indication: The first pegylated uric acid specific enzyme approved for treatment of chronic gout in adults refractory to conventional therapy. It is not recommended in patients with asymptomatic hyperuricemia.
- Efficacy: The safety and efficacy of pegloticase 8mg every 2 weeks or every 4 weeks were evaluated in adult patients with chronic gout refractory to conventional therapy in two, randomized, placebo-controlled, double-blind, 6-month replicate studies.[2,3] All subjects were defined as having a uric acid level of 8mg/dl or higher, intolerance or failure of response to allopurinol treatment, and at least 1 of the following: 3 or more gouty attacks in the previous 18 months, a tophus or gouty arthritis. The primary endpoint in both trials was the proportion of responders, defined as patients achieving serum uric acid < 6 mg/dL for at least 80% of the time during Month 3 and Month 6.

Treatment Group	N	Number (%) with PUA levels less than 6 mg/dL	95% Confidence Interval*	P-Value#
Study 1 (C0405)	104			
Pegloticase 8 mg biweekly	43	20 (47%)	[32%, 61%]	< 0.001^
Pegloticase 8mg monthly	41	8 (20%)	[7%, 32%]	0.044^
Placebo	20	0 (0%)	--	--
Study 2 (C0406)	108			
Pegloticase 8 mg every 2 weeks	42	16 (33%)	[23%, 53%]	0.001^
Pegloticase 8 mg every 4 weeks	43	21 (49%)	[34%, 64%]	< 0.001^
Placebo	23	0 (0%)	--	--

*Confidence interval is for difference in responder rate between Krystexxa and placebo; ^Compared to placebo; #Composite P-Value (GOUT1 and GOUT2) is < 0.001 compared to placebo.

- Safety: Because of risks of hemolysis and methemoglobinemia, pegloticase is contraindicated in G6PD deficiency. Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy. Patients treated with pegloticase are at risk of anaphylaxis and must be pre-treated with antihistamines and corticosteroids (Black box warning). Risk of anaphylaxis is further increased in those with serum uric acid (SUA) levels above 6 mg/dL. Uric acid (UA) levels should be monitored prior to infusion with consideration of discontining pegloticase if UA levels increase above 6 mg/dL, particularly if two consecutive levels > 6 mg/dL are observed. In clinical trials, the most common serious adverse events (SAEs) noted were anaphylaxis (5%), infusion reactions (e.g., urticaria, dyspnea, chest discomfort, chest pain, erythema, pruritus)(26%), and gout flares in the first three months (77%).

Other adverse events occurring in ≥ 5% were: nausea and vomiting,, contusion or ecchymosis, nasopharyngitis, constipation, and chest pain.

- Dosing: 8mg IV over no less than 2 hours every 2 weeks; premedicate with antihistamines and corticosteroids. Pegloticase must be administered in a healthcare setting by a healthcare professional with appropriate medical therapy available in case there is an anaphylactic or infusion reaction

New FDA Indications:
None

New FDA safety alerts:
None

Other FDA alerts:
In 2010, the FDA stopped the marketing of unapproved single-ingredient oral colchicine.[4] This included all generic products. Colcrys is currently the only FDA-approved single-ingredient oral colchicine product available. Multisource colchicines products have not demonstrated bioequivalence to an innovator product and are not considered generics nor have the multisource products received Food and Drug Administration (FDA) approval.4

New Systematic Reviews:
None identified

Guidelines:
None identified.

Recommendations:
1. Since pegloticase is IV and only administered by a healthcare professional; no further research or review needed.

2. Block pegloticase claims billed by pharmacies.

Appendix 1:

1. Terkeltaub RA, Furst, DE, Bennett K, et al. High versus low dosing of oral colchicines for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicines study. *Arthritis Rheum.* 2010;62(4):1060-1068.

   Objective: Despite widespread use of colchicine, the evidence basis for oral colchicine therapy and dosing in acute gout remains limited. The aim of this trial was to compare low-dose colchicine (abbreviated at 1 hour) and high-dose colchicine (prolonged over 6 hours) with placebo in gout flare, using regimens producing comparable maximum plasma concentrations in healthy volunteers
   Methods: This multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared self-administered low-dose colchicine (1.8 mg total over 1 hour) and high-dose colchicine (4.8 mg total over 6 hours) with placebo. The primary end point was > or = 50% pain reduction at 24 hours without rescue medication.
   Results: There were 184 patients in the intent-to-treat analysis. Responders included 28 of 74 patients (37.8%) in the low-dose group, 17 of 52 patients (32.7%) in the high-dose group, and 9 of 58 patients (15.5%) in the placebo group (P = 0.005 and P = 0.034, respectively, versus placebo). Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose group (P = 0.027 versus placebo), 18 patients (34.6%) in the high-dose group (P = 0.103 versus placebo), and 29 patients (50.0%) in the placebo group. The low-dose group had an adverse event (AE) profile similar to that of the placebo group, with an odds ratio (OR) of 1.5 (95% confidence interval [95% CI] 0.7-3.2). High-dose colchicine was associated with significantly more diarrhea, vomiting, and other AEs compared with low-dose colchicine or placebo. With high-dose colchicine, 40 patients (76.9%) had diarrhea (OR 21.3 [95% CI 7.9-56.9]), 10 (19.2%) had severe diarrhea, and 9 (17.3%) had vomiting. With low-dose colchicine, 23.0% of the patients had diarrhea (OR 1.9 [95% CI 0.8-4.8]), none had severe diarrhea, and none had vomiting.
   Conclusion: Low-dose colchicine yielded both maximum plasma concentration and early gout flare efficacy comparable with that of high-dose colchicine, with a safety profile indistinguishable from that of placebo.

2. Wortmann RL, MacDonald PA, Hunt B, Jackson RL. Effect of Prophylaxis on Gout Flares After the Initiation of Urate-Lowering Therapy: Analysis of Data From Three Phase III Trials. *Clinical Therapeutics*. 2010;32(14):2386-2397.

   Objective: The present analysis examined flare rates during the 3 Phase III trials of febuxostat based on mean postbaseline serum urate (sUA) concentrations and duration of prophylaxis. Adverse events (AEs) were assessed by prophylaxis with colchicine or naproxen.
   Methods: This investigator-initiated, post hoc reanalysis of data on gout flares from the 3 randomized, placebo-controlled, Phase III trials evaluated the proportion of patients requiring treatment for gout flares at 4-week intervals based on mean postbaseline sUA concentrations <6.0 and ≥6.0 mg/dL. The 3 trials enrolled males or females aged 18–85 years who had a diagnosis of gout and a baseline sUA concentration ≥8.0 mg/dL. Patients received ULT (febuxostat or allopurinol) or placebo for 6 months or 1 year and flare prophylaxis with colchicine 0.6 mg/d or naproxen 250 mg BID for 8 weeks or 6 months. The prophylactic regimen was chosen at the discretion of the investigator, based on renal function and known intolerance to either drug. Patients with an estimated creatinine clearance <50 mL/min were not to receive naproxen. AEs were summarized based on prophylaxis with colchicine or naproxen.
   Results: The 3 trials enrolled a total of 4101 patients with gout. The majority were white (80.1%), male (94.5%), and obese (body mass index ≥30 kg/m2) (62.8%). The mean duration of gout ranged from 10.9–11.9 years, and the mean baseline sUA concentration ranged from 9.6–9.9 mg/dL. Flare rates increased sharply (up to 40%) at the end of 8 weeks of prophylaxis and then declined gradually, whereas flare rates were consistently low (range, 3%–5%) at the end of 6 months of prophylaxis. Mean postbaseline sUA concentrations were correlated with flare rates; by the end of each study, patients with a mean postbaseline sUA concentration <6.0 mg/dL had fewer flares than did those with a mean postbaseline sUA concentration ≥6.0 mg/dL. There were differences in rates of AEs between prophylaxis groups, but the rates did not increase with increased duration of prophylaxis.
   Conclusion: This analysis of gout flare data from the 3 Phase III trials of febuxostat found that flare prophylaxis for up to 6 months during the initiation of ULT appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in AEs.

3. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment. *JAMA: The Journal of the American Medical Association*. 2011;306(7):711 -720.

   Objective To assess the efficacy and tolerability of pegloticase in managing refractory chronic gout.

Design, Setting, and Patients Two replicate, randomized, double-blind, placebo-controlled trials (C0405 and C0406) were conducted between June 2006 and October 2007 at 56 rheumatology practices in the United States, Canada, and Mexico in patients with severe gout, allopurinol intolerance or refractoriness, and serum uric acid concentration of 8.0 mg/dL or greater. A total of 225 patients participated: 109 in trial C0405 and 116 in trial C0406.
Intervention Twelve biweekly intravenous infusions containing either pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase alternating with placebo at successive infusions (monthly treatment group), or placebo (placebo group).
Main Outcome Measure Primary end point was plasma uric acid levels of less than 6.0 mg/dL in months 3 and 6.
Results In trial C0405 the primary end point was reached in 20 of 43 patients in the biweekly group (47%; 95% CI, 31%-62%), 8 of 41 patients in the monthly group (20%; 95% CI, 9%-35%), and in 0 patients treated with placebo (0/20; 95% CI, 0%-17%; $P < .001$ and <.04 for comparisons between biweekly and monthly groups vs placebo, respectively). Among patients treated with pegloticase in trial C0406, 16 of 42 in the biweekly group (38%; 95% CI, 24%-54%) and 21 of 43 in the monthly group (49%; 95% CI, 33%-65%) achieved the primary end point; no placebo-treated patients reached the primary end point (0/23; 95% CI, 0%-15%; $P = .001$ and $< .001$, respectively). When data in the 2 trials were pooled, the primary end point was achieved in 36 of 85 patients in the biweekly group (42%; 95% CI, 32%-54%), 29 of 84 patients in the monthly group (35%; 95% CI, 24%-46%), and 0 of 43 patients in the placebo group (0%; 95% CI, 0%-8%; $P < .001$ for each comparison). Seven deaths (4 in patients receiving pegloticase and 3 in the placebo group) occurred between randomization and closure of the study database (February 15, 2008).
Conclusion Among patients with chronic gout, elevated serum uric acid level, and allopurinol intolerance or refractoriness, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower uric acid levels compared with placebo.

References:

1. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010;62(4):1060-1068.

2. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment. *JAMA: The Journal of the American Medical Association*. 2011;306(7):711 -720.

3. Center for Drug Evaluation and Research. Summary Review. application number125293. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125293Orig1s000SumR.pdf.

4. FDA news release. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227796.htm.

Oregon State University College of Pharmacy
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

Month/Year of Review: January 2012
PDL Class: Drugs for Alzheimer's disease (AD)

Date of Last Review: October 2006
Source Document: HRC Report

Current Preferred Agents:
Galantamine
Donepezil (Aricept®)
Memantine (Namenda®)

Current Non-Preferred Agents:
Rivastigmine (Exelon Patch®)
Donepezil ODT (Aricept ODT®)

Previous Recommendations

- There is insufficient evidence that any one of the AD drugs, donepezil, galantamine, rivastigmine, tacrine, or memantine is superior to the others in terms of efficacy or effectiveness.
- There is no evidence that any of the AD drugs prevent the progression of disability or delay institutionalization.
- Tacrine has an increased incidence of liver enzyme elevation compared to the other AD drugs.
- There is insufficient evidence that donepezil, galantamine, rivastigmine, or memantine has less adverse effects than each other.
- Memantine may have some pharmacological differences from the other medications, but there is inadequate data to conclude that these are clinically significant differences.

PA Criteria/QL:
Patient must have an OHP covered diagnosis

Methods:
A MEDLINE Ovid search was conducted using all treatments for AD and including: Alzheimer's Dementia, Alzheimer$, dementia$, anticholinergic agents, Anticholinergic$, donepezil, galantamine, memantine, rivastigmine. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from October 2009 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:
In April 2010, the AHRQ produced a comprehensive review of evidence based literature for Alzheimer's Dementia in preventing AD and cognitive decline (Appendix B).[1] This systematic review evaluated current evidence for interventions to prevent the onset of AD, as well as assessed research on risk factors and protective factors for the development of AD for possible development of recommendations for behavioral, lifestyle, or pharmaceutical interventions. This review did not evaluate treatment strategies or tolerability in established AD or treating symptoms associated with AD. Cholinesterase inhibitors were evaluated for any effect on the progression to AD or dementia as well as the ability to maintain or improve cognitive ability in patients who met diagnostic criteria for mild cognitive impairment. However, evidence was insufficient to currently support the use of pharmaceutical agents to prevent cognitive decline or onset of AD.