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, November 29, 2012 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff.

I. CALL TO ORDER
- 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. HERC COVERAGE GUIDANCE
- a. ADHD Draft Coverage Guidance — C. Livingston (HERC)
- b. Therapies With Marginal Benefit and/or High Cost
- c. Public Comment

III. DUR ACTIVITIES
- a. ProDUR Report — R. Holsapple (HP)
- b. RetroDUR Report — T. Williams (OSU)
- c. Quarterly Utilization Reports — R. Citron (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
  1. *Do Spinosad or Ivermectin Have a Place in Head Lice Eradication?*
- e. Low Dose Aripiprazole (Abilify®) Education Proposal — A. Burns (OSU)

IV. OLD BUSINESS
- a. Vascular Endothelial Growth Factors (VEGF) Inhibitors* — M. Herink (OSU)
  1. Retisert New Drug Evaluation
  2. Class Update (new Lucentis 0.3 strength)
  3. Proposed PA criteria
  4. Public Comment
  5. Discussion of clinical recommendations to OHA
- b. Erythropoiesis Stimulating Agents* — M. Herink (OSU)
  1. Proposed PA Criteria Update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- c. Phosphate Binders* — K. Ketchum (OSU)
  1. Executive Session Follow-up
  2. Discussion of clinical recommendations to OHA
- d. DPP-4 Inhibitors* — K. Ketchum (OSU)
  1. Executive Session Follow-up
  2. Discussion of clinical recommendations to OHA

**Agenda items 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

a. Physician Administered Drugs* — K. Ketchum (OSU)
   1. Drug Use Evaluation
   2. Public Comment
   3. Discussion of clinical recommendations to OHA

b. Obesity Drugs* — M. Herink (OSU)
   1. Lorcaserin New Drug Evaluation
   2. Phentermine/Topiramate New Drug Evaluation
   3. Public Comment
   4. Discussion of clinical recommendations to OHA

c. Benign Prostatic Hypertrophy* — M. Herink (OSU)
   1. Abbreviated Class Update
   2. Updated PA Criteria
   3. Public Comment
   4. Discussion of clinical recommendations to OHA

d. Pancreatic Enzyme Replacement Products* — B. Fouts (OSU)
   1. Abbreviated Class Review
   2. Public Comment
   3. Discussion of clinical recommendations to OHA

e. Drug Class Scans* — M. Herink (OSU)
   1. Estrogens
   2. Cephalosporins
   3. Ophthalmic Antibiotic-Steroid Combinations
   4. Public Comment
   5. Discussion of clinical recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

**Agenda items 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)*

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, September 27, 2012 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

Members Present: Andris Antoniskis, MD; Zahia Esber, MD; Tracy Klein, PhD, FNP; Phillip Levine, PhD; William Origer, MD; David Pass, MD; Cathy Zehrung, RPh
Members Present by Phone: James Slater, PharmD
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA:HA; Ted Williams, PharmD; Valerie Smith; Richard Holsapple, RPh; Trevor Douglass, DC, MPH; Israel Harden; Amy Burns, PharmD
Staff Present by Phone: Kathy Sentena, PharmD
Audience: David Barhoum (Genentech); Sean Murphy (Genentech); Brady Blaser (Genentech); Jim Graves (BMS); Kim Laubmeier (Otsuka); Michelle Mattox (Vertex); Gregg Rasmussen (Vertex); Paul Bonham (NovoNordisk); Bobon Guty (Lundbeck); Deron Grothe (Teva); Cary Eastman; Shane Hall (Purdue); Venus Holder (Lilly); Jeana Colabianchi (Sunovion); Linda Craig (AZ); Michel Estuis (Pfizer); Bruce Smith (GSK); Jamie Damm (Vertex); Don Stecher (Novartis); Mary Kemhus (Novartis); Steve Faloon (Otsuka); Todd Landwehr

I. CALL TO ORDER
a. The meeting was called to order at approximately 1pm.
b. Conflict of interest declarations were reviewed; no new conflicts were reported.
c. The minutes from the August 30, 2012 meeting were reviewed.

ACTION: The minutes were approved with the addition of Phillip Levine, PhD in the Members Present section of the minutes.

II. NEW BUSINESS
a. Dr. Herink presented an abbreviated drug evaluation on hypertonic saline use for cystic fibrosis patients and presented additional requested information on dornase alfa therapy past 2 years. Recommendations were that inhaled hypertonic saline be preferred, and to make dornase alfa preferred with a quantity limit of 30 vials per 30 days.

***ACTION:** The committee approved the recommendations after Executive Session.
b. Ms. Ketchum presented an abbreviated class update on bone metabolism agents, recommending that tiludronate, alendronate with vitamin D3, zoledronic acid and denosumab be non-preferred and make risedronate preferred. Ms. Ketchum also recommended limiting zoledronic acid to medical claims and a RetroDUR intervention of bisphosphonates to notify clinicians to re-evaluate patient FRAX score after 5 years of therapy.

***ACTION:** The committee approved the recommendations after Executive Session.
c. Dr. Burns presented an abbreviated class update on colony stimulating factors, recommending that all drugs continue to be listed as preferred and evaluate use of

**Agenda items 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)*

CSFs for hepatitis C and if inappropriate use is noted, bring back recommendation of prior authorization criteria for consideration.

***ACTION:** The committee approved the recommendations after Executive Session.

d. Dr. Sentena presented an abbreviated class review on intravenous/sub-Q Pulmonary Arterial Hypertension (PAH) agents, recommending that all IV/SQ products be made non-preferred and require prior authorization to include: diagnosis of PAH with NYHA functional class III or IV and prescribed in consultation with a specialist (pulmonologist or cardiologist), and make tadalafil non-preferred when sildenafil generics warrant a change.

***ACTION:** The committee approved the recommendations after Executive Session.

e. Dr. Herink presented drug class scans:

1. Growth hormone, recommending Omnitrope be preferred, Nutropin and Genotropin be non-preferred and stop grandfathering non-preferred products as of January 1, 2013. Sean Murphy with Genentech provided public comment.

***ACTION:** The committee approved the recommendations after Executive Session.

2. Ulcerative colitis, recommending Canasa suppository and generic balsalazide be made preferred and mesalamine rectal enemas and kits be non-preferred.

***ACTION:** The committee approved the recommendations after Executive Session.

3. Ophthalmic antibiotics, recommending Ciloxan ointment be preferred, levofloxican drops be non-preferred, and maintain Moxeza as non-preferred.

***ACTION:** The committee approved the recommendations after Executive Session.

4. Phosphate binders, recommending Renagel and Calphron be preferred.

***ACTION:** The committee deferred the recommendation until the November meeting.

f. Ms. Ketchum presented the annual PDL review:

1. Recommended changes to the Antipsychotics- 2nd Generation class include making olanzapine preferred on the voluntary mental health PDL, removing risperidone rapid dissolving tabs from the voluntary mental health PDL, and consider restricting IM products to medical claims only.

***ACTION:** The committee approved the recommendations for PDL updates, and deferred restricting IM products until an evaluation of current billing practices can be done.

2. Recommended changes to the ADHD class include making Focalin XR preferred, making Concerta and Ritalin LA and their generic equivalents non-preferred, and perform DUE of appropriate use of the class, appoint an ad-hoc expert and bring back to November meeting.

***ACTION:** The committee approved the recommendations after Executive Session.

3. Recommended changes to the Hepatitis C (peginterferons) class include making Pegasys non-preferred and grandfather current patients and perfom a RetroDUR outreach to high volume prescribers. Recommended that no change be made to the current PDL status or clinical PA edits for protease inhibitors.

***ACTION:** The committee approved the recommendations after Executive Session.

4. The Hematopoietic Agents class was reviewed and recommendations were made at the August 30, 2012 meeting so there are no new actions.

5. Recommended changes to the Asthma Controllers class include making Asmanex non-preferred, make Alvesco preferred as an ICS alternative, and adding Advair, Dulera and Symbicort as preferred ICS/LABA combination agents with step edit and pending SSDC negotiations.

***ACTION:** The committee approved the recommendations after Executive Session.

6. Recommended changes to the Insulins class include making insulin detemir (Levemir) preferred.

***ACTION:** The committee approved the recommendations after Executive Session.

**Agenda items 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)*

7. Recommended changes to the Other Lipotropics class include making Antara, Tricor and gemfibrozil preferred and make all other fibrates non-preferred. No changes to the other drugs in the class

***ACTION:** The committee approved the recommendations after Executive Session.

8. Recommended changes to the DPP-4 Inhibitors class include listing no drugs as preferred and continue with current clinical PA criteria.

***ACTION:** The committee deferred the recommendation until the November meeting.

9. Recommended no changes to the DRIs, ACE-Is and ARBs class at this time and revisit when multiple generic ARBs become available.

***ACTION:** The committee approved the recommendations after Executive Session.

10. Recommended no changes to the DRIs, ACE-Is and ARBs + HCT class at this time and revisit when multiple generic ARBs become available.

***ACTION:** The committee approved the recommendations after Executive Session.

11. Recommended changes to the Otic Antibiotics class include making Ciprodex non-preferred.

***ACTION:** The committee approved the recommendations after Executive Session.

12. Recommended changes to the Topical Antiprasitics include making Natroba preferred with step therapy use of OTC permethrin first.

***ACTION:** The committee approved the recommendations after Executive Session.

III. The meeting adjourned at approximately 3:45pm.

**Agenda items 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)*

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

DATE: XX/XX/XXXX

HERC COVERAGE GUIDANCE

For children under 6 with disruptive behavior disorders, including those at risk for ADHD, specific parent behavior training* should be covered as first-line therapy. Pharmacotherapy** should be considered second line, with weighing of the benefits and harms to determine if it is appropriate for an individual child.

For children 6 and over with ADHD, pharmacotherapy** alone or pharmacotherapy** with behavioral treatment are considered first-line therapy and should be covered.

*Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program

**Limited to medications that are FDA-approved for the condition

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. In addition to an evidence-based guideline developed by the Evidence-based Guideline Subcommittee and a health technology assessment developed by the Heath Technology Assessment Subcommittee, coverage guidance may utilize an existing evidence report produced in the last 5 years by the Agency for Healthcare Research and Quality, the Medicaid Evidence-based Decisions Project or the Washington Health Technology Assessment Program.

EVIDENCE SOURCE

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, overactivity, and impulsivity. While ADHD can begin before children enter school, it is most commonly identified and treated in primary school. Boys are classified with ADHD approximately twice as frequently as girls, and primary school–age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a "disorder" to a greater or lesser degree. Symptoms are clinically significant when they cause impaired functioning. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive.

Although the condition now classified as ADHD was first described clinically in 1902, few treatments were available until the 1950s, when methylphenidate (brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder. The diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America. By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002% of the U.S. child population at that time. In contrast, the U.S. National Survey of Child Health provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8% of that population, of which 2.5 million (56%) were receiving medication. Within the United States, the estimated prevalence of adult ADHD stands at 4.4%. Prescriptions for the treatment of ADHD have increased as well, with methylphenidate prescriptions increasing from 4 million to 11 million, and prescriptions for amphetamines increasing from 1.3 million to 6 million in an eight year period of time (1991-1999).

Drugs currently FDA approved for treatment of ADHD and their maximum recommended daily dosages are listed in Table 1. In addition, a variety of antidepressants are used off-label to treat this condition.

Table 1. FDA Approved Medications for the Treatment of ADHD

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
Amphetamine preparations		
Mixed amphetamine salts	Adderall	40mg
	Adderall XR	30mg
Dextroamphetamine	Dexedrine, Dextrostat	40mg
	Dexedrine spanule	40 mg
Lisdexamfetamine	Vyvanse	70mg
Methylphenidate preparations		
Dexmethylphenidate	Focalin	20mg
	Focalin XR	30mg
Methylphenidate HCL	Methylin, Ritalin, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER	60mg
	Daytrana	30mg
	Concerta	72mg
SNRIs		
Atomoxetine	Strattera	1.4mg/kg or 100mg
Other		
Guanfacine extended release	Intuniv	4mg
Clonidine extended release	Kapvay	0.4mg/day

Evidence Review

The purpose of this review is to critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD and to similarly examine the comparative long-term effectiveness and adverse events of interventions for ADHD.

Treatment of Preschoolers with Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD[1], evidence was grouped into two broad categories of treatment: behavioral interventions and psychostimulant medication. A total of 31 studies evaluated parent behavior training, which was primarily defined as one of four manualized programs[2]. Nearly all studies showed positive effects, and pooled results for eight good-quality studies also found a significant improvement in child behavior with parent behavior training. In addition, the single good-quality study of methylphenidate finds that it appears to be effective. The strength of evidence for use of parent behavior training was judged high due to number of studies and consistency of results. The strength of evidence for methylphenidate was judged low because there is only one good-quality study.

Long-term extension (follow-up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years, although no long-term study (lasting 12 months or more) of parent behavior training alone included untreated comparison groups, and attrition was high. A recent study examining parent behavior training with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of parent behavior training at two years. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorder and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources, although direct comparisons of identical interventions offered to families of different SES have not yet been performed. All behavioral interventions showed benefits relative to no-treatment controls, and a dose response to the number of parent behavior training sessions attended by parents was also identified, enhancing the overall strength of evidence for effectiveness of parent behavior training.

Several small, short-term trials of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe. In addition, the Preschool ADHD Treatment Study (PATS), a large, high quality trial funded by the National Institute of Mental Health also suggests that methylphenidate is effective for improving parent-rated child behavior in preschoolers. This multisite trial had multiple phases, beginning with 10 sessions of parent behavior training. The training was followed by an open label safety lead-in phase of a psychostimulant medication, then a titration phase, a cross-over phase and open-label maintenance phase that lasted 10 months. The PATS study offers information about both the potential benefits and

[1] The ADHD diagnosis has not been widely applied in children under age 6 because of uncertainty regarding the reliability and validity of the diagnostic criteria in this age group. Because ADHD in this age group is commonly identified in the context of other disruptive behaviors, and in children with diagnoses of Disruptive Behavior Disorders including Oppositional Defiant Disorder and Conduct Disorder, the evidence review includes studies of children less than six with Disruptive Behavior Disorders.
[2] Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program.

limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth, and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication. These findings are supported by two additional “fair” quality RCTs.

In conclusion, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. This favors the use of parent behavior training for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents
The long-term effectiveness and safety (at least 12 months of treatment and/or follow up) of several psychostimulants (e.g., methylphenidate immediate release amphetamine, Osmotic-controlled Release Oral delivery System methylphenidate, dextroamphetamine, mixed amphetamine salts, atomoxetine, clonidine and guanfacine extended release) have all been examined prospectively in children and adolescents age 6 and over. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to three years, and few serious adverse events were noted, although guanfacine extended release appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry (12 of 21), there may be enhanced representations of effectiveness and safety. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time.

Fewer children experienced adverse events with methylphenidate than with dextroamphetamine. Concerns about adverse events led to discontinuation of medications for 15% to 20% of children age 6 and over using extended release mixed amphetamine salts. Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small. Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs. There are many similarities between methylphenidate immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to three years in adults. Discontinuation in children and teens appears to be higher (26%) due to ineffectiveness and lower (3%) due to adverse

events than with other agents, although these are not direct comparisons. As with psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases. There is only one study of a pharmacologic intervention over an extended time period (three years) in adults with ADHD, and that study found symptom improvement was maintained for those on atomoxetine, and discontinuation due to adverse events was somewhat higher for adults (11%) than for children (3%).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to two years; however, high rates (40% to 60%) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial six to eight months of treatment. A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects. Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia. Serious adverse events include syncope clinically significant changes on electrocardiogram.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved.

Psychosocial and Behavioral Interventions, Alone and in Combination with Medication
Investigations comparing psychosocial/behavioral interventions, alone and in combination with psychostimulant medication management, showed that both medication and combined medication/behavioral treatment are more effective in treating ADHD and oppositional defiant disorder symptoms than psychosocial or behavioral interventions alone.

Longer Term Outcomes
Evaluation of long-term outcomes (five or more years follow up) following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7 to 9 years with DSM-IV ADHD, combined subtype. The best quality data come from the Multimodal Treatment of ADHD Study, which compared 14 months of management with immediate release methylphenidate to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. No clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at three years or beyond. In contrast, a few long-term cohort studies lasting five years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement. No prospective studies have been designed to investigate the question of long-term functional outcomes directly. There appear to be long-term academic benefits with medication interventions in some domains.

In conclusion, the evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate and a

single good study for atomoxetine. These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions. The evidence for other pharmaceutical agents is insufficient, as is the evidence pertaining to parent behavior training and academic interventions.

[Evidence Source]

Overall Summary

Both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. There is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with psychosocial interventions, in children age six and over. There is evidence for only the short-term effectiveness for other FDA approved medications and guanfacine, the latter of which has more frequent adverse events.

PROCEDURE

Parent behavior training
Medication management

DIAGNOSES

Attention Deficit Hyperactivity Disorder

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
312.9	Unspecified disturbance of conduct
314	Hyperkinetic syndrome of childhood
314.0	Attention deficit disorder of childhood
314.00	Attention deficit disorder without mention of hyperactivity
314.01	Attention deficit disorder with hyperactivity
314.1	Hyperkinesis with developmental delay
314.2	Hyperkinetic conduct disorder
314.8	Other specified manifestations of hyperkinetic syndrome
314.9	Unspecified hyperkinetic syndrome
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
90862	Pharmacologic management, including prescription, use, and review of medication with now more than minimal medical psychotherapy
98960	Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient

CODES	DESCRIPTION
	(could include caregiver/family) each 30 minutes; individual patient
98961	2-4 patients
98962	5-8 patients
99201	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 20 minutes face-to-face with the patient and/or family.
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 45 minutes face-to-face with the patient and/or family.
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 10 minutes face-to-face with the patient and/or family.

CODES	DESCRIPTION
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 25 minutes face-to-face with the patient and/or family.
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99241	Office consultation for a new or established patient, which requires these 3 key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self limited or minor. Physicians typically spend 15 minutes face-to-face with the patient and/or family.
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low severity. Physicians typically spend 30 minutes face-to-face with the patient and/or family.
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate severity. Physicians typically spend 40 minutes face-to-face with the patient and/or family.
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 60 minutes face-to-face with the patient and/or family.

CODES	DESCRIPTION
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other providers or agencies are provided consistent with the nature of the problems(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Physicians typically spend 80 minutes face-to-face with the patient and/or family.
HCPCS Codes	
S9444	Parenting classes, non-physician provider, per session
T1027	Family training and counseling for child development, per 15 minutes

Note: Inclusion on this list does not guarantee coverage

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Therapies with marginal benefit and/or high cost issue summary

Question: Shall a guideline be adopted dealing with therapies with marginal benefit and high cost?

Question Source: HERC Staff, P&T Committee

Issue Summary: A number of recent issues have come up in which there are decisions around therapies that have marginal benefit and very high cost. HERC staff has been working with the Pharmacy and Therapeutics (P&T) Committee on how the Prioritized List interfaces with the work of the P&T committee.

Historically, when there is a condition with treatments that have significantly different cost-effectiveness or marginal benefit, HERC has chosen to prioritized treatments both above and below the funded region of the List or not put the treatment of questionable benefit on the List at all. P&T is performing assessments on benefit as well as cost for a number of medications and interventions. HERC could potentially refer to assessments completed by the P&T as it relates to the Prioritized List. In this way, the principles for prioritization can take into account evidence and cost-effectiveness research that the P&T committee performs.

The Prioritized List currently has a guideline that provides broad-based principles for cancer treatment at the end of life with marginal benefit and may serve as a model for developing a guideline of other treatments of little or no benefit and/or high cost.

GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT PROVIDED NEAR THE END OF LIFE

Lines 102,103,123-125,144,159,165,166,170,181,197,198,207,208,218,220,221,228,229,231,243,249,252,275-278,280,287,292,310-312,320,339-341,356,459,586,622

This guideline only applies to patients with advanced cancer who have less than 24 months median survival with treatment.

All patients receiving end of life care, either with the intent to prolong survival or with the intent to palliate symptoms, should have/be engaged with palliative care providers (for example, have a palliative care consult or be enrolled in a palliative care program).

Treatment with intent to prolong survival is not a covered service for patients with any of the following:

- Median survival of less than 6 months with or without treatment, as supported by the best available published evidence
- Median survival with treatment of 6-12 months when the treatment is expected to improve median survival by less than 50%, as supported by the best available published evidence
- Median survival with treatment of more than 12 months when the treatment is expected to improve median survival by less than 30%, as supported by the best available published evidence

- Poor prognosis with treatment, due to limited physical reserve or the ability to withstand treatment regimen, as indicated by low performance status.

Unpublished evidence may be taken into consideration in the case of rare cancers which are universally fatal within six months without treatment.

The Health Evidence Review Commission is reluctant to place a strict $/QALY (quality adjusted life-year) or $/LYS (life-year saved) requirement on end-of-life treatments, as such measurements are only approximations and cannot take into account all of the merits of an individual case. However, cost must be taken into consideration when considering treatment options near the end of life. For example, in no instance can it be justified to spend $100,000 in public resources to increase an individual's expected survival by three months when hundreds of thousands of Oregonians are without any form of health insurance.

Treatment with the goal to palliate is addressed in Statement of Intent 1, Palliative Care.

HERC Staff Recommendation:

1) Discuss general framework of THERAPIES WITH MARGINAL BENEFIT AND/OR HIGH COST

   Therapies prioritized lower include those with:

   i. Marginal or subclinical benefit,
   ii. Very high cost in which the cost does not justify the benefit, and
   iii. Equivalent efficacy to a therapy prioritized higher, that are significantly more costly.

   Additional specific therapies considered to be prioritized lower are those found by the Pharmacy and Therapeutics Committee to be of marginal benefit and/or poor cost-effectiveness found in Table XX located at www… (e.g. *as of October 1, 2013*).

ProDUR Report for August 2012- October 2012

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	62,365	18,802	557	42,904	66.20%
PG (Pregnancy/Drug Interaction)	3,595	2,460	16	1,112	3.80%
ID (Ingredient Duplication)	15,602	5,913	87	9,512	16.67%
TD (Therapeutic Duplication)	6,605	2,697	23	3,796	6.97%

Summary of Override Codes by DUR Alert

DUR Alert	1A False Positive	1B Filled As Is	1C Different Dose	1D Different Directions	1E Different Drug	1F Different Quantity	1G Prescriber Approval	Totals
ER Total	**262**	**14,268**	**1,354**	**471**	**31**	**0**	**2,416**	**18,802**
ER (Prescriber Consulted)	167	5,197	359	269	6	0	2,105	8,103
ER (Patient Consulted)	11	607	2	17	1	0	5	643
ER (Other Consulted)	84	8,464	993	185	24	0	306	10,056
PG Total	**106**	**2,090**	**5**	**9**	**1**	**0**	**249**	**2,460**
PG (Prescriber Consulted)	33	764	3	8	0	0	236	1,044
PG (Patient Consulted)	31	328	0	1	0	0	3	363
PG (Other Consulted)	42	998	2	0	1	0	10	1,053
ID Total	**73**	**4,481**	**404**	**108**	**16**	**0**	**831**	**5,913**
ID (Prescriber Consulted)	50	1,558	108	65	4	0	730	2,515
ID (Patient Consulted)	4	169	1	2	1	0	0	177
ID (Other Consulted)	19	2,754	295	41	11	0	101	3,221
TD Total	**21**	**1,984**	**211**	**69**	**11**	**0**	**401**	**2,697**
TD (Prescriber Consulted)	12	688	63	49	4	0	358	1,174
TD (Patient Consulted)	2	79	0	0	0	0	0	81
TD (Other Consulted)	7	1,217	148	20	7	0	43	1,442

ProDUR Report for August 2012- October 2012							
Top Drugs in Enforced DUR Alerts							
DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Oxycodone HCl	326	164	158	4,566	7.1%	50.3%
	Clonazepam	781	286	492	7,182	10.9%	36.6%
	Lorazepam	2,863	1,035	1,824	32,466	8.8%	36.2%
	Gabapentin	549	197	352	3,944	13.9%	35.9%
	Hydrocodone Bit/APAP	552	192	360	10,349	5.3%	34.8%
	Zyprexa (Olanzapine)	1,196	415	770	9,475	12.6%	34.7%
	Risperdal (Risperidone)	1,942	673	1,267	15,049	12.9%	34.7%
	Geodon (Ziprasidone)	670	219	448	5,350	12.5%	32.7%
	Depakote (Divalproex Sodium)	1,337	433	898	11,556	11.6%	32.4%
	Lithium Carbonate	792	255	537	6,277	12.6%	32.2%
	Diazepam	1,107	345	762	14,054	7.9%	31.2%
	Seroquel (Quetiapine)	2,154	658	1,489	16,446	13.1%	30.5%
	Lamictal (Lamotrigine)	2,189	666	1,519	18,021	12.1%	30.4%
	Alprazolam	1,993	584	1,408	21,901	9.1%	29.3%
	Albuterol	507	145	362	8,012	6.3%	28.6%
	Buspar (Buspirone)	758	211	546	8,401	9.0%	27.8%
	Abilify (Aripiprazole)	1,774	492	1,282	14,371	12.3%	27.7%
	Prilosec (Omeprazole)	515	140	375	6,636	7.8%	27.2%
	Paxil (Paroxetine)	863	230	633	8,921	9.7%	26.7%
	Effexor (Venlafaxine)	1,079	283	796	11,788	9.2%	26.2%
	Trazodone	3,316	862	2,453	29,141	11.4%	26.0%
	Zoloft (Sertraline)	2,774	710	2,062	25,161	11.0%	25.6%
	Prozac (Fluoxetine)	2,191	556	1,635	22,411	9.8%	25.4%
	Lexapro (Escitaloprim)	1,185	292	893	12,053	9.8%	24.6%
	Amitriptyline	1,379	337	1,042	14,578	9.5%	24.4%
	Cymbalta (Duloxetine)	1,604	382	1,221	16,906	9.5%	23.8%
	Remeron (Mirtazapine)	628	148	480	5,407	11.6%	23.6%
	Wellbutrin (Bupropion)	2,025	465	1,559	20,956	9.7%	23.0%
	Celexa (Citalopram)	2,541	576	1,963	25,583	9.9%	22.7%
	Straterra (Atomoxetine)	588	131	457	6,504	9.0%	22.3%
PG	Ibuprofen	673	535	137	4,726	14.2%	79.5%
	Lorazepam	367	290	76	32,466	1.1%	79.0%
	Norethindrone	223	172	51	736	30.3%	77.1%
	Alprazolam	322	248	74	21,901	1.5%	77.0%
	Paroxetine	137	103	34	8,921	1.5%	75.2%

Early Refill (Overutilization)

In Process: MMIS project underway to activate and require a clarification code from pharmacy when overriding an early refill ProDUR alert. Values include:

3= Vacation supply - The pharmacist is indicating that the cardholder has requested a vacation supply of the medication.
4= Lost prescription - The pharmacist is indicating that the cardholder has requested a replacement of medication that has been lost.
5= Therapy change - The pharmacist is indicating that the physician has determined that a change in therapy was required; either the medication was used faster than expected or a different dosage form is needed, etc.
6= Starter dose - The pharmacist is indicating that the previous medication was a starter dose and now additional medication is needed to continue treatment.
7= Medically necessary - The pharmacist is indicating that this medication has been determined by the physician to be medically necessary.
13=Payer-Recognized Emergency/Disaster Assistance Request-The pharmacist is indicating that an override is needed based on an emergency/disaster situation recognized by the payer.
14=Long Term Care Leave of Absence - The pharmacist is indicating that the cardholder requires a short-fill of a prescription due to a leave of absence from the Long Term Care (LTC) facility.

Plan: An analysis of submission clarification code use will be presented to P&T and decision about limiting overrides for certain situations will be discussed.

Pediatric Psychotropic Screening Criteria and Review Outcomes

As of: 8/2/2012

Level	Criteria	Foster Children			Non-Foster Children		
		Receiving Psychotropic		Overall	Receiving Psychotropic		Overall
		#	%	%	#	%	%
3	5 Or More Psychotropics	59	3.98%	0.92%	180	1.71%	0.05%
3	4 psychotropics	98	6.62%	1.52%	387	3.68%	0.12%
3	3 Psychotropics	201	13.57%	3.12%	999	9.50%	0.31%
3	2 or more antipsychotics	49	3.31%	0.76%	130	1.24%	0.04%
3	Too young for otherwise appropriate therapy ORS 418.517 Section 1 (3)	80	5.40%	1.24%	435	4.14%	0.13%
3	No diagnosis with an approved pharmacotherapy ORS 418.517 Section 1	2	0.14%	0.03%	32	0.30%	<0.01%
3	No age appropriate indication ORS 418.517 Section 1 (3)	930	62.80%	14.45%	5,724	54.42%	1.75%
3	No Mental Health Services for 18 months	254	17.15%	3.95%	4,468	42.48%	1.36%
2	Medication Without Approved Use in Children ORS 418.517 Section 1 (3)	181	12.22%	2.81%	1,355	12.88%	0.41%
2	Antipsychotic without Annual Lipid Monitoring	630	42.54%	9.79%	2,572	24.45%	0.79%
2	Antipsychotic without Annual Glucose Monitoring	303	20.46%	4.71%	1,432	13.61%	0.44%
2	Lithium without adequate monitoring (annual Li, SCr, TSH)	8	0.54%	0.12%	38	0.36%	0.01%
1	Appropriate Psychotropic Therapy - No exception criteria met	308	20.80%	4.78%	2,166	20.59%	0.66%

Total Foster Children Receiving Psychotropics:	1,481
Total Foster Children:	6,438
Total Non-Foster Children Receiving Psychotropics:	10,519
Total Non-Foster Children	327,408

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 40 Drugs (brand name) - Third Quarter 2012

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**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	ABILIFY	$3.69	$3.48	6.1%	0.55	0.58	-5.5%	$671	$598	12.3%
2	11	CYMBALTA	$1.70	$1.40	21.4%	0.71	0.68	4.2%	$240	$206	16.5%
3	10	METHYLPHENIDATE ER	$1.37	$1.29	5.5%	0.80	0.74	7.7%	$171	$175	-2.1%
4	71	REMODULIN	$1.32	$1.55	-14.9%	0.00	0.01	-33.3%	$27,587	$21,525	28.2%
5	33	ATRIPLA	$0.75	$1.35	-44.9%	0.04	0.08	-48.0%	$1,695	$1,600	5.9%
6	15	PROAIR HFA	$0.74	$0.50	46.9%	1.35	0.97	38.3%	$55	$52	6.2%
7	33	TRUVADA	$0.73	$1.08	-32.6%	0.07	0.12	-42.3%	$1,091	$935	16.7%
8	58	LANTUS	$0.70	$0.61	15.1%	0.31	0.31	-1.3%	$225	$193	16.7%
9	42	HUMIRA	$0.66	$0.51	29.3%	0.03	0.03	8.5%	$2,180	$1,827	19.3%
10	7	SEROQUEL XR	$0.63	$0.56	12.8%	0.13	0.14	-6.1%	$469.16	$390.73	20.1%
11	40	OXYCONTIN	$0.60	$1.25	-51.9%	0.12	0.27	-54.7%	$484.34	$457.32	5.9%
12	99	PULMOZYME	$0.55	$0.40	38.7%	0.02	0.02	21.0%	$2,471.80	$2,155.00	14.7%
13	7	GEODON	$0.54	$0.92	-41.5%	0.11	0.20	-41.8%	$468.69	$466.42	0.5%
14	11	STRATTERA	$0.53	$0.55	-4.5%	0.24	0.26	-10.3%	$221	$208	6.4%
15	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.48	$0.41	16.1%	0.27	0.22	25.2%	$174	$187	-7.3%
16	51	FLOVENT HFA	$0.46	$0.45	2.2%	0.28	0.27	2.5%	$167.45	$168.18	-0.4%
17	11	INTUNIV	$0.45	$0.29	53.8%	0.22	0.16	35.2%	$201.60	$177.26	13.7%
18	11	LEXAPRO	$0.44	$0.60	-27.4%	0.30	0.48	-38.0%	$145.48	$124.25	17.1%
19	15	ADVAIR DISKUS	$0.43	$0.70	-37.8%	0.17	0.29	-42.4%	$262.43	$243.14	7.9%
20	15	SINGULAIR	$0.43	$0.80	-46.4%	0.27	0.52	-48.7%	$161.53	$154.88	4.3%
21	40	HYDROCODONE-ACETAMINOPHEN	$0.42	$0.46	-8.2%	2.84	3.20	-11.2%	$14.75	$14.27	3.4%
22	42	ENBREL	$0.41	$0.51	-19.5%	0.02	0.03	-28.4%	$1,974.94	$1,757.06	12.4%
23	23	TOBI	$0.40	$0.27	48.2%	0.01	0.01	13.8%	$5,110.74	$3,927.10	30.1%
24	12	VYVANSE	$0.39	$0.35	13.4%	0.24	0.21	10.0%	$167.05	$162.05	3.1%
25	58	NOVOLOG	$0.38	$0.39	-3.1%	0.15	0.17	-10.9%	$242.45	$222.78	8.8%
26	15	COMBIVENT	$0.36	$0.39	-7.3%	0.17	0.19	-11.6%	$217.67	$207.54	4.9%
27	15	SPIRIVA	$0.36	$0.38	-4.4%	0.14	0.16	-11.4%	$256.48	$237.62	7.9%
28	30	REVLIMID	$0.35	$0.11	229.9%	0.00	0.00	103.9%	$8,044.89	$4,985.09	61.4%
29	33	REYATAZ	$0.35	$0.53	-34.5%	0.04	0.07	-44.1%	$929.14	$791.95	17.3%
30	30	XELODA	$0.34	$0.21	59.7%	0.01	0.01	17.7%	$2,446.05	$1,800.18	35.9%
31	58	HUMALOG	$0.34	$0.32	6.2%	0.14	0.13	2.4%	$248.90	$239.86	3.8%
32	1	OMEPRAZOLE	$0.32	$0.33	-2.1%	1.78	1.77	0.6%	$18.15	$18.66	-2.7%
33	7	INVEGA SUSTENNA	$0.31	$0.22	41.3%	0.03	0.02	35.3%	$1,198.06	$1,147.18	4.4%
34	77	LOVENOX	$0.31	$0.15	101.5%	0.03	0.02	49.8%	$1,096.25	$816.51	34.3%
35	11	MODAFINIL	$0.27			0.03			$957.10		
36	33	ISENTRESS	$0.26	$0.36	-26.6%	0.03	0.04	-29.9%	$993.90	$946.93	5.0%
37	69	CREON	$0.26	$0.32	-20.5%	0.03	0.03	-4.9%	$955.36	$1,143.11	-16.4%
38	7	INVEGA	$0.26	$0.25	3.4%	0.04	0.05	-13.2%	$649.08	$544.80	19.1%
39	40	OXYCODONE HCL	$0.24	$0.32	-24.2%	1.08	1.24	-13.3%	$22.56	$25.81	-12.6%
40	33	PREZISTA	$0.24	$0.22	9.7%	0.02	0.02	10.2%	$959.97	$965.12	-0.5%
		Aggregate	$53.12	$61.29	-13.3%	97.21	103.82	-6.4%	$66	$77	-15.3%
		75th Percentile			22.1%			13.8%			12.0%
		50th Percentile (Median)			-8.9%			-7.8%			0.0%

Last updated: October 22, 2012

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 – Third Quarter 2012

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**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	Ataractics, Tranquilizers	$7.31	$11.21	-34.8%	6.0	6.3	-5.4%	$123	$178	-31.1%
2	11	Psychostimulants, Antidepressants	$4.93	$4.73	4.1%	9.0	9.1	-1.2%	$55	$52	5.4%
3	33	Antivirals	$3.97	$5.40	-26.5%	0.6	0.8	-21.7%	$609	$663	-8.2%
4	15	Bronchial Dilators	$3.14	$3.62	-13.2%	3.3	3.5	-6.4%	$96	$102	-6.7%
5	99	Miscellaneous	$2.92	$2.85	2.6%	1.5	1.5	0.0%	$190	$188	1.2%
6	48	Anticonvulsants	$2.58	$2.73	-5.2%	5.3	5.7	-5.6%	$45	$43	5.1%
7	58	Diabetic Therapy	$2.49	$2.51	-0.8%	2.1	2.3	-10.1%	$120	$109	9.8%
8	71	Other Hypotensives	$2.15	$2.31	-7.2%	2.8	3.0	-7.9%	$74	$75	-2.2%
9	40	Narcotic Analgesics	$2.14	$3.31	-35.2%	6.8	8.2	-16.6%	$31	$41	-22.7%
10	10	CNS Stimulants	$2.13	$2.38	-10.3%	1.7	1.9	-11.4%	$127	$125	1.2%
11	30	Antineoplastic	$1.59	$0.77	106.3%	0.4	0.3	16.1%	$371	$211	75.8%
12	42	Antiarthritics	$1.46	$1.42	2.4%	2.2	2.2	-1.8%	$67	$65	4.0%
13	12	Amphetamine Preps	$1.26	$1.18	6.8%	0.9	0.9	0.0%	$136	$128	6.8%
14	51	Gluco Corticoids	$1.16	$1.12	3.4%	1.8	1.9	-6.6%	$66	$59	11.0%
15	63	Oral Contraceptives	$1.12	$1.11	0.5%	2.4	2.5	-6.5%	$47	$44	7.3%
16	1	Antacids	$1.02	$1.29	-21.4%	3.4	3.9	-14.4%	$30	$33	-8.2%
17	64	Other Hormones	$0.86	$0.94	-9.3%	0.1	0.1	3.1%	$664	$805	-17.6%
18	41	Non-narcotic Analgesics	$0.84	$0.90	-6.1%	5.1	5.2	-2.4%	$16	$17	-4.8%
19	65	Lipotropics	$0.69	$1.16	-40.5%	2.0	2.3	-11.5%	$34	$51	-33.1%
20	6	Laxatives	$0.68	$0.67	1.2%	5.3	5.5	-3.3%	$13	$12	4.7%
21	27	Other Antibiotics	$0.63	$0.74	-14.5%	0.8	0.9	-11.7%	$74	$81	-7.8%
22	87	Electrolytes and Misc Nutr	$0.60	$0.66	-9.4%	2.7	3.0	-9.0%	$22	$22	-1.4%
23	77	Anticoagulants	$0.52	$1.21	-57.1%	0.4	0.6	-33.1%	$126	$193	-34.6%
24	23	Streptomycins	$0.43	$0.32	35.8%	0.0	0.0	-1.4%	$1,408	$989	42.3%
25	69	Enzymes	$0.41	$0.45	-7.6%	0.0	0.1	-2.0%	$841	$915	-8.1%
26	80	Fat Soluble Vitamins	$0.37	$0.38	-3.6%	3.7	3.6	1.2%	$10	$11	-4.7%
27	82	Multivitamins	$0.37	$0.37	-1.4%	3.4	3.6	-3.5%	$10	$10	0.4%
28	88	Hematinics with/without Iron	$0.35	$0.40	-11.7%	1.4	1.4	-1.3%	$25	$28	-11.4%
29	14	Antihistamines	$0.32	$0.34	-7.5%	2.8	2.7	0.5%	$11	$12	-8.8%
30	76	Other Cardiovascular Preps	$0.31	$0.37	-15.2%	1.8	2.1	-14.0%	$17	$18	-5.9%
		Aggregate	$53.12	$61.29	-13.3%	97.21	103.82	-6.4%	$66	$77	-15.3%
		75th Percentile			6.3%			2.0%			4.7%
		50th Percentile (Median)			-7.6%			-5.5%			-4.5%

Last updated: October 22, 2012

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

Pharmacy Utilization Summary Report: October 2011 - September 2012

	2011			2012									
	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	AVG/YTD
Eligibility													
Total Members	600,779	603,146	607,560	610,951	614,598	617,154	618,741	619,071	619,994	618,940	619,527	621,099	614,297
FFS Members	95,835	90,655	93,725	98,287	94,464	95,551	98,227	93,871	95,264	97,124	95,914	103,144	96,005
Standard	5,893	5,238	5,843	6,499	5,939	5,581	5,743	5,631	5,627	5,694	5,626	6,046	5,780
Plus	64,748	60,321	62,633	66,336	63,022	64,361	66,770	62,683	63,941	65,530	64,208	70,621	64,598
Medicare Wrap	25,194	25,096	25,249	25,452	25,503	25,609	25,714	25,557	25,696	25,900	26,080	26,477	25,627
Gross Figures													
Total Cost	$13,719,958	$13,724,847	$13,931,214	$14,781,908	$14,414,741	$14,816,197	$13,128,888	$12,928,316	$11,752,943	$12,053,715	$12,186,246	$11,041,679	$158,480,651
FFS Drugs	$4,077,247	$4,097,603	$4,188,110	$4,339,904	$4,277,617	$4,436,872	$4,297,243	$4,320,536	$3,891,043	$3,943,448	$3,977,163	$3,709,395	$49,556,181
Mental Health Carveout Drugs	$9,642,711	$9,627,244	$9,743,103	$10,442,004	$10,137,124	$10,379,325	$8,831,645	$8,607,780	$7,861,899	$8,110,267	$8,209,083	$7,332,284	$108,924,470
Total Rx	176,898	178,276	180,264	185,768	179,784	187,561	182,814	190,053	178,054	179,709	183,811	174,808	2,177,800
FFS Drugs	78,896	78,957	79,793	81,641	80,029	83,636	80,859	84,526	77,989	78,642	80,816	78,629	964,413
Mental Health Carveout Drugs	98,002	99,319	100,471	104,127	99,755	103,925	101,955	105,527	100,065	101,067	102,995	96,179	1,213,387
Cost/Rx	$77.56	$76.99	$77.28	$79.57	$80.18	$78.99	$71.82	$68.02	$66.01	$67.07	$66.30	$63.16	$72.75
FFS Drugs	$51.68	$51.90	$52.49	$53.16	$53.45	$53.05	$53.14	$51.11	$49.89	$50.14	$49.21	$47.18	$51.37
Mental Health Carveout Drugs	$98.39	$96.93	$96.97	$100.28	$101.62	$99.87	$86.62	$81.57	$78.57	$80.25	$79.70	$76.24	$89.75
Generic	$43.22	$43.79	$43.41	$44.34	$44.65	$43.07	$34.98	$30.62	$28.35	$28.24	$27.44	$25.00	$36.43
Brand	$327.02	$322.11	$327.07	$341.73	$344.47	$345.16	$346.39	$344.51	$347.24	$356.76	$357.21	$348.65	$342.36
PMPM Figures													
Cost PMPM	$58.59	$61.16	$60.72	$61.25	$61.78	$63.25	$58.02	$59.93	$53.53	$53.71	$54.72	$47.77	$57.87
Standard	$144.34	$160.69	$158.34	$151.48	$151.58	$166.43	$151.86	$156.16	$146.73	$143.20	$152.63	$128.32	$150.98
Plus	$60.84	$64.19	$62.95	$63.06	$64.42	$66.38	$58.93	$62.87	$55.53	$55.42	$56.20	$49.37	$60.01
Medicare Wrap	$15.41	$17.02	$15.76	$15.98	$18.05	$14.70	$17.85	$17.15	$14.16	$15.86	$17.04	$15.20	$16.18
FFS Drugs	$42.54	$45.20	$44.69	$44.16	$45.28	$46.43	$43.75	$46.03	$40.84	$40.60	$41.47	$35.96	$43.08
Mental Health Carveout Drugs	$16.05	$15.96	$16.04	$17.09	$16.49	$16.82	$14.27	$13.90	$12.68	$13.10	$13.25	$11.81	$14.79
Rx PMPM	0.99	1.04	1.02	1.00	1.01	1.04	0.99	1.07	0.98	0.97	1.01	0.92	1.00
Standard	2.00	2.22	2.06	1.95	2.04	2.21	2.10	2.22	2.07	2.05	2.19	1.95	2.09
Plus	0.85	0.90	0.88	0.86	0.88	0.91	0.85	0.93	0.84	0.82	0.86	0.78	0.86
Medicare Wrap	1.00	1.01	1.01	1.02	0.99	1.02	0.99	1.05	0.98	1.01	1.02	0.95	1.00
FFS Drugs	0.82	0.87	0.85	0.83	0.85	0.88	0.82	0.90	0.82	0.81	0.84	0.76	0.84
Mental Health Carveout Drugs	0.16	0.16	0.17	0.17	0.16	0.17	0.16	0.17	0.16	0.16	0.17	0.15	0.16
Utilization Percentages													
Generic %	87.9%	88.1%	88.1%	88.2%	88.2%	88.1%	88.2%	88.1%	88.2%	88.2%	88.2%	88.2%	88.1%
FFS Drugs	89.5%	89.8%	89.8%	90.1%	90.2%	90.2%	90.4%	90.5%	90.6%	90.7%	90.8%	90.7%	90.3%
Mental Health Carveout Drugs	86.6%	86.7%	86.7%	86.6%	86.5%	86.4%	86.4%	86.2%	86.3%	86.2%	86.2%	86.2%	86.4%
PDL %	92.6%	92.5%	92.5%	91.3%	91.7%	92.0%	92.2%	92.9%	93.2%	93.2%	94.0%	94.3%	92.7%

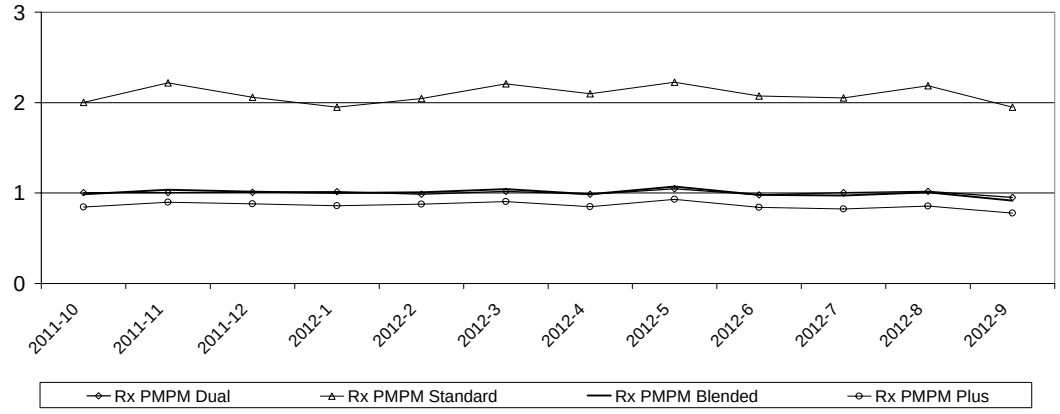
PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

Last Updated: October 22, 2012

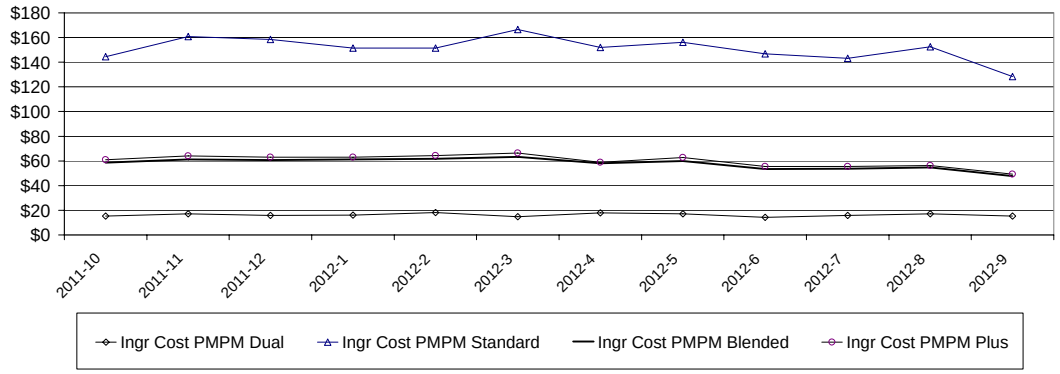
Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: October 2011 - September 2012

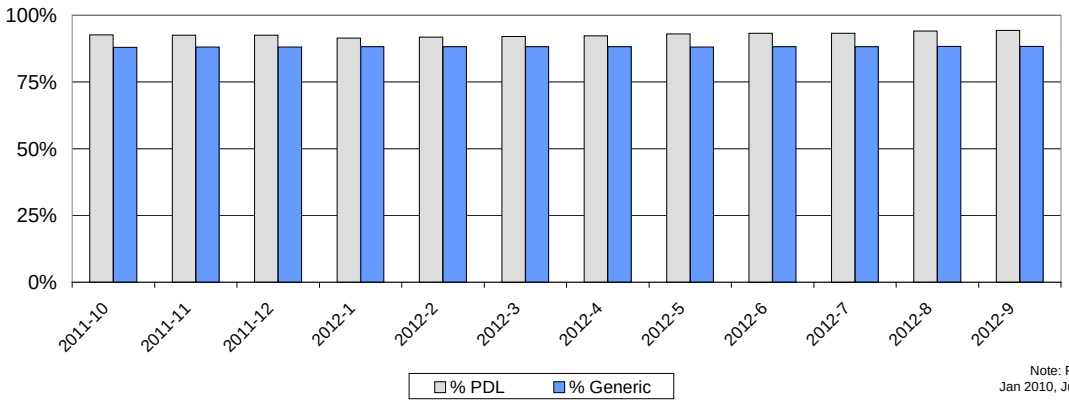
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



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

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter
September 2012 Volume 2, Issue 6

Do Spinosad or Ivermectin Have a Place in Head Lice Eradication?

By Lauren Armijo, Pharm.D. Candidate 2013, Oregon State University and Kathy L. Ketchum, B.Pharm, MPA:HA, OSU College of Pharmacy

An estimated 6 million to 12 million infestations of head lice occur each year in the United States (US) among children 3 to 11 years of age.[1] Some studies suggest that girls get head lice more often than boys, probably due to more frequent head-to-head contact and length of hair. [2] African-Americans are less commonly infested with lice due to their hair shape and width.[2] In the US, infestation with head lice is most common among preschool and elementary school-age children and their household members.[1] Increased incidence of resistance with evidence that common therapies are losing their effectiveness has lead to the production of new products.[2] This article will discuss two new treatments for head lice to determine their place in therapy.

Lice are small insects that bite through the skin and survive on the blood of its host.[2] The life span of a female louse is about one month and is likely to lay about 7-10 eggs (a.k.a. nits) daily. [2] The nits are cemented to the base of host hair and hatch in eight days releasing nymphs that mature in another eight days.[2] There are three known varieties of parasitic lice affecting humans: Pediculus humanus capitis (head lice), Pediculus humanus humanus (body lice) and Phthirus pubis (pubic lice or crabs).[2] The most prevalent of the three is head lice which are found worldwide. Disease is spread through direct contact via playmates, clothing, combs, headphones, towels and beds. Head lice manifestations are not typically associated with morbidity, are not a sign of uncleanliness, and do not transmit systemic disease, although secondary streptococcal and staphylococcal pyoderma may occur.[6]

Topical pediculicides are the initial treatment of choice for head lice. The previous 2002 American Academy of Pediatrics (AAP) Head Lice Guidelines, which were updated in 2010, recommended over the counter (OTC) permethrin 1% cream rinse (Nix) as first-line topical drug of choice for head lice, followed by malathion if resistance is high.[4,5] Since then, two new drugs have been approved by the Food and Drug Administration (FDA) for the treatment of peduculosis capitis (spinosad 0.9% topical suspension and ivermectin 0.5% lotion).[6,7] In addition, oral ivermectin has been studied for treatment of head lice off-label.[8] Clinical evidence (June 2010) and The Canadian Agency for Drugs and Technologies in Health (May 2010) published comparative reviews recommending permethrin 1% as first line.[9,10]

Recommended Therapy

Permethrin (Nix) is the gold standard for the treatment of lice.[4,5] Permethrin, a FDA pregnancy category B drug, is a synthetic pyrethroid which inhibits sodium ion influx through nerve cell membrane channels in ectoparasites, resulting in delayed repolarization and resultant paralysis and death of the parasites.[11] The 1% lotion is indicated for patients > 2 months old and the 5% cream has been shown safe and effective on infants <1 month old. Pyrethroid resistance is mediated by mutation of the alpha subunit gene of the neuronal voltage-gated sodium channel, conferring decreased sensitivity of the channel to pyrethroid (knock-down resistance).[11] The most recent AAP guidelines recommend that unless resistance has been proven in the community, 1% permethrin or pyrethrins can be used for treatment of active infestations because it has such low toxicity.[5,10] None of the current pediculicides are 100% ovicidal so applying permethrin at least twice is recommended. The most common adverse events of permethrin include rash and irritation to the application site.[11]

Malathion, a prescription medication, is thought to act via cholinesterase inhibition to exert both lousicidal and ovicidal actions. It is a FDA pregnancy category B drug and is indicated in individuals >2 years old.[11] According to the AAP guidelines, malathion is only recommended in cases in which resistance to other products, like permethrin, is strongly suspected or if failure to respond to permethrin occurs.[4,5] Despite some evidence that malathion lotion is more effective for lice eradication than permethrin, it is not recommended first line due to the major concern of alcohol content which makes this drug highly flammable and at risk for causing severe respiratory depression if accidently ingested.[9,12]

Lindane shampoo is FDA approved for the treatment of head lice. It is directly absorbed by parasites and ova through the exoskeleton.[4,5] It then stimulates the nervous system resulting in seizures and death of parasitic arthropods. Lindane is an FDA pregnancy category C drug. In 2003, the FDA issued a public health advisory concerning lindane that cites increased risk of neurologic side effects and death in younger patients and adults weighing less than 110 pounds.[13] According to APP guidelines, 1% lindane shampoo is no longer recommended as a treatment option because of concerns regarding the FDA health risks of central nervous system (CNS) toxicity and risk of seizure, as well as increased resistance documented in the United States.[4,5,14] With increased failures of treatment over time and the current black box warning, use of lindane has been banned in California and is considered unsafe and not as effective as other products.[15,16]

Spinosad

Spinosad, FDA approved for the treatment of lice in January of 2011, leads to insect paralysis and death by causing central nervous system excitation and involuntary muscle contractions.[17] It is thought to be both pediculocidal and ovicidal. Spinosad is a FDA pregnancy category B drug and is approved for those >4 years.[17]

The Stough et al trial was an investigator blinded, randomized controlled trial (RCT) including two identical phase III studies comparing spinosad 0.9% topical suspension without nit-combing to permethrin 1% with nit-combing for 7 days and possibly an extra 7 days if live lice were still present after first applcation.[18] A third arm with spinosad 0.9% topical suspension with nit-combing was performed but results were only reported in combination with the first spinosad arm for adverse events. The study included 1038 patients ≥6 months old with active head lice. The primary endpoint was the proportion of participants lice free at 14 days. The secondary endpoint was the proportion of patients lice free at 7 days.[18]

The primary endpoint occurred in 87.4% of the patients treated with spinosad compared to 48.3% of patients treated with permethrin (relative risk [RR] 1.93; 95% CI, 1.73 - 2.16; P<0.001). The secondary endpoint occurred in 73.4% of the patients treated with spinosad compared to 24.8% of patients treated with permethrin (RR 2.83; 95%CI, 2.39 - 3.37). Application site erythema was experienced with spinosad in 3.1% of patients compared to 6.8% of patients treated with permethrin (RR 0.45; 95% CI, 0.25 - 0.81; P=0.007). Adverse events were very similar between groups with application site erythema as the only significant difference with a higher occurrence in the permethrin group.[18]

This study was rated poor quality because it was not blinded to patient or care-giver, it was unclear if the evaluators were blinded and allocation concealment was not described.[19] In addition, withdrawals were not reported and the FDA agreed to reduce safety evaluations based upon proven safety in Phase II trials. Only the first 25 qualifying pediatric participants in each study had clinical laboratory assessments on days 0 (screening) and day 14. The safety results were not reported but the authors stated in the text there were no serious adverse events in spinosad group and three serious adverse events in permethrin group.[19] The results of this study are suspect due to lack of data. Therefore, spinosad should be further evaluated before it can be recommended over permethrin.

Ivermectin

Ivermectin lotion was FDA approved for lice in February of 2012. It is a semisynthetic anthelminthic agent that binds selectively and with strong affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells.[20] This leads to increased permeability of cell membranes to

chloride ions then hyperpolarization of the nerve or muscle cell, and death of the parasite. Ivermectin is a FDA pregnancy category C drug. The topical form is available for children ≥6 months.[20]

There are no current published studies comparing ivermectin 0.5% lotion to either permethrin or malathion, but there were two identical multi-center, randomized, double-blind, vehicle-controlled studies conducted on patients 6 months of age and older with head lice infestation. In both studies, all subjects received a single application of either ivermectin lotion or vehicle control with instructions not to use a nit comb.[22] In study 1, there were 16.2% (12/74) in the vehicle group and 76.1% (54/71) in the ivermectin group who were lice free at the end of the treatment period. In study 2, there were 18.9% (14/74) in the vehicle group and 71.4% (50/70) in the ivermectin group who were lice free at the end of the treatment period.[22] The quality of these studies cannot be evaluated and the placebo evidence does not allow a comparison to currently available therapies.

Oral ivermectin is FDA approved for strongyloidiasis of the intestinal tract. The use of oral ivermectin (400 mcg/kg in 3 mg tablets on days 1 and 8) for off-label head lice treatment was compared to a single application of malathion 0.5% lotion in a double-blind RCT.[21] The study only included patients 2 years and older that had previously failed either permethrin or malathion within the 2-6 week prior. It was pre-established as a non-inferiority study at absolute risk reduction (ARR) of 5% for the primary outcome of proportion of patients lice free at day 15. The secondary outcome was lice free on day 29.[21]

The primary outcome occurred in 95.2% of the patients treated with oral ivermectin compared to 85% of patients treated with malathion lotion (RR 1.12; 95%CI, 1.07 - 1.17; P<0.001).[21] The secondary outcome occurred in 96.2% of the patients treated with ivermectin compared to 87.4% of patients treated with malathion (RR 1.10; 95% CI, 1.06 - 1.15; P<0.001). In addition, 1.76% ivermectin and 1.21% malathion patients withdrew from the study due to adverse events (RR 1.46; 95% CI, 0.47 - 4.56). The ivermectin patients discontinued due to impetigo, nausea or vomiting, gastroenteritis and convulsions. The malathion patients discontinued due to rash or urticaria and gastroenteritis.[21]

The study met non-inferiority, but even though there was a response of 95.2% in the ivermectin group compared to 85% in the malathion group, it did not establish superiority because the lower CI dropped below 5% (ARR 10.2%; 95% CI, 4.6 - 15.7). Withdrawals due to adverse events were not appreciably different.[21] This was a good quality study because it was blinded, the treatment allocation was concealed, and it included an intention to treat analysis. [19] Oral ivermectin can be considered a second-line treatment option for head lice in those patients 2 years of age and older that have failed previous treatments.

Challenges

Increased resistance to permethrin 1% has been documented in the United States approaching 50% with different resistance rates dependent on geographical location.[23] Criteria for documenting resistance is based on correct use of a product and is generally accepted as the presence of lice two to three days after a treatment or after two treatments for a pediculicidal agent like permethrin or malathion.[24] Recent trials have monitored allele frequencies and identified mutations.[25,26] Not one mutation has been shown to cause all resistant occurrences.

Place in therapy

There is limited data from two poor quality RCTs that the use of topical spinosad is superior to permethrin for treatment of head lice not resistant to permethrin. Safety data was not reported. Topical ivermectin was evaluated only against placebo so comparisons to permethrin cannot be made. One small RCT trial concluded oral ivermectin was non-inferior to topical malathion for treatment resistant head lice. Until more evidence is available permethrin is recommended first line with malathion as an alternative in cases where resistance is high or permethrin fails to effectively treat head lice.[23] Table 1 summarizes the products discussed.

Table 1. Formulation, directions for use, and adverse effects of each agent.[27,28]

Agent	Formulation	Directions for use	Adverse effects	Retail Cost
Permethrin (Nix)	1% cream rinse, 5% cream	Apply after shampooing, leave on 10 minutes, rinse. Retreat in 7-10 days if live lice are seen	Local irritation	$20, $60
Malathion (Ovide)	0.5% lotion	Apply to dry hair, leave on 8-12 hours, rinse. Repeat in 7-10 days if live lice are seen	Flammable vehicle	$185
Lindane	1% shampoo, lotion	Apply to dry hair, leave on 4 minutes, rinse. No re-treatment	CNS toxicity, increased seizure risk	$125, $85
Spinosad (Natroba)	0.9% topical suspension	Apply to dry hair, leave on for 10 minutes, rinse.	Local irritation	$220
Ivermectin (Sklice)	0.5% lotion	Apply to dry hair, leave on 10 minutes, rinse.	Local irritation	$250
Ivermectin (Stromectol)	3mg, 5mg tablets (off label)	200mcg/kg/dose; repeat in 7-10 days	Headache, dizziness, nausea	$33 (6 tabs)

Reviewed by: Dr.Bill Origer, MD, Medical Director, Samaritan Health Services and Tracy Klein, PhD, FNP, FAANP, FRE, Advanced Practice Consultant, Oregon State Board of Nursing.

References:

1. Commissioner O of the. Consumer Updates - Treating Head Lice. Available at: http://www.fda.gov/forconsumers/consumerupdates/ucm171730.htm. Accessed July 27, 2012.
2. Goldstein A, Goldstein B. Pediculosis capitis. 2012. Available at: www.uptodate.com. Subscription Required. Accessed July 10, 2012.
3. Burgess IF. Current treatments for pediculosis capitis. *Current Opinion in Infectious Diseases*. 2009;22(2):131.
4. Frankowski B, Bocchini J, Council on School Health and Committe on Infectious Diseases. Head Lice. *Pediatrics*. 2010;126(2):392–403.
5. Frankowski BL, Weiner LB. Head Lice. *Pediatrics*. 2002.
6. DPT Laboratories LTD. SKLICE Lotion Product Labeling. 2012. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 20, 2012.
7. ParaPro LLC. Natroba Topical Suspensioin Product Labeling. 2011. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 20, 2012.
8. Merck & Co., Inc. Stromectol Product Labeling. 2009. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 20, 2012.
9. Canadian Agency for Drugs and Technologies in Health. Lindane and Other Treatments for Lice and Scabies: a Review of Clinical Effectiveness and Safety. 2010. Available at: http://http://cadth.ca/media/pdf/l0186_treatments_for_lice_scabies_htis-2.pdf. Accessed July 11, 2012.
10. Clinical Evidence. Head Lice. 2010. Available at: http://clinicalevidence.bmj.com/x/systematic-review/1703/overview.html. Accessed July 10, 2012.
11. Goldstein A, Goldstein B. Permethrin. Available at: www.uptodate.com. Subspriction Required. Accessed July 10, 2012.
12. Clinical Evidence. Head Lice: Malathion. 2008. Available at: http://clinicalevidence.bmj.com/x/systematic-review/1703/intervention/sr-1703-i1.html. Accessed July 12, 2012.
13. Research C for DE and. Public Health Advisories (Drugs) - Safety of Topical Lindane Products for the Treatment of Scabies and Lice. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm052201.htm. Accessed July 20, 2012.
14. Jones K, English JC 3rd. Review of common therapeutic options in the United States for the treatment of pediculosis capitis. *Clin Infect Dis*. 2003;36:1355–1361.
15. Anon. California Department of Health Service. State health director offers tips for protecting children from head lice [news release]. 2000.
16. Hall RC, Hall RC. Long-term psychological and neurological complications of lindane poisoning. *Psychosomatics*. 1999;40(6):513–517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10581981. Accessed July 20, 2012.
17. Goldstein A, Goldstein B. Spinosad. Available at: www.uptodate.com. Subscription Required. Accessed July 11, 2012.
18. Stough D, Shellabarger S, Quiring J, Gabrielsen AA. Efficacy and Safety of Spinosad and Permethrin Creme Rinses for Pediculosis Capitis (Head Lice). *Pediatrics*. 2009;124(3):e389–e395. Available at: http://pediatrics.aappublications.org/content/124/3/e389. Accessed July 23, 2012.
19. Ketchum K. Drug class review: lice and scabies. Final update report. 2012. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/reviews/articles/2012_05_31_Peduculosis_Capitis_CU_MN.pdf. Accessed July 11, 2012.
20. Goldstein A, Goldstein B. Ivermectin. Available at: www.uptodate.com. Subscription Required. Accessed July 11, 2012.
21. Chosidow O, Giraudeau B, Cottrell J, et al. Oral Ivermectin versus Malathion Lotion for Difficult-to-Treat Head Lice. *New England Journal of Medicine*. 2010;362(10):896–905. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa0905471. Accessed July 20, 2012.
22. Sanofi Pasteur. Bridgewater, NJ 08807. Prescribing information for Sklice®.2012.
23. American Academy of Pediatrics, Committee on School Health and Committee on Infectious Diseases. Pediculosis capitis (Head Lice). In: Pickering LK, Backer CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics*. 2009:495–497.
24. Hansen R. Overview: the state of head lice management and control. *Am J Manag Care*. 2004;10:S260–S263.
25. Lee SH, Yoon K-S, Williamson MS, et al. Molecular Analysis of kdr-like Resistance in Permethrin-Resistant Strains of Head Lice, Pediculus capitis. *Pesticide Biochemistry and Physiology*. 2000;66(2):130–143. Available at: http://www.sciencedirect.com/science/article/pii/S0048357599924604. Accessed July 23, 2012.
26. Yoon KS, Gao J-R, Lee SH, et al. Permethrin-Resistant Human Head Lice, Pediculus capitis, and Their Treatment. *Arch Dermatol*. 2003;139(8):994–1000. Available at: http://archderm.jamanetwork.com/article.aspx?articleid=479452. Accessed July 23, 2012.
27. Drugstore.com. Available at: http://www.drugstore.com. Accessed July 27, 2012.
28. Diamantis SA, Morrell DS, Burkhart CN. Treatment of head lice. *Dermatologic Therapy*. 2009;22(4):273–278. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1529-8019.2009.01242.x/abstract. Accessed July 20, 2012.

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

Low Dose Aripiprazole (Abilify®) Education Proposal

Conclusions

- Aripiprazole is the most prescribed second-generation antipsychotic for Oregon Health Plan (OHP) members
- For adults, 2 mg aripiprazole is only indicated as adjunctive treatment for major depressive disorder (MDD)
- 20% of new OHP aripiprazole prescriptions for adults in 2011 were for 2 mg strength, of which only 18.4% were followed by a higher strength prescription
- New evidence published in 2012 found no difference with placebo in depression response with 2 mg aripiprazole used adjunctively with an antidepressant
- There are safety concerns associated with aripiprazole use: akathisia and weight gain are two commonly experienced side effects

Recommendations

Ongoing low dose (2 mg) monotherapy and adjunctive aripiprazole prescribing should be dissuaded. To accomplish this, an educational program is proposed that would target providers who routinely prescribe low-dose aripiprazole for adults.

Program Goal: The goal of the program is to decrease the number of low dose aripiprazole prescriptions in adults.

Educational Approach: The proposed primary educational intervention will be Academic Detailing. Academic Detailing uses specially-trained medical professionals (such as pharmacists) to deliver unbiased, evidence-based educational messages to providers.

Target Audience: Depending upon the setting, providers will be invited to attend one-on-one or larger group educational sessions covering evidence regarding the safety and efficacy of low dose aripiprazole use.

Topic(s) of Discussion: It is speculated that the majority of low-dose aripiprazole use is for the treatment of MDD. For this reason, Academic Detailing sessions will include a discussion of the risks and benefits of low-dose aripiprazole as well as the appropriate treatment of MDD. This will be assessed through drug use evaluations conducted prior to the program and one year following the initiation.

Additional Outreach: Academic Detailing will be complemented by other forms of provider communication such as a statewide mass faxing and emailing campaign for all providers who prescribe second-generation antipsychotics (SGA) to dissuade low-dose aripiprazole prescribing. *The Oregon State Drug Review* newsletter will address the topic in a forthcoming issue. In addition, providers identified as the most frequent prescribers of low-dose aripiprazole will receive letters through the drug utilization review (DUR) process.

Background

Aripiprazole (brand name Abilify®) has become one of the most prescribed medications for Oregon Health Plan (OHP) members. Classified as an atypical or second-generation antipsychotic (SGA), it is FDA indicated in adults for the treatment of schizophrenia or schizoaffective disorder, bipolar disorder, or as an adjunct for treatment-resistant major depressive disorder (MDD). Typically, schizophrenia and bipolar disorder have a low prevalence in the population, about 1.1%[1] and 2.6%[2] respectively. Aripiprazole, however, was the eleventh most prescribed medication for OHP members in the first quarter of 2012.

From the large volume of prescription claims, it is probable that a large percentage of aripiprazole use is for the treatment of MDD. In 2011, 20% of new OHP aripiprazole prescriptions in 2011 were for the 2 mg strength. Aripiprazole 2 mg has not been studied for psychotic or bipolar disorders and its only labeled indication for adults is for MDD.[3] It is possible that some patients may be started on 2 mg and then titrated to more effective doses for other indications; however in 2011, 81.6% of adult OHP patients prescribed 2 mg aripiprazole did not receive a higher dose. The popularity of low-dose aripiprazole necessitates some scrutiny as recent evidence indicates that adjunctive 2 mg aripiprazole may not be effective for MDD.

In the two pivotal studies[4-5] for FDA approval of aripiprazole for MDD, the drug was dosed starting at 5 mg and titrated up to 15 to 20 mg or to the maximum tolerated dose. Patients were allowed a decrease in dose to 2 mg if side effects were intolerable. Efficacy separated out by dose strength was not analyzed and the average end dose for the treatment population in both trials was between 11 and 12 mg.[4-5] In both trials and a subsequent third trial[6], less than ten percent of the study population was taking 2 mg at the end of the study.

The recent ADAPT-A study[7] conducted with funding from the drug manufacturer, assessed the efficacy of 2 mg aripiprazole added to antidepressant therapy for adults with MDD. The results showed no difference in depression response with 2 mg aripiprazole compared with placebo. Unlike the original pivotal trials and many other depression RCTs (including STAR*D), ADAPT-A results did not measure remission which is more difficult to achieve, and clinically a more relevant measure, than response as an endpoint. A follow up[8] to the ADAPT-A trial took the 2 mg non-responders titrated them to 5 mg. Again no difference was found between aripiprazole and placebo in depression response.

Guidelines[9-10] for the treatment of resistant MDD recommend adding a SGA as third-line. First and second-line strategies suggest switching antidepressants or adding a second antidepressant with a different mechanism of action after treatment failure. The STAR*D trial rates of

remission ranging from 25% to 30% with the different treatment strategies of switching[11] or adding[12] an antidepressant. Adding liothyronine or lithium for MDD is another third-line option. A recent meta analysis found adding lithium to an antidepressant showed response rate of up to 40%.[13] In comparison, with aripiprazole augmentation, the pivotal trials showed rates of remission of 25.4% and 26% on average doses of 11 mg and 11.8 mg respectively.[4-5]

In addition to demonstrating minimal effectiveness in the treatment of depression, the use of 2 mg aripiprazole has been associated with unnecessary risks. Although aripiprazole has the perception of being safer than other SGA, there are serious side effects associated with its use. Aripiprazole has consistently been shown to cause akathisia. Akathisia[14] is a feeling of physical or motor restlessness which causes the need to move constantly or the inability to sit still. It can occur at any time during antipsychotic drug treatment and may persist after treatment is discontinued. In the pivotal trials for MDD, aripiprazole was found to cause high rates of akathisia over the 6 week duration: 25.9% and 23.1% for each trial respectively.[4-5] Recently, a retrospective cohort study examined the occurrence of tardive dyskinesia in patients treated with aripiprazole. The authors found a rate of occurrence of 3.4% over an average duration of use of 18 months.[15] Unlike akathisia, tardive dyskinesia is a permanent disability.[14]

There have been several recent systematic reviews comparing SGA head-to-head that further dispute aripiprazole's reputation as the safer SGA. Authors Edwards and Smith looked at head-to-head trials to compare the safety issues of five SGA with one another. They found the following trends: aripiprazole was more likely than ziprasidone to cause weight gain; more likely than risperidone and olanzapine to cause tiredness or weakness; and more likely than olanzapine, quetiapine, ziprasidone and risperidone to cause tremor and restlessness. In this review, only patients on risperidone were more likely than aripiprazole patients to experience EPS effects. [16] Another systematic review by Maher et al. examined the safety and efficacy of SGA off-label use and compared the adverse event profiles of aripiprazole with that of other SGAs. They found patients on aripiprazole were more likely to experience weight gain than those taking quetiapine, risperidone or ziprasidone; more likely to experience fatigue than patients on risperidone or olanzapine; more likely to experience akathisia than those on olanzapine, quetiapine, and ziprasidone; and more likely to experience EPS symptoms than patients on olanzapine and quetiapine.[17]

Clinical studies demonstrate that although aripiprazole has a lower rate of some metabolic abnormalities than some antipsychotics, it is not benign. A recent meta-analysis[18] and RCT[19] each examined the differences between the SGA and the relative propensity to cause metabolic effects. Both studies found aripiprazole was significantly less likely to cause increased cholesterol than other SGAs.[18-19] Whether aripiprazole causes less of an increase in blood glucose than other SGA was inconclusive. Aripiprazole has been shown to cause weight gain: in the MDD trials, patients gained an average of 1.5 kg[4] and 2 kg[5]during the six weeks. Studies differ on if it causes more[16-17] or less[18-19] weight gain than other SGA. Other medications used to treat MDD do not have the same metabolic effects as SGA including aripiprazole. Bupropion, buspirone and liothyronine are all recommended for adjunct use in refractory MDD before starting an SGA.

References

1. Anon. NIMH · Statistics · Schizophrenias. Available at: http://www.nimh.nih.gov/statistics/1SCHIZ.shtml. Accessed July 11, 2012.

2. Anon. NIMH · Statistics · Bipolar Disorder Among Adults. Available at: http://www.nimh.nih.gov/statistics/1BIPOLAR_ADULT.shtml. Accessed July 11, 2012.

3. Anon. Drug summary - MICROMEDEX® 2.0. Available at: http://www.thomsonhc.com/micromedex2/. Accessed July 9, 2012.

4. Marcus RN, McQuade RD, Carson WH, et al. The Efficacy and Safety of Aripiprazole as Adjunctive Therapy in Major Depressive Disorder. *J Clin Psychopharmacol*. 2008;28(2):156–165.

5. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843–853.

6. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009;14(4):197–206.

7. Fava M, Mischoulon D, Iosifescu D, et al. A Double-Blind, Placebo-Controlled Study of Aripiprazole Adjunctive to Antidepressant Therapy among Depressed Outpatients with Inadequate Response to Prior Antidepressant Therapy (ADAPT-A Study). *Psychother Psychosomat*. 2012;81(2):87–97.

8. Mischoulon D, Witte J, Levy M, et al. Efficacy of Dose Increase Among Nonresponders to Low-Dose Aripiprazole Augmentation in Patients With Inadequate Response to Antidepressant Treatment: *J Clin Psychiatry*. 2012;73(03):353–357.

9. Anon. PsychiatryOnline | APA Practice Guidelines | Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. Available at: http://psychiatryonline.org/. Accessed July 11, 2012.

10. Anon. MDD_FULL_3c.pdf. Available at: http://www.healthquality.va.gov/MDD_FULL_3c.pdf. Accessed July 11, 2012.

11. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression. *N Engl J Med*. 2006;354(12):1231–1242.

12. Trivedi MH, Fava M, Wisniewski SR, et al. Medication Augmentation after the Failure of SSRIs for Depression. *N Engl J Med*. 2006;354(12):1243–1252.

13. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2007;68(6):935–940.

14. Anon. Tardive dyskinesia: Clinical features and diagnosis. Available at: http://www.uptodate.com/contents/tardive-dyskinesia-clinical-features-and-diagnosis. Accessed July 11, 2012.

15. Peña MS, Yaltho TC, Jankovic J. Tardive dyskinesia and other movement disorders secondary to aripiprazole. *Movement Disorders*. 2011;26(1):147–152.

16. Edwards SJ, Smith CJ. Tolerability of atypical antipsychotics in the treatment of adults with schizophrenia or bipolar disorder: a mixed treatment comparison of randomized controlled trials. *Clin Ther*. 2009;31 Pt 1:1345–1359.

17. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359–1369.

18. Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*. 2010;123(2-3):225–233.

19. Stroup TS, McEvoy JP, Ring KD, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry*. 2011;168(9):947–956.

30

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

Oregon Health Authority

Abbreviated Review:
Vascular endothelial growth factor (VEGF) inhibitors

Month/Year of Review: November 2012 **End of Literature Search:** September 2012
Drugs Included: aflibercept, bevacizumab, pegaptanib, ranibuizumab

Research Questions:

- What is the evidence for effectiveness and safety for VEGF inhibitors to treat of diabetic macular edema?
- Is there evidence to determine if one anti-VEGF is more effective or safer than another agent for age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO)?

Conclusions:

- There is moderate to high quality evidence that VEGF inhibitors improve visual acuity in patients with neovascular AMD and are recommended as first line treatment.
- There is low quality evidence that bevacizumab is equivalent to ranibizumab in improving visual outcomes over two years in neovascular AMD (difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters; 95% CI -3.7 to 0.8) and that bevacizumab is associated with a higher rate of serious, nonspecific systemic adverse events over 2 years (31.7% vs. 39.9%; p=0.004, RR 1.30).
- There is insufficient evidence to make comparative conclusions for the use of pegaptanib in AMD.
- There is low quality evidence that aflibercept is equivalent to ranibizumab in maintaining vision at 1 year in the treatment of AMD.
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.
- There is insufficient evidence to determine whether there are clinically meaningful differences in health outcomes between the available agents for the treatment of DME.
- There is insufficient direct comparative evidence (no RCTs and indirect observational data) comparing intravitreal bevacizumab with ranibizumab in patients with DME.
- There is insufficient evidence to support the use of pegaptanib in the use of DME.

- There is moderate quality evidence that anti-VEGF therapy improves visual acuity compared to sham injections in central RVO related macular edema with no direct comparative evidence of any agents.

Recommendations:

- Due to a lack of clinical benefit in both AMD and DME over other anti-VEGF agents, make pegaptanib non-preferred.
- There is not strong evidence of superiority of one anti-VEGF agent over another for the treatment of AMD or DME and low quality evidence demonstrating equivalence of bevacizumab to ranibizumab and aflibercept to ranibizumab in AMD. Compare costs of bevacizumab, ranibizumab, and aflibercept.

Reason for Review: There were previously no anti-VEGF agents approved in the U.S. for treatment of DME. However, on August 10, 2012, the Food and Drug Administration (FDA) approved ranibizumab 0.3 mg per month for treatment of DME based on the RISE and RIDE studies.[1] Currently bevacizumab is reportedly used off-label in clinical practice to improve visual acuity in patients with diabetic macular edema refractory to laser therapy and for age-related macular degeneration (AMD). Aflibercept was FDA approved for the treatment of AMD in November 2011 and while ranibizumab was the only agent approved for the indication of RVO, aflibercept recently gained FDA approval for macular edema following central retinal vein occlusion (CRVO). This review will evaluate the available evidence to compare efficacy and safety of the VEGF-inhibitors in the treatment or DME, AMD, and RVO.

Background: DME is a frequent result of diabetic retinopathy and is the foremost cause of central vision loss and a leading cause of blindness in the diabetic population.[2,3] DME is the swelling of the retina due to leakage of fluid from blood vessels within the macula. Vision impairment is very much related to how well the diabetes is controlled and intensive metabolic control remains a highly effective means of controlling retinopathy. The goal of treatment is to preserve current visual acuity and reduce the progression to visual loss. Previous treatment approaches include laser photocoagulation, intravitreal steroid injections, and vitrectomy. Laser photocoagulation has become the gold standard but has not been successful in improving vision, only preserving it, reducing the risk of visual loss by 50% of patients with focal DME.[4,5] Intravitreal steroids may improve visual outcomes associated with DME based on moderate evidence from a Cochrane review of 7 trials (two with low risk of bias, 1 with medium risk of bias, 2 with high risk of bias, and 2 unable to assess).[5] Evidence suggests that intravitreal triamcinolone results in improved visual acuity compared with no treatment, and it can offer short-term improvements in acuity in eyes refractory to laser treatment.[3] However, the risk of elevated intraocular pressure (IOP) and cataracts are increased with steroid use, and are no longer used in favor.[6]

Change in visual acuity is one of the important outcomes evaluated in trials of patients with vascular eye diseases. It is commonly measured as the best-corrected visual acuity (BCVA). The Eye Disease Prevalence Research Group (EDPRS) developed a series of

charts to standardize visual acuity evaluation which are commonly used as a standard outcome measure in RCTs.[6] Serious adverse events of interest include endophthalmitis, glaucoma, stroke, myocardial infarction, other cardiovascular events, and death.

There are currently four anti-VEGF agents available, although only ranibizumab is approved for treatment of DME and only three are approved for one or more ophthalmologic indications. Approval of ranibizumab for the treatment of DME was based on a review of data from two phase III trials, RIDE and RISE, comparing sham injections to ranibizumab 0.3mg and 0.5mg over 24 months. These studies demonstrated a statistically significant difference between treatment and sham groups in the proportion of subjects who gained 15 letters or more in BCVA from baseline to month 24.[7] Ranibizumab treated patients were also less likely to need laser therapy than sham treated patients. Bevacizumab was originally approved for the treatment of colorectal cancer, but has been used off-label for many vascular diseases of the eye, including AMD and DME.[2] Ranibizumab comes from the same parent molecule as bevacizumab but is a humanized monoclonal antibody fragment that binds active forms of VEGF-A, whereas bevacizumab is a full-length antibody and binds to all types of VEGF. In final guidance from NICE in November 2011, ranibizumab was not recommended for use in patients with DME, although the evidence was found to be acceptable supporting its efficacy in sustained gains in BCVA over 2 years, whereas improvement with laser photocoagulation alone is significantly less marked, and it does not provide distinctive innovation above other treatments.[8]

Current guidelines from the American Diabetes Association (ADA) give a recommendation based on level A evidence for laser photocoagulation to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy (PDR), clinically significant macular edema, and in cases of severe nonproliferative diabetic retinopathy (NPDR).[9] These guidelines state that emerging therapy with anti-VEGF seems to halt progression of DME and may in fact improve vision in some patients but do not give specific recommendations regarding therapy. The American Academy of Ophthalmology (AAO) 2008 guidelines also recommend laser photocoagulations as the standard of care, as well as virectomy for advanced proliferative diabetic retinopathy (PDR) which has been shown to increase vision-related quality of life.[10] These guidelines refer that adjunctive treatments such as intravitreal corticosteroids or anti-VEGF may be considered with laser treatment only when in the presence of clinically significant macular edema (CSME). Guidelines from the American Optometric Association (AOA) on care of patient of diabetes mellitus again recognizes the potential impact of anti-VEGF treatment in clinically significant macular edema but has yet to develop recommendations with any specifics regarding treatment with these agents.[11]

A randomized clinical trial by the Diabetic Retinopathy Clinical Research Network found that ranibizumab therapy with either prompt or deferred focal/grid laser treatment provided better visual acuity outcomes compared with prompt laser alone through two years in patients with DME.[12–14] In addition, the RESTORE study was a 12-month, double blind, randomized trial comparing

ranibizumab 0.5mg monotherapy or combined with laser to laser treatment alone and found that ranibizumab alone and in combination with laser were superior to laser monotherapy in improving BCVA at 12 months ($p<0.0001$).[15] Another prospective RCT confirmed that bevacizumab through two years also improved BCVA compared to laser therapy alone.[16,17] At 12 months, there was a significant difference between the mean ETDRS BCVA in the bevacizumab group (61.3±10.4; range 34–79) and laser arm (50.0±16.6; range 8–76; $p = 0.0006$).[16] This was maintained at 24 months (64.4±13.3; range 34-88 vs. 54.8±12.6; range 33-75 for bevacizumab and laser groups, respectively, $p=0.005$). [16]

AMD is a progressive chronic disease of the central retina and leading cause of vision loss worldwide.[18] Patients are typically over 50 years of age and the goal of treatment is to minimize or reverse loss of vision and to maximize the vision-related quality of life related to AMD. Treatment options for AMD include observation, antioxidant vitamin and mineral supplements, photodynamic therapy (PDT) with verteporfin, intravitreal injection of VEGF inhibitors, and laser photocoagulation surgery.[19] VEGF inhibitors have become the standard of care for neovascular AMD and are recommended first line. They have demonstrated improved visual outcomes compared with other therapies. 2008 guidelines from The American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first line treatment for AMD with no specific distinctions between ranibizumab, bevacizumab, or pegaptanib. These guidelines were developed before the approval of aflibercept. Two controversies in the treatment of AMD with VEGF inhibitors include the preferred dosing regimen and systemic safety. Trials have evaluated a stricter monthly dosing regimen versus a less frequent, as needed protocol based on clinical and imaging features. Safety is a concern as the drugs enter the systemic circulation after ocular injection and there exists a theoretical higher risk of systemic vascular events. Clinical data on the systemic safety is sparse and available studies are not large enough to address safety concerns.

The National Institute for Health and Clinical Excellence (NICE) recommends ranibizumab as an option for wet AMD if the best-corrected visual acuity is between 6/12 and 6/96, there is no permanent structural damage, the lesion size is less than or equal to 12 disc areas, and there is evidence of recent presumed disease progression.[20] It is also recommended that it only be continued in people who maintain adequate response to therapy. NICE guidance states that pegaptanib is not recommended for the treatment of AMD. Based on four randomized controlled trials (RCTs) of ranibizumab and two of pegaptanib, the committee concluded that ranibizumab is more clinically effective than pegaptanib in improving visual acuity, although both are clinically effective in the treatment of wet AMD. [20]

RVO is the second most common retinal vascular disease after diabetic retinopathy with main risk factors being age over 50 and hypertension. [21,22] There are two types of RVO: branch retinal vein occlusion (BRVO) occurring 2-3 times more often than central retinal vein occlusion (CRVO).[21,22] Ophthalmological treatments focus on the prevention and management of the main sight

threatening complications – ocular neovascularization and macular edema. [21] In the absence of either of these complications, there is no evidence that treatment improves outcomes, and treatment is associated with some adverse effects. Macular edema is the most common cause of visual loss in patients with RVO. Laser photocoagulation, steroids, and intravitreal injections of anti-VEGF have been evaluated as treatments, with laser photocoagulation and VEGF inhibitors as the primary treatment options.

Methods:

A Medline literature search ending September 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing VEGF inhibitors in patients with DME, AMD, and RVO was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually 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. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class review. Randomized controlled trials (RCTs) will be emphasized only if evidence is lacking or insufficient from those preferred sources. The literature search for RCT's was done from the date of search in high quality systematic reviews to current.

Drugs included in review

Anti-VEGF	FDA approved Indications	Mechanism of Action	Dosing
Pegaptanib (Macugen®)	Age-related macular degeneration	Targets only the VEGF 165 isoform	Intravitreous injection every 6 weeks
Bevacizumab (Avastin®)	Tumor therapy	Binds to all types of VEGF	Intravitreous injection every 4 weeks
Aflibercept (Eylea®)	Neovascular (wet) Age-related macular degeneration and macular edema following retinal vein occlusion	Binds VEGF-A and placental growth factor, another angiogenic factor	Intravitreous injection every 4 weeks x 3 months, then every 8 weeks (AMD) Intravitreous injection every 4 weeks (CRVO)
Ranibizumab (Lucentis®)	Neovascular (Wet) Age-related macular degeneration, macular edema following retinal vein occlusion, and diabetic macular edema	Binds all active forms of VEGF-A	Intravitreous injection every 4 weeks. Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible for AMD only.

Systematic Reviews: Diabetic Macular Edema

CADTH

In May 2012, CADTH performed a rapid response report including a systematic review of intravitreal bevacizumab for the treatment of DME to evaluate if bevacizumab provides a therapeutic advantage on visual acuity, morbidity, and/or mortality, in comparison with other standard therapy, including ranibizumab.[3] A literature search up to May 2012 was conducted and ten publications were included in the review; one RCT comparing bevacizumab versus placebo, five with laser photocoagulation, and four with triamcinolone therapy. No trials compared bevacizumab with ranibizumab in patients with DME. Mortality and serious adverse events did not differ versus any comparator, and no trials reported on activities of daily living or quality of life.
Bevacizumab was found to improve vision compared to laser therapy. Three trials with a low risk of bias measured effect on BCVA and showed that more subjects demonstrated improvement in 3 lines or greater in the bevacizumab group compared to those in the laser groups at 6 weeks (15% vs. 5% at 6 weeks, risk ratio (RR) 3.33, 95% CI 0.56 to 19.74, p=0.009), 12-16 weeks (21% vs. 7%, RR 3.73 95% CI 1.51 to 9.25, p=0.005; NNT 6), and at 36-52 weeks (23% vs. 9%, RR 2.57 95% CI 1.21 to 5.44, p=0.01; NNT 8). [3]

There was insufficient evidence comparing bevacizumab to triamcinolone (4 trials). None of the trials reported all-cause mortality, mean visual acuity change, activities of daily living, quality of life, or withdrawals due to adverse events. All of the trials had both inadequate masking and allocation concealment. [3]

There was a consistent lack of evidence for the long term safety profile and sparse reporting of adverse events in the reviewed trials. Therefore, in addition to the reviewed literature, an additional non-systematic safety analysis was performed to include systematic reviews in other ocular conditions, a trial comparing bevacizumab and ranibizumab in age-related macular edema, cohort analyses, and a multicentre case series. [3] These results showed no conclusive evidence of serious safety signals with bevacizumab or important differences with other agents, such as ranibizumab, due to the generally lower quality of harms data for bevacizumab. The single head-to-head randomized trial between bevacizumab and ranibizumab for the treatment of AMD suggested an increased risk of non-specific serious systemic adverse events for bevacizumab-treated patients over two years, however the importance of the difference remains unclear.[3]

Institute for Clinical and Economic Review (ICER)

A technology assessment report was prepared by ICER and systematically included 15 RCTs and 8 observational studies of VEGF-inhibitors for DME.[6] Since there are no head-to-head trials comparing VEGF-inhibitors for DME, the authors conducted a series of pairwise indirect meta-analyses to find the mean difference in BCVA change, and the rate ratio of the likelihood of gaining 10 or

more letters of vision, including only fair or good quality trials of 6-24 months duration. For the outcome of mean difference in BCVA, these results found no statistically significant differences between ranibizumab and bevacizumab (MD -4.32; 95% CI -9.13 to 0.49), ranibizumab and aflibercept (MD 0.34; 95% CI -2.81 to 3.49), or bevacizumab and aflibercept (MD 4.66; 95% CI -0.05 to 9.37). Data for pegaptanib were unable to be used for the analysis in change in BCVA. Indirect analyses also demonstrated no significant difference in the likelihood of gain of >10 letters between any anti-VEGF therapies (ranibizumab vs. bevacizumab RR 0.71; 95% CI 0.34 to 1.46). Conclusions from these indirect comparisons need to be drawn with caution. Relatively few trials have been conducted in DME and there was between-agent trial heterogeneity in patient populations, duration of follow-up, and treatment regimens.

Zechmeister, et al.

A recent systematic review evaluated whether anti-VEGF leads to better clinical outcomes than current treatments in patients with DME including laser photocoagulation, intravitreal application of glucocorticoids, and vitrectomy.[4] Eleven RCTs were included in the review; 6 of bevacizumab, 3 evaluated ranibizumab, and 1 on pegaptanib. The principles of GRADE were used to assess the quality of evidence and the overall quality of the evidence of anti-VEGF therapy is moderate. There were no head-to-head comparative trials between the three products. This review did not find the evidence to strongly support the superiority of one anti-VEGF agent over another, although overall the quality of evidence was higher for ranibizumab efficacy than for bevacizumab. Quality of evidence for safety of any of the anti-VEGF products is very low and ocular events were the most frequently reported. There was insufficient evidence to support the use of pegaptanib in DME. One study was found comparing pegaptanib with sham injections, and the differences in visual acuity were either not clinically relevant or of unknown significance.

Based on one study comparing bevacizumab with sham injections, low quality evidence demonstrated a significant and clinically relevant improvement in mean visual acuity (effect size -0.21 better). Two studies comparing bevacizumab with laser photocoagulation showed greater and clinically relevant gains in mean visual acuity (high quality evidence). One small study did not demonstrate a difference in visual acuity between bevacizumab and intravitreal steroids.

There was moderate quality evidence, based on one single high quality study that compared with sham injections, ranibizumab significantly improved mean visual acuity and the percentage of patients who gained at least 15 letters was significantly higher. There was also moderate quality evidence that ranibizumab significantly improved visual acuity and vision-related quality of life compared to laser photocoagulation, although the difference was not clinically relevant. No evidence was available comparing ranibizumab to intravitreal steroids.

Goyal, et al.:

A meta-analysis and systematic review was performed to evaluate the effect of bevacizumab in DME.[2] This review was evaluated by the Centre for Reviews and Dissemination (CRD) and met the criteria for inclusion in the Database of Abstracts of Reviews and Effects (DARE). Four randomized controlled trials were included in the review and were assessed for quality using criteria from the Delphi List including randomization, allocation concealment, baseline group similarity, specified eligibility criteria, blinding, and intention to treat analysis. All four trials were rated as moderate to good quality. Trials included comparisons of bevacizumab with bevacizumab plus intravitreal triamcinolone, with macular laser photocoagulation, or with sham control groups.

At 6 weeks, there was a significant reduction in center subfield macular thickness (WMD -48.2µm, 95% CI -86.2 to -10.2; I^2=71.4%; three RCCTs), but no significant differences at 12 or 24 weeks between bevacizumab and photocoagulation. No significant between group differences were found for intravitreal bevacizumab versus intravitreal bevacizumab plus intravitreal triamcinolone acetonide at any time point. At 6 weeks, there was also a significant improvement in best-corrected visual acuity (BCVA) with bevacizumab compared to control (WMD -0.13 log MAR, 95% CI -0.23 to -0.02; I^2=85.1%; three RCCTs) and at 24 weeks (only 2 trials), but no significant difference was seen at 12 weeks. There was no significant gain in outcomes with the combination of bevacizumab and intravitreal steroids compared to bevacizumab alone. This review demonstrated the short-term beneficial effects of bevacizumab compared to standard laser therapy and that there is no significant benefit of adding steroids to bevacizumab, with an added risk of cumulative side effects. There was insufficient evidence to make conclusions regarding its long term efficacy either used alone or in combination with other treatments for DME. This meta-analysis was limited due to the small number of trials eligible for analysis and most of them were conducted in Iran. CRD concluded that the conclusions should be interpreted with caution due to this main limitation.

Systematic Reviews: Age-related Macular Degeneration

CADTH

A systematic drug class review and economic evaluation for the management of neovascular AMD was conducted by CADTH in 2008 and concluded that uncertainty still exists with no direct evidence demonstrating the effect of timing or retreatment on health and that evidence for bevacizumab's effectiveness was less compelling than other anti-VEGF agents. Pegatanib or ranibizumab were recommended as optimal treatment strategies.[23]

Cochrane Collaboration:

A 2008 Cochrane systematic review was conducted to investigate the effects of, and quality of life associated with, anti-VEGF therapies for the treatment of neovascular AMD.[24] The primary outcome was BCVA after at least one year of follow up, as

demonstrated by loss of 15 or more letters. The literature search was through February 2008 and resulted in five trials in ten reports for the analysis. All five trials were of good methodological quality and there were no direct head to head trials comparing ranibizumab to pegaptanib. At the time of this review, all trials evaluating bevacizumab were still ongoing or were uncontrolled and did not meet the criteria for inclusion. [24]

Compared to sham injections, pegaptanib demonstrated fewer patients losing 15 letters or more (RR 0.70; 95% CI 0.6 to 0.84) based on two trials. The calculated number needed to treat (NNT) was 6.67 for 0.3mg, 6.25 for 1 mg, and 14.28 for 3 mg pegaptanib. [24] The final mean visual acuity was also greater in all three dosages compared to sham, with the weighted mean difference (WMD) ranging from 3.64 to 7.2 letters. [24]

The overall RR for ranibizumab versus sham for loss of 15 or more letters of visual acuity was 0.14 (95% CI 0.10 to 0.22). The calculated NNT was 3.13 for 0.3mg ranibizumab and 3.13 for 0.5 mg (3 trials). [24] Patients treated with ranibizumab had greater mean visual acuity at one year compared with those treated with sham. The WMD for the mean change was 16.9 for 0.3 mg and 17.6 for 0.5mg. [24]

The authors concluded that based on trials of good methodological quality, ranibizumab and pegaptanib demonstrate efficacy in terms of proportion with loss of 15 letters of more and ranibizumab resulted in a greater proportion with loss of 15 letters or more than pegaptanib.[24]

Mitchell, et al:

A literature search up to June 2010 was used to review ocular and systemic events in AMD with the treatment of ranibizumab and bevacizumab. Nine prospective, randomized, controlled trials considered Level I evidence (8 for ranibizumab and 1 for bevacizumab) and 11 studies considered to be Level II evidence (five ranibizumab and 6 bevacizumab) were included. Level I evidence was defined as strong evidence and level II indicates substantial evidence that lacks some qualities or study flaws. One comparative study of the two agents was included.[25]

Seven large trials of level I evidence including 1301 demonstrated significant improvements in visual acuity in patients with AMD with the use of ranibizumab versus sham, in combination with PDT versus PDT, and in combination with PDT versus sham-PDT. The range of mean visual acuity change in letters from the studies was -1.6 to +11.3 and comparators from -16.3 to -7.8. Four additional open-label studies with 4484 patients also demonstrated significant improvements versus usual care following, although these studies compared different dosing and treatment schedules of ranibizumab. [25]

Six studies (5 being of level II evidence) of bevacizumab included 424 patients and demonstrated significant improvements in visual acuity, as assessed by mean gain of letters. The one trial of Level I evidence compared bevacizumab 1.25mg to PDT/pegaptanib/sham in 131 patients. There was a significant improvement in mean gain of letters (+7 for bevacizumab versus -9.4, p<0.001). There were low rates of serious ocular adverse events and two myocardial infarctions (3.1%).[25]

One small (n=20) study compared the efficacy of ranibizumab and bevacizumab over 6 months and resulted in bevacizumab with a tendency to be associated with a greater gain of letters from baseline, and ranibizumab with a greater reduction in central macular thickness. Differences between the groups were not statistically significant. One year data demonstrated similar results (+6.3 letters for ranibizumab vs. _12.1 for bevacizumab). [25]

Limited safety results could be concluded from the bevacizumab trials, as only three of the studies reported details of adverse ocular or systemic events. Results of this study demonstrated that Level I and Level II evidence supports the efficacy and safety of ranibizumab in wet AMD and that data suggests bevacizumab may also provide efficacy, with insufficient evidence to determine the safety profile of bevacizumab. [25]

Systematic Reviews: Retinal Vein Occlusion

Cochrane Collaboration

A 2010 Cochrane systematic review was performed to investigate the effectiveness and safety of anti-VEGF therapies for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).[26] A literature search through August 10, 2010 found only two RCTs comparing an anti-VEGF agent to sham injection that met the inclusion criteria; both considered to have a low risk of bias although both with relatively small sample sizes and short follow-up periods (six months and 30 weeks). The primary outcome was defined as the proportion of patients with an improvement from baseline in BCVA of greater than or equal to 15 letters or 3 lines on the ETDRS Chart, which has been the standard primary outcome measure for evaluating the efficacy of treatments for retinal diseases. [26]

One of the included trials (Wroblewski) compared pegaptanib (n=33) with sham injection (n=32) for 30 weeks in patients with CRVO-macular edema. The other study (CRUISE) was a sham-controlled trial of ranibizumab comparing 0.3 mg (n=132) or 0.5 mg (n=130) ranibizumab to sham injection (n=130) for six months. The two trials included patients with similar baseline characteristics and mean age. [26]

In the Wroblewski study, there was no significant difference demonstrated between the groups in the primary endpoint. In the sham group, 28% of patients gained 15 or more letters compared to 36% in the 0.3 pegaptanib group (p=0.48) and 39% in the 1.0 mg group (p=0.35). [26] There was a significant difference in average visual acuity gain at week 30 in the 1.0 mg group compared to sham (+9.9 letters vs. +3.2 letters, p=0.02; 95% CI 1.5 to 24.6 letters). The difference was not statistically significant between 0.3 mg pegaptanib and sham (+7.1 letters vs. +3.2, p=0.09, 95% CI -1.3 to 21.8 letters). [26] No quality of life or visual functioning data were included.

In CRUISE, there was a significant difference in mean change BCVA at 6 months between both ranibizumab 0.3 mg and 0.5 mg compared to sham (+12.7 letters 0.3 mg vs. +14.9 letters 0.5 mg vs. +0.8 letters sham, p<0.00001). At six months, the percentage of patients gaining 15 letters or more from baseline was also significantly higher in both treatment groups compared to sham (P<0.0001). For the 0.3 mg group the RR was 2.73 (95% CI 1.79 to 4.17) and was 2.82 (95% CI 1.85 to 4.29) for the 0.5 mg ranibizumab group compared to sham. [26] There were few serious adverse ocular events at six months and some systemic serious adverse events occurred in all groups (one non-fatal myocardial infarct in each group). [26] There was also an improvement in quality of life as measured by the National Eye Institute Visual Functioning Questionnaire 25 item instrument (NEI VFQ-25) in the treatment groups compared to sham.

The authors of this review concluded that the available RCT data presents relatively good evidence that repeated treatment of non-ischemic CRVO related macular edema with the anti-VEGF agents' ranibizumab or pegaptanib may improve numerous outcomes at six months. However, the applicability of the evidence to clinical practice is relatively limited, and there were no data on bevacizumab or other agents. [26]

The Royal College of Ophthalmologists

Guidance for the management of RVO was updated in 2010 due to developments in treatment options.[27] This was based on a literature search through February 2010 for selected RCT's, systematic reviews, and observational studies. Relevant literature was identified and the level of evidence was graded. Guidelines are separated into recommendations for BRVO and CRVO. For macular edema associated with CRVO, the guidelines give grade A strength of evidence for the use of ranibizumab in macular edema based on results of the CRUISE trial and grade D for the strength of the evidence supporting the use of bevacizumab due to an unknown dosing schedule and unclear long-term outcomes. [27]

In macular edema associated with BRVO, guidance also demonstrated grade A strength of evidence for ranibizumab based on results from the BRAVO study which compared it to sham over six months. [27] The BRAVO study was a 12-month, randomized trial that

included a 6-month, injection-controlled treatment period followed by a 6-month observation period In this study, sixty-one percent of subjects in the ranibizumab 0.5mg group achieved a 15 letter gain vs. 29% in the sham treated group and the mean improvement in BCVA at month 12 in the sham group than that of the 0.3 mg and 0.5 mg treatment groups ($p<0.01$). Bevacizumab was given grade B strength of evidence based on increasing short-term data supporting that multiple injections may reduce macular edema associated with BRVO. [27]

Ranibizumab vs. Bevacizumab (details in evidence table in Appendix 1):

Subramanian et al.
The first head to head trial of bevacizumab and ranibizumab in AMD was a small (n=22), 1-year, prospective, single-center, randomized, double-blind study comparing bevacizumab and ranibizumab for the treatment of neovascular AMD. Patients were randomized 2:1 to bevacizumab or ranibizumab. Patient's received monthly treatment for 3 months followed by an as needed dosing schedule. Twenty-two (78.6%) patients completed the year of follow-up, 15 in the bevacizumab and 7 in the ranibizumab groups. There were no significant differences in mean change in visual acuity (+6.3 letters for ranibizumab and +7.6 etters for bevacizumab, p=0.74) or central macular thickness at one year. The quality of this trial is fair due to the small sample size and inadequate power to detect a real difference. The applicability to the real world population is also limited; as the study population was an almost entirely male, Caucasian patient population in a VA setting.[28]

CATT
Ranibizumab and bevacizumab have been compared in the treatment of age-related macular degeneration (AMD) in the Comparison of AMD Treatment Trials (CATT), a randomized, single-blind, noninferiority trial.[29,30] Patients were randomly assigned and treated with one of four regimens. They received ranibizumab monthly or as needed, or bevacizumab monthly or as needed. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. One year results demonstrated that bevacizumab and ranibizumab had nearly identical effects on visual acuity (99.2% confidence interval for the difference in the mean change in visual-acuity score within -5 to +5 letters) both when drugs were given monthly and when given as needed. Ranibizumab given as needed was also equivalent to ranibizumab given monthly. The comparison between bevacizumab as needed and bevacizumab monthly and ranibizumab monthly was inconclusive. At 1 year, 24 of the 1185 patients had died and the proportions of patients with arteriothrombotic events were similar among the groups, at 2 to 3% (p=0.97). One or more serious systemic adverse events occurred in 255 patients (21.5%) with no statistically significant differences between the four

groups (p=0.11), but when dosing regimens groups were combined there were 24.1% for bevacizumab and 19% for ranibizumab (p=0.04; RR 1.29 95% CI 1.01 to 1.66), driven primarily by hospitalizations. The rates of death, myocardial infarction, and stroke were numerically higher in the bevacizumab-treated groups, but the differences were not statistically significant when compared to ranibizumab (p>0.2). One major limitation of the fair-poor quality CATT trial is the incomplete blinding to the assigned study groups. If receiving ranibizumab, this was displayed in patients' billing documents which unblinded drug assignments, although the assessors remained blinded. The study size was also not sufficient to evaluate drug safety.

After year 1 of the CATT study, patients initially assigned to monthly treatment were reassigned randomly to either continue receiving monthly treatments or switch to as-needed treatments and year two was conducted to describe longer-term effects and the impact of switching from monthly to as-needed treatment.[30] Patients assigned to as-needed treatment initially had no change in assignment. Most of the change in mean visual acuity occurred during year 1, with relatively little change during year 2. There was no significant difference in visual acuity score between the drugs or between the different regimens. The difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters (95% CI -3.7 to 0.8) and the difference between those treated by an as-needed regimen compared to those treated monthly was -2.4 letters (95% CI -4.8 to -0.1). [30] There was no significant difference in the proportion of patients without a decrease in vision of 15 letters or more between the groups (88.4% for bevacizumab vs. 93.3% for ranibizumab, p=0.24). Small differences in mean gain in visual acuity emerged between dosing regimens.[30]

Two year data demonstrated no significant difference in the number of patients who died (5.3% vs. 6.1%; p=0.62), proportion of patients with arteriothrombotic events (4.7% vs. 5.0%; p=0.89), or venous thrombotic events (0.5% vs. 1.7%; p=0.054) between patients assigned to ranibizumab and bevacizumab, respectively. [30] The higher rate of serious adverse events observed in patients in the bevacizumab group persisted during year 2 (31.7% vs. 39.9%; p=0.004, RR 1.30). Patients treated as-needed had higher rates of serious adverse events than patients treated monthly (RR 1.20; 95% CI 0.98-1.47; p=0.08). [30]

IVAN

A UK equivalent of the CATT study (IVAN trial) was conducted to compare the efficacy and safety of ranibizumab and bevacizumab in AMD in a noninferiority trial. Although still ongoing, interim results from a pre-specified 1 year analysis have been published. A total of 610 patients were randomized to 4 groups: ranibizumab or bevacizumab, given either every month or as-needed.[31] Both groups received 3 months of treatment and then were allocated to continuous or as needed treatment. Patients and clinicians were blinded to drug allocation but not to treatment regimen allocation. The primary outcome was best-corrected distance visual acuity measured as ETDRS letters, with a noninferiority limit of 3.5 letters. The difference between drugs (bevacizumab minus

ranibizumab) was -1.99 letters (95% CI -4.04 to 0.06) and between treatment regimens was -0.35 letters (95% CI -2.40 to 1.70), favoring continuous therapy. [31] Overall, the comparison between study drugs was inconclusive using the 3.5 letter limit and as-needed treatment was shown to be equivalent to monthly treatment. There were no significant differences between drugs or regimens for quality of life. There were no differences at year 1 between drugs or treatment regimens in mortality, the odds of a serious adverse event, and arteriothrombotic events occurred infrequently, but more often with ranibizumab than bevacizumab. [31]

Authors of the IVAN study also combined results from the CATT study and by Subramanian to develop a weighted mean difference in visual acuity of 1.06 letters in favor of ranibizumab (95% CI -0.29 to 2.41 letters), meeting the noninferiority margin to establish equivalence of the two drugs. The pooled analysis also showed no difference between the drugs in mortality or arteriothrombotic events (p=0.34 and p=0.55, respectively). [31]

There are no head-to-head trials comparing bevacizumab to ranibizumab in patients with DME. There has been one retrospective study with many limitations, including its design, small population studied (n=29), short duration of only 1 injection, and potential unblinding of the patients. This low quality study demonstrated no significant difference in median change in BCVA between bevacizumab and ranibizumab (4.5 letters vs. 6 letters, p=0.58).[32]

<u>New Drug: Aflibercept (Eylea)</u>

Aflibercept was FDA approved for the treatment of AMD in November 2011.[33] Approval was based on two fair to good quality randomized, double blinded, non-inferiority Phase III trials (VIEW 1 and VIEW 2) in 2,412 patients, comparing monthly and every-2-month dosing of aflibercept with monthly ranibizumab in patients with neovascular AMD. [33,34] Doses of 2mg every 4 weeks, 0.5mg every 4 weeks, and 2mg every 8 weeks were compared to ranibizumab 0.5 mg monthly. The primary end point was noninferiority in the proportion of patients maintaining vision at week 52 (losing <15 letters on the ETDRS chart). Patients were at least 50 years of age with active primary subfoveal choroidal neovascularization lesions secondary to AMD. Treatment failure was defined as a decrease from baseline in the BCVA by 15 or more letters at two consecutive assessments that were 4 weeks apart.[34]

In both studies, all three doses of aflibercept were non-inferior to ranibizumab in regards to the primary endpoint; the proportion of patients who maintained vision at week 52 with a noninferiority margin of 10% and none of the doses were found to be superior. [33] In addition, all treatment groups experienced improvements in the ETDRS letter scores versus baseline with the most rapid improvement during the first three months of treatment.[33] Only the aflibercept 2mg every 4 week group was statistically superior to ranibizumab (gain of +10.9 versus -8.1 letters), and only in VIEW 1. [34] The proportion of patients who gained more than 15 letters was similar in all treatment groups. The most common side effects include conjunctival hemorrhage, eye pain, cataract,

vitreous detachment, vitreous floaters and increased intraocular pressure.[33],[34] The VIEW studies were not powered to see differences in serious intraocular complications and there was no difference in serious systemic adverse events between the groups.

Aflibercept has also been evaluated in the treatment of DME in one fair quality phase II RCT (DA VINCI) comparing four different doses to macular laser photocoagulation in 221 patients for 6 months.[35] This was a double-blind, sham-controlled study. At 6 months, mean BCVA improved by 8.5-11.4 letters in each group vs. 2.5 letters in the laser group ($p<0.009$ for all comparisons). Greater numbers of patients in each aflibercept group gained greater than 10 and greater than 15 letters compared to laser but the differences were not statistically tested. [35] There was an overall attrition rate of close to 20% and the treatment group had a higher prevalence of proliferative diabetic retinopathy and history of cardiac disease. Statistically significant differences in improvements in BCVA continued to be seen up to week 52 with all treatment groups compared to laser ($p<0.001$) and no significant differences were seen between the treatment groups. The proportion of eyes that gained 15 letters or more was also statistically greater than in the laser treatment group in all groups except the group dosed every 8 weeks.[35]

The Phase III COPERNICUS study was a randomized, double-blind study assessing the efficacy and safety of aflibercept in patients with macular edema associated with CRVO randomized 3:2 to receive aflibercept 2 mg or sham injection monthly for 6 months.[36] This is currently an ongoing, 2 year study with six month data reported and published. A total of 189 subjects were evaluated and the primary efficacy end point was the proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24. In the efficacy analysis, 56.1% of eyes treated with aflibercept gained 15 letters or more from baseline, compared with 12.3% of sham-treated eyes, with a difference of 43.8% (95% CI 33.0%-56.6%; $p<0.0001$). There were similar occurrences of ocular adverse events in each group (68.4% aflibercept vs. 68.9% sham). Five patients in the sham group compared to one patient receiving treatment discontinued study drug because of ocular adverse events. [36]

References:

1. Genentech: Newsroom: Press Releases: News Release July 26, 2012. Available at: http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=14067. Accessed July 30, 2012.

2. Goyal S, Lavalley M, Subramanian ML. Meta-analysis and review on the effect of bevacizumab in diabetic macular edema. *Graefes Arch. Clin. Exp. Ophthalmol.* 2011;249(1):15–27.

3. Fortin P, Mintzes B, Innes M. A Systematic Review of Intravitreal Bevacizumab for the Treatment of Diabetic Macular Edema [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012 (Rapid Response Report: Peer-Reviewed Summary with Critical Appraisal). Available at: http://www.cadth.ca/media/pdf/RD0028_avastin_L3_e.pdf.

4. Zechmeister-Koss I, Huic M. Vascular endothelial growth factor inhibitors (anti-VEGF) in the management of diabetic macular oedema: a systematic review. *Br J Ophthalmol*. 2012;96(2):167–178.

5. Grover D, Li TJ, Chong CCW. Intravitreal steroids for macular edema in diabetes. *Cochrane Database Syst Rev*. 2008;(1):CD005656.

6. Ollendorf D, Migliaccio-Walle K, Colby J, Person S. Anti-vascular endothelial growth factor treatment for diabetic macular edema [Internet]. Boston (MA): Institute for Clinical and Economic Review (ICER); 2012. Available at: http://www.icer-review.org/index.php/Completed-Appraisals/dme.html.

7. Food and Drug Administration Center for Drug Evaluation and Research. Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Briefing Package for sBLA 125156 LUCENTIS (ranibizumab injection) Proposed Indication: Treatment of diabetic macular edema July 26, 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM313088.pdf.

8. National Institute for Health and Clinical Excellence. Final appraisal determination. Ranibizumab for the treatment of diabetic macular oedema. November 2011.

9. American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care*. 2012;35 Suppl 1:S11–63.

10. American Academy of Ophthalmology. /Vitreous Panel, Preferred Practice Patterns Committee. Diabetic retinopathy. San Francisco (CA): American Academy of Ophthalmology (AAO); 2008. 39 p.

11. American Optometric Association. Optometric Clinical Practice Guideline. Care of the Patient with Diabetes Mellitus. 2009. Available at: http://www.aoa.org/documents/CPG-3.pdf.

12. Aiello LP, Beck RW, Bressler NM, et al. Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. *Ophthalmology*. 2011;118(12):e5–14.

Author: Megan Herink, Pharm.D.

13. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064–1077.e35.

14. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2011;118(4):609–614.

15. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615–625.

16. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010;117(6):1078–1086.e2.

17. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema: 24-Month Data: Report 3. *Archives of ophthalmology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22491395. Accessed July 31, 2012.

18. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379(9827):1728–1738.

19. American Academy of Ophthalmology. Age-related macular degeneration. San Francisco (CA): American Academy of Ophthalmology (AAO); 2008.37p. [152 references].

20. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance 155. 2008. Available at: http://www.nice.org.uk/nicemedia/live/12057/41719/41719.pdf.

21. Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ*. 2012;344:e499.

22. Coscas G, Loewenstein A, Augustin A, et al. Management of retinal vein occlusion--consensus document. *Ophthalmologica*. 2011;226(1):4–28.

23. Hodge W, Brown A, Kymes S, et al. Pharmacologic management of neovascular age-related macular degeneration: systematic review of economic evidence and primary economic evaluation. *Can. J. Ophthalmol.* 2010;45(3):223–230.

24. vedula s, Krzystolik M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration - Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005139.DOI: 10.1002/14651858.CD005139.pub2. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005139.pub2/pdf. Accessed July 6, 2012.

25. Mitchell P. A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab. *Curr Med Res Opin*. 2011;27(7):1465–1475.

Author: Megan Herink, Pharm.D.

26. Braithwaite T, Nanji AA, Greenberg PB. Anti-vascular endothelial growth factor for macular edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*. 2010;(10):CD007325.

27. Royal College of Ophthalmologists. Interim guidelines for management of retinal vein occlusion. 2010. Available at: www.rcophth.ac.uk/core/core_picker/download.asp?id=728.

28. Subramanian ML, Abedi G, Ness S, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. *Eye (Lond)*. 2010;24(11):1708–1715.

29. Martin DF, Maguire MG, Ying G, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* 2011;364(20):1897–1908.

30. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: Two-Year Results. *Ophthalmology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22555112. Accessed May 17, 2012.

31. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. *Ophthalmology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22578446. Accessed May 17, 2012.

32. Ozturk BT, Kerimoglu H, Bozkurt B, Okudan S. Comparison of intravitreal bevacizumab and ranibizumab treatment for diabetic macular edema. *J Ocul Pharmacol Ther*. 2011;27(4):373–377.

33. Center for drug evaluation and research. Application Number: 125387Orig1s000. FDA Medical Review - afilbercept. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000MedR.pdf.

34. Heier JS, Brown DM, Chong V, et al. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration. *Ophthalmology*. 2012.

35. Do DV, Nguyen QD, Boyer D, et al. One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema. *Ophthalmology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22537617. Accessed June 21, 2012.

36. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024–1032.

Appendix 1: Evidence Table

ef/ Study esign[1]	Drug Regimens[2]	Patient Population	N	Duration	Efficacy Results[3] (CI, p-values)	ARR/ NNT[4]	Safety Results (CI, p-values)	ARI/ NNH[4]	Quality Rating[5]; Comment
bramanian et 28 3, RCT	Ranibizumab (RZ) Bevacizumab (BZ) Both given every month for the first 3 months. Following the third injection, decision to administer further treatment was guided primarily by optical coherence tomography changes	All Caucasian descent, all but one subject were male, mean age for patients in the BZ and RZ group was 78 and 80 respectively Inclusion criteria: age greate than 50, symptomatic CNV, cooperative patient, baseline visual acuities equal to or better than 20/400 Exclusion criteria: previous treatment for AMD within past year, advanced glaucoma, coexisting macular disease, history of malignant or uncontrolled hypertension, history of thromboembolic phenomena.	RZ = 7 BZ = 15	One year	Visual Acuity: Mean change (letters): RZ: +6.3 BZ: +7.6 Difference between the two groups: + 1.3 ±14.9 (95% CI 0.64-15.5) P=0.74 Mean Number of injections: RZ:4 BZ: 8 P=0.001	N/A N/A	Details of events not provided but stated that no major ocular adverse effects reported and no systemic adverse events were found in those who completed 1-year follow-up.		**Quality Rating**: Fair **Internal Validity**: Selection –2:1 randomizati the research pharmacist re for randomization Performance – Patients an physicians blinded Detection- All other investi office personnel masked to treatment assignments, to a sample size to detect a re moderate effect size differ Attrition – 78.6% of randor patients completed one ye follow-up **External Validity** Recruitment –Subjects volu from clinic; costs of medica were covered by VA. Patient Characteristics – lin applicability due to entire V population, Caucasian male Setting – outpatient VA clir Outcomes – Visual Acuity is outcome, limited safety da available.

ATT[29] , NI, MC, RCT	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2)	Mean age : RZ1: 79.2 BZ1: 80.1 RZ2: 78.4 Bz2: 79.3 Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZ1=301 BZ1=286 RZ2=298 BZ2=300	One year	Mean change in visual acuity (VA) at 1 year (no. of letters; non-inferiority limit of 5 letters): RZ1: +8.5±0.8 BZ1: +8.0±1.0 RZ2: +6.8±0.9 BZ2: +5.9±1.0 P=0.16 Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline: RZ1: 94.4% BZ1: 94% RZ2: 95.4% BZ2: 91.5% P=0.29	NA NS	Serious Systemic Events: RZ1: 53 (17.6%) BZ1: 64 (22.4%) RZ2: 61 (20.5%) BZ2: 77 (25.7%) P=0.11 BZ (1+2): 24.1% RZ (1+2):19.0% RR 1.29; 95% CI (1.01 to 1.66). P=0.04 Arteriothrombotic event: RZ1: 7 (2.3%) BZ1: 6 (2.1%) RZ2: 6 (2.0%) BZ2: 8 (2.7%) P=0.97	NS ARI 5.1% NNH 20 NS	**Quality Rating**: Fair-poor **Internal Validity**: Selection –adequate rando Computerized treatment a with eligibility review prece enrollment; significant diffe baseline medical history fo (7.6% vs. 4.2% vs. 4%, 8.7% mean age in bevacizumab g (80.1 years vs. 79.2 for rani Performance – Ophthalmol blinded to drug but not dos schedule (identify known ir Patients were initially mask study drug but may find ou identity of the drug from bi documents. Detection- VA examiner bli image graders masked to d schedule; Attrition – Low overall attri analysis which can bias tow equivalence. **External Validity** Recruitment –Most patient were identified from the cl practices at the participatir and from referring ophthalmologists in the co Patient Characteristics – Setting –in US, where many ophthalmologists already c bevacizumab Outcomes – no significant

ATT two year sults[30] , NI, MC, RCT	RZ monthly (RZm): RZ switched (RZs): BZ monthly (BZm): BZ switched (BZs): RZ PRN (RZp): BZ PRN (BZp): RZ monthly = RZ1 BZ monthly = BZ1 RZ PRN = RZ2 BZ PRN = BZ2	Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZm=146 RZs=138 BZm=135 BZs=131 RZp=287 BZp=270	2 years	Patients with same dosing regimen Mean change in visual acuity (VA) at year 2 (no. of letters; non-inferiority limit of 5 letters): RZ1: +8.8 BZ1: +7.8 RZ2: +6.7 BZ2: +5.0 P=0.21; between drug P=0.046; between regimen Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline: RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24 Patients with dosing regimen reassigned Mean change in visual acuity (VA) at year 2 RZ: -1.8 BZ-3.6 P=0.03; regimen		Deaths: RZ: 32 (5.3%) BZ: 36 (6.1%) P=0.62 RR1.15, 95% CI (0.7-1.9) Serious Systemic Events: RZ: 190 (31.7%) BZ: 234 (39.9%) P=0.004 RR 1.3; 95% CI (1.07-1.57)	NS ARI 8.2% NNH 12	**Quality Rating**: Fair-poor **Internal Validity**: Selection –adequate rando Computerized treatment a with eligibility review prece enrollment; Performance – Ophthalmologist blinded t assignment; patients were informed of drug assignme insurance and billing docur specified ranibizumab but bevacizumab. In exit interv assigned to RZ and 24.8% a BZ responded they knew w they were on. Detection- VA examiner bli image graders masked to d schedule; Attrition – Low overall attri ITT analysis **External Validity** Recruitment –Most patient were identified from the cl practices at the participatir and from referring ophthalmologists in the co Patient Characteristics – Setting – in US, where man ophthalmologists already c bevacizumab Outcomes - no significant c

'AN[31] C, NI, RCT, DB	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2) RZ = total RZ patients (RZ1 + RZ2) BZ = total BZ patients (BZ1 + BZ2)	Mean age 77.7 ±7.4 40% male Inclusions Criteria: patients aged 50+ years, newly referred for the treatment o nAMD in the first or second eye, with BCVA ≥25 letters read on a standard ETDRS chart. Exclusion criteria: long standing CNV (fibrosis >50% of the total lesion), a greatest linear diameter >6000µm, thick blood involving the centre of the fovea, 8 or more dioptres of myopia or other active ocular disease causing concurrent vision loss. Previous treatment	RZ1=157 BZ1=149 RZ2=155 BZ2=145	Two years; Interim one year results here	Best corrected visual acuity, letters RZ (total): 69 BZ (total): 66.1 Difference of -1.99 95% CI(-4.04 to 0.06)* Monthly (BZ+RZ): 66.8 PRN (BZ + RZ) : 68.4 Difference of -0.35 95% CI (-2.4 to 1.7)* * bevacizumab and discontinuous treatment inferior to continuous treatment if the lower limit of the 95% confidence interva is >-3.5 Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline: RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24	N/A NS NS	Deaths: RZ (total): 6 (1.9%) BZ (total): 5 (1.7%) P=0.81; drug Monthly (BZ+RZ): 1.6% PRN (BZ + RZ) : 2% P=0.74; regimen Serious Systemic Events: RZ (total): 30 (9.6%) BZ (total): 37 (12.5%) P=0.25 RR 1.3; 95% CI (1.07-1.57) Arteriothrombotic events: BZ (total): 1(0.7%) RZ (total): 6(2.9%) OR 0.23; 95% CI (0.05 to 1.07); p=0.03 P=0.34; between regimens	NS NS NS ARI 2.2% NNH 45 NS	**Quality Rating**: Fair **Internal Validity**: Selection – Block randomiz allocations generated by cc and concealed using an int based system; patients sim baseline Performance – Participants clinicians blinded, except ophthalmologists who inje drug were unblinded and h other role in trial. Nobody blinded to whether patient allocated to continue or sto treatment at 3 months. Ac of 98.2% Detection- Trial personnel Attrition – overall attrition ITT analysis performed **External Validity** Recruitment – recruited fro teaching and general hospi Patient Characteristics – m slightly younger than other Setting – United Kingdom Outcomes – Small differen between drugs in BCVA fro clinical perspective

tudy design abbreviations: DB = double-blind, RCT = randomized trial, NI = noninferiority, MC = multicentre, SB = single blinded [2]**Drug Regimens:** RZ = ranibizumab, BZ = bevacizumab, PRN = as needed
breviations: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confi
erval, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

CRITERIA RE-WRITTEN

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

- Cover ESAs according to OHP guidelines[1] and current medical literature.
- Cover preferred products when feasible.

Length of Authorization:

- 12 weeks initially, then up to 12 months
- Quantity limit of 30 day per dispense

Megan Herink 10/30/12 7:28 AM
Deleted: 8

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to #Error! Reference source not found.	No: Pass to RPH; Deny (not covered by the OHP).
3. Is this continuation therapy?	Yes: Go to #12	No: Go to #4
4. Is the requested product preferred?	Yes: Go to #6	No: Go to #5
5. Will the Prescriber change to a preferred product?	Yes: Inform provider of covered alternatives in class. Go to #6	No: Go to #Error! Reference source not found.
6. Is the diagnosis anemia due to chronic renal failure[2] or chemotherapy[3,4] ?	Yes: Go to #7	No: Go to #8
7. Is Hb < 10g/dl or Hct < 30% AND Transferrin saturation >20% and/or ferritin >100ng/ml?	Yes: Approve for 12 weeks with additional approval based upon adequate response.	No: Pass to RPH; Deny (not medically appropriate).
8. Is the diagnosis anemia due to HIV[5]?	Yes: Go to #9	No: Go to #10
9. Is the Hb < 10g/dL or Hct < 30% AND Transferrin saturation > 20% AND Endogenous erythropoietin < 500 iu/L AND If on Zidovudine is dose < 4200mg/week?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).

Megan Herink 10/31/12 9:40 AM
Deleted: 3

Megan Herink 10/31/12 9:40 AM
Deleted: 6

Kathy Ketchum 10/30/12 7:41 AM
Deleted: 8

Approval Criteria		
10. Is the diagnosis anemia due to ribavirin treatment[6]?	Yes: Go to #11	No: Pass to RPh; Deny, (not medically appropriate).
11. Is the Hb < 10g/dL or Hct < 30% AND Is the transferrin saturation >20% and/or ferritin >100ng/ml AND Has the dose of ribavirin been reduced by 200mg/day and anemia persisted > 2 weeks?	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh; Deny (not medically appropriate).
12. Has the patient responded to initial therapy?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).

References:

1. Oregon Health Policy and Research Current Prioritized List of Health Services. Available at: http://cms.oregon.gov/oha/OHPR/pages/herc/current-prioritized-list.aspx. Accessed September 12, 2012.

2. National Kidney Foundation. NKF KDOQI Guidelines. *NKF KDOQI Guidelines*. 2006. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm. Accessed May 25, 2012.

3. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO*. 2010;28(33):4996–5010. Available at: http://jco.ascopubs.org.liboff.ohsu.edu/content/28/33/4996. Accessed May 1, 2012.

4. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*. 2010;116(20):4045–4059.

5. Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV Infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis.* 2004;38(10):1454–1463. Available at: http://cid.oxfordjournals.org/content/38/10/1454. Accessed May 8, 2012.

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

P&T / DUR Board Action: *11/29/12; 6/28/12(KK); 2/23/12, 09/16/2010 (DO)*
Revision(s): *9/24/12, 5/14/12*
Initiated: *1/1/11*

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

Drug Use Evaluation: Physician Administered Drugs (PADs)

The goal of this drug use evaluation is to 1) Identify the cost and utilization centers of the PADs by drug class. 2) Look for opportunities to improve prescribing efficiency and/or cost effectiveness within drug classes. 3) Propose prescribing interventions with the highest return on investment.

Background

Nationally, traditional drug costs are growing at less than 1% annually while specialty drugs are growing at more than 17% annually.[1] The Oregon Health Plan fee-for-service traditional drug costs are actually trending down largely due to the new generic antipsychotics. The PAD trend is also flat over the last two years probably due to two successful initiatives: 1) implementation of ASP based reimbursement and 2) implementation of a sole source 340b contract for hemophilia management. In addition, PAD costs have been reduced by the capture of PAD claim NDCs for federal rebate collection. However, it is estimated there are over 30 new molecular entities in the specialty drug pipeline that will be approved by the end of 2014. Oncology is a target area, with an increase in the number of more targeted and specialized therapies. With that, there is an expectation that the PAD trend will again increase at a high rate due to the lack of generic competition and the complexity of the drug therapy. [2]

Methods:

All paid, clean, fee-for-service outpatient and professional claims (Types: O, C, M, B) with a procedure code beginning in Jxxxx or in group 6069 (i.e. the codes captured for rebate collection) with service dates from July 1, 2011 through June 30, 2012 were reviewed. These were linked to the drug file for classification using the most prevalent National Drug Code (NDC) captured on the claims for a single procedure code. This classification was manually reviewed and where the procedure code description was in conflict with the NDC code, the claim was reclassified to the procedure code description. Preferred Drug List (PDL) classes were used where possible. Other high cost (>$50,000/year) procedure codes were manually grouped by a pharmacist.

Results

Over $16 million was spent on PADs during the time period. This is roughly 10% of all fee-for-service drug costs. However, the total is skewed by the mental health drug carve out. So, the PADs are likely more than 20% drug costs if only fee-for-service patients are considered.

The top ten drugs by the amount paid are displayed in Table 1. They represent 56% of the total PAD costs and just 5% of the total PAD claims billed.

TABLE 1 – TOP TEN PHYSICIAN ADMINISTERED DRUGS BY PAID AMOUNT

Class	Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
HEMO	J7192	Factor Viii Recombinant Nos	$1,977,723	12.34%	150	0.15%
ONC	J9355	Trastuzumab Injection	$1,650,472	10.30%	736	0.71%
CSF	J2505	Injection, Pegfilgrastim 6mg	$1,620,405	10.11%	699	0.68%
ONC	J9171	Docetaxel Injection	$754,596	4.71%	414	0.40%
HEMO	J7186	Antihemophilic Viii/Vwf Comp	$630,238	3.93%	41	0.04%
CONTRACEPT	J7302	Levonorgestrel Iu Contracept	$561,305	3.50%	1463	1.42%
HEMO	J7185	Xyntha Inj	$496,659	3.10%	21	0.02%
TIM	J1745	Infliximab Injection	$496,463	3.10%	545	0.53%
ONC	J9310	Rituximab Injection	$417,645	2.61%	255	0.25%
EPO	Q4081	Epoetin Alfa, 100 Units Esrd	$408,248	2.55%	1321	1.28%

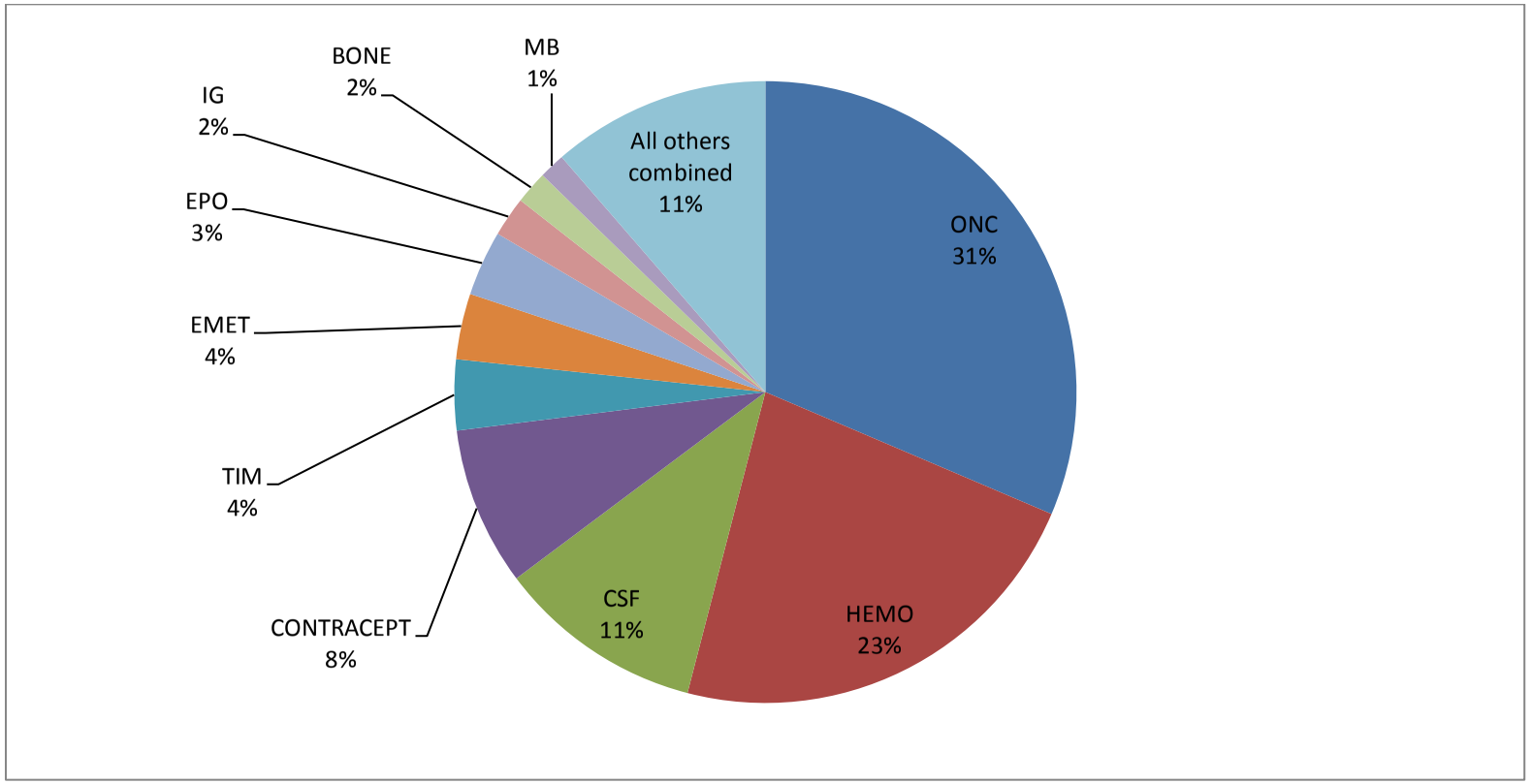
The top ten drugs by claim count are displayed in Table 2. In contrast these represent just 4% of PAD costs but 38% of PAD claims billed.

TABLE 1 – TOP TEN PHYSICIAN ADMINISTERED DRUGS BY CLAIM COUNT

Class	Code	Code Description	Sum Amt Paid	Pct Total	Sum ClmCnt	Pct Total
EMET	J2405	Ondansetron Hcl Injection	$107,823	0.67%	7166	6.94%
CONTRACEPT	J1055	Medrxyprogester Acetate Inj	$114,786	0.72%	6731	6.52%
SAO	J3010	Fentanyl Citrate Injeciton	$67,819	0.42%	4505	4.36%
SAO	J1170	Hydromorphone Injection	$76,345	0.48%	4257	4.12%
DEXAMETHASONE	J1100	Dexamethasone Sodium Phos	$30,664	0.19%	3936	3.81%
NSAID	J1885	Ketorolac Tromethamine Inj	$37,832	0.24%	3397	3.29%
MIDAZOLAM	J2250	Inj Midazolam Hydrochloride	$44,630	0.28%	3285	3.18%
Infusion Fluids	J7030	Normal Saline Solution Infus	$58,278	0.36%	3024	2.93%
SAO	J2270	Morphine Sulfate Injection	$46,096	0.29%	2789	2.70%
Infusion Fluids	J7050	Normal Saline Solution Infus	$88,746	0.55%	2704	2.62%

The top ten drug classes represent 89% of PAD costs with oncology and oncology-related drugs (CSF, EMET, and BONE) accounting for 47%. See Figure 1 below.

FIGURE 1 – PHYSICIAN ADMINISTER DRUG CLASS DISTRIBUTION BY AMOUNT PAID



Additional detail about drug distribution by class is included in the Appendix.

Discussion

The overwhelming majority of PAD costs are associated with oncology treatment. It is an area that has been largely devoid from drug use management with the exception of the erythropoietin clinical use criteria. Siddiqui and Rajkumar postulate several reasons for this including; "…most cancers are incurable, patients are treated with each approved agent (sequentially or in combination), creating a virtual monopoly because the use of one drug does not automatically mean that the others are no longer needed. Third, even when the monopoly is broken with the arrival of "new and improved" versions of an approved drug, the older (and by now generic) drug tends to be viewed as substandard treatment, thereby perpetuating the situation. Fourth, the very nature of cancer, and the seriousness of the diagnosis, plays a role in that patients and physicians are often willing to pay the high price of treatment even for marginal improvements in outcome. Finally, our systems provide an incentive to administer more chemotherapy, and there are legal barriers that prevent agencies such as the FDA from taking economic and cost-effectiveness considerations into account when approving new drugs." [3] However, they and others have recommended value-based coverage to blunt the rising costs of these and other PADs.[4] There is opportunity to optimize the cost-effectiveness of oncology related anti-emetic use and bone metabolism drug use through implementation of the PDL on medical claims. The recent review of CSF drug use did not identify any opportunities. Erythropoetin drug use is primarily associated with end stage renal disease and will benefit from implementation of the PDL on medical claims.

Hemophilia drug use was optimized with implementation of the sole source 340b contract for both drug procurement and disease management.

Surprisingly, contraception is associated with 8% of total PAD costs. The apparent high use of vaginal rings and IUD needs to be evaluated for value. While these state expenditures are matched from the federal government at 95%, they warrant closer scrutiny. Other areas that need further investigation are the use of immunoglobulin and drugs for muscle blockade.

Of particular note is that natalizumab, a drug with limited indications for Multiple Sclerosis and Crohn's Disease and which has a black box warning for increased risk of progressive multifocal leukoencephalopathy, ranks in the top 25 drugs by cost at $174,000 per year on 145 claims.

Recommendations:

1) Close any new PAD HCPC codes until reviewed by P&T for appropriateness (PDL class, OHP coverage, etc.)
2) Coordinate coverage of drugs billed via drug claims and medical claims
   a. Close HCPC codes for self-administered drugs and close NDCs for clinic administered drugs
   b. Establish a duplicate claim edit across all claims (same patient, same drug, same DOS) where it is appropriate to bill in either program.
   c. Phase in the current drug PA requirements for medical claims starting with classes with limited numbers of providers to target education of the PA process (i.e. BONE, EMET, EPO, MS, TIMS)
   d. Insure that provider reimbursed amounts are similar in both programs.
3) Work with oncology specialists to develop a management plan using best practices to possibly include the following:
   a. Implement PA for NCCN guidelines adherence of high cost/high risk oncology drugs
   b. Implement value-based reimbursement of oncology drugs
      i. Higher reimbursement margin to providers and no barriers for high value drugs
      ii. Limit coverage or limit reimbursement margin for drugs with marginal benefit at higher cost
4) Evaluate use of IU and vaginal ring contraception versus other forms.
5) Consider prior authorization of natalizumab, a drug with limited indications for Multiple Sclerosis and Chron's Disease and a black box warning for risk of progressive multifocal leukoencephalopathy.
6) Follow-up with specific DUEs of immune globulin and musclular blockade drugs.

[1] The Express Scripts Research & New Sollutions Lab. Express Scripts 2011 Drug Trend Report. *Research - Express-Scripts.com*. 2012. Available at: http://www.express-scripts.com/research/research/dtr/archive/2012/dtrFinal.pdf. Accessed October 29, 2012.

[2] RxOutlook. SxC Health Solutions, Inc. 6 (5) 4th quarter 2012. Subscription required.

[3] Siddiqui M, Rajkumar SV. The High Cost of Cancer Drugs and What We Can Do About It. Mayo Clinic Proceedings. 2012;87(10):935–943.

[4] James C. Robinson. Applying Value-Based Insurance Design To High-Cost Health Services. Health Affairs, 29, no.11 (2010):2009-2016

Appendix 1

ONCOLOGY DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J9355	Trastuzumab Injection	$1,650,472	31%	736	7%
J9171	Docetaxel Injection	$754,596	14%	414	4%
J9310	Rituximab* Injection	$417,645	8%	255	2%
J9035	Bevacizumab^ Injection	$326,944	6%	941	9%
J9263	Oxaliplatin	$300,091	6%	193	2%
J9041	Bortezomib Injection	$196,413	4%	227	2%
J9264	Paclitaxel Protein Bound	$180,355	3%	121	1%
J9305	Pemetrexed Injection	$167,607	3%	65	1%
J9201	Gemcitabine Hcl Injection	$160,859	3%	424	4%
J9055	Cetuximab Injection	$122,559	2%	81	1%
J9395	Injection, Fulvestrant	$108,510	2%	115	1%
J9265	Paclitaxel Injection	$81,587	2%	664	6%
J9070	Cyclophosphamide 100 Mg Inj	$74,272	1%	564	5%
J9033	Bendamustine Injection	$71,319	1%	53	0%
J9266	Pegaspargase Injection	$70,185	1%	14	0%
J9207	Ixabepilone Injection	$36,636	1%	17	0%
J9179	Eribulin Mesylate Injection	$34,801	1%	20	0%
J9045	Carboplatin Injection	$29,479	1%	421	4%
J9351	Topotecan Injection	$27,840	1%	52	0%
	All others combined	$222,870	4%	2727	25%

* ALSO USED OFF-LABEL FOR RHEUMATOID ARTHRITIS, ITP, LUPUS AND SEVERAL OTHER INDICATIONS

^ALSO USED OFF-LABEL FOR AMD, DME, BREAST CA AND SEVERAL OTHER INDICATIONS

HEMOPHILIA DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J7192	Factor Viii Recombinant Nos	$1,977,723	55%	150	58%
J7186	Antihemophilic Viii/Vwf Comp	$630,238	17%	41	16%
J7185	Xyntha Inj	$496,659	14%	21	8%
J7198	Anti-Inhibitor	$314,630	9%	18	7%
J7195	Factor Ix Recombinant	$188,409	5%	26	10%
J7189	Factor Viia	$16,898	0%	1	0%

CSF DETAIL

62

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J2505	Injection, Pegfilgrastim 6mg	$1,620,405	94%	699	77%
J1441	Filgrastim 480 Mcg Injection	$50,809	3%	77	8%
J1440	Filgrastim 300 Mcg Injection	$30,621	2%	134	15%
J2562	Plerixafor Injection	$19,198	1%	2	0%
J2820	Sargramostim Injection	$282	0%	1	0%

CONTRACEPTION DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J7302	Levonorgestrel Iu Contracept	$561,305	42%	1463	12%
J7307	Etonogestrel Implant System	$274,751	21%	749	6%
J7303	Contraceptive Vaginal Ring	$173,863	13%	1944	16%
J1055	Medrxyprogester Acetate Inj	$114,786	9%	6731	54%
J7300	Intraut Copper Contraceptive	$105,999	8%	389	3%
J7304	Contraceptive Hormone Patch	$88,213	7%	1075	9%
J1380	Estradiol Valerate 10 Mg Inj	$2,183	0%	31	0%
J1410	Inj Estrogen Conjugate 25 Mg	$355	0%	9	0%
J1051	Medroxyprogesterone Inj	$239	0%	12	0%
J2675	Inj Progesterone Per 50 Mg	$0	0%	1	0%
J1000	Depo-Estradiol Cypionate Inj	$0	0%	5	0%

63

TIMS DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J1745	Infliximab Injection	$496,463	84%	545	73%
J0129	Abatacept Injection	$59,362	10%	128	17%
J3262	Tocilizumab Injection	$32,886	6%	78	10%

ANTIEMETIC DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J2469	Palonosetron Hcl	$251,840	46%	1669	12%
J1453	Fosaprepitant Injection	$135,502	25%	635	5%
J2405	Ondansetron Hcl Injection	$107,823	20%	7166	51%
J2550	Promethazine Hcl Injection	$23,400	4%	2328	17%
J2765	Metoclopramide Hcl Injection	$8,342	2%	672	5%
Q0179	Ondansetron Hcl 8 Mg Oral	$6,005	1%	236	2%
J1790	Droperidol Injection	$5,648	1%	405	3%
J1626	Granisetron Hcl Injection	$3,779	1%	447	3%
S0181	Ondansetron 4 Mg	$3,268	1%	108	1%
J0780	Prochlorperazine Injection	$1,045	0%	97	1%
J8501	Oral Aprepitant	$439	0%	2	0%
J1260	Dolasetron Mesylate	$350	0%	11	0%
J8499	Oral Prescrip Drug Non Chemo	$137	0%	17	0%
Q0170	Promethazine Hcl 25 Mg Oral	$98	0%	27	0%
J8597	Antiemetic Drug Oral Nos	$71	0%	1	0%
J3490	Drugs Unclassified Injection	$59	0%	22	0%
Q0166	Granisetron Hcl 1 Mg Oral	$55	0%	2	0%
Q0169	Promethazine Hcl 12.5mg Oral	$47	0%	11	0%
J9999	Chemotherapy Drug	$33	0%	5	0%
S0119	Ondansetron 4 Mg	$29	0%	99	1%
Q0165	Prochlorperazine Maleate10mg	$13	0%	5	0%
Q0164	Prochlorperazine Maleate 5mg	$9	0%	3	0%
Q0181	Unspecified Oral Anti-Emetic	$3	0%	3	0%

ERYTHROPOETIC DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
Q4081	Epoetin Alfa, 100 Units Esrd	$408,248	75%	1321	55%
J0881	Darbepoetin Alfa, Non-Esrd	$92,489	17%	633	26%
J0885	Epoetin Alfa, Non-Esrd	$31,392	6%	352	15%
J0882	Darbepoetin Alfa, Esrd Use	$12,009	2%	99	4%

IMMUNE GLOBULIN DETAIL

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J1569	Gammagard Liquid Injection	$206,154	62%	43	30%
J1572	Flebogamma Injection	$59,529	18%	56	39%
J1459	Inj Ivig Privigen 500 Mg	$52,295	16%	20	14%
J1568	Octagam Injection	$12,983	4%	22	15%
J1561	Gamunex/Gamunex C	$970	0%	1	1%

BONE METABOLISM DRUGS

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J3487	Zoledronic Acid	$190,302	69%	334	54%
J0897	Denosumab Injection	$39,321	14%	78	13%
J3488	Reclast Injection	$33,473	12%	84	14%
J3490	Drugs Unclassified Injection	$6,487	2%	12	2%
J2430	Pamidronate Disodium /30 Mg	$4,149	2%	99	16%
J1740	Ibandronate Sodium Injection	$799	0%	12	2%

MUSCLE BLOCKADE DRUGS

Code	Code Description	Sum Amount Paid	Pct Total	Unique Claim Count	Pct Total
J0475	Baclofen 10 Mg Injection	$111,156	51%	200	29%
J0585	Injection,Onabotulinumtoxina	$94,957	44%	170	25%
J0330	Succinycholine Chloride Inj	$3,692	2%	241	35%
J0586	Abobotulinumtoxina	$3,312	2%	29	4%
J0588	Incobotulinumtoxin A	$2,019	1%	15	2%
J3490	Drugs Unclassified Injection	$501	0%	8	1%
J0476	Baclofen Intrathecal Trial	$497	0%	11	2%
J0587	Inj, Rimabotulinumtoxinb	$0	0%	6	1%

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

Oregon Health Authority

New Obesity Drug Evaluations: Phentermine/Topiramate and Lorcaserin

Month/Year of Review: November 2012
Generic Name: Phentermine and topiramate extended-release
Generic Name: Lorcaserin Hydrochloride
PDL Class: Weight Loss Medications

End date of literature search: August 2012
Brand Name (Manufacturer): Qsymia® (Vivus, Inc.)
Brand Name (Manufacturer): Belviq® (Arena Pharmaceuticals, Inc.)
Dossier Received: Pending

FDA Approved Indications: [1]

Phentermine/topiramate is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related co-morbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of Use

- The effect of phentermine/topiramate on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of phentermine/topiramate in combination with other products intended for weight loss, including prescription and over-the-counter drugs and herbal preparations have not been established.

Lorcaserin is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of: [2]

- 30 kg/m2 or greater (obese), or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight related co-morbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

Limitations of Use:

- The safety and efficacy of co-administration of lorcaserin with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established.
- The effect of lorcaserin on cardiovascular morbidity and mortality has not been established.

Research Questions:

- Is there evidence for the efficacy and safety of phentermine/topiramate and lorcaserin for the long-term treatment of obesity?
- Is there any evidence that phentermine/topiramate and lorcaserin improves long term clinical outcomes such as prevention of type 2 diabetes and reduction of cardiovascular related morbidity and mortality?
- Are there any subgroup populations in which these drugs offer improved efficacy or safety?

Conclusions for phentermine/topiramate:

- There is insufficient evidence to make conclusions about phentermine/topiramate's effects on cardiovascular morbidity and mortality or long term maintenance of weight loss.
- There is moderate strength evidence that phentermine/topiramate 7.5mg/46mg demonstrated an increase in the number of patients who achieved a ≥5% weight loss at 56 weeks in overweight and obese patients compared to placebo (RR 2.9, 95% CI 2.6-3.3) and demonstrated a difference in mean weight loss of ≥5% compared to placebo, meeting both FDA efficacy requirements.
- There is low strength evidence that phentermine/topiramate caused a greater number of withdrawals due to adverse events than placebo.
- There is insufficient evidence to compare phentermine/topiramate with other currently available long-term weight loss agents, lifestyle modifications, and surgery options. There are currently no direct head-to-head comparison trials with other weight loss agents

Conclusions for lorcaserin:

- There is insufficient evidence to make conclusions about lorcaserin's effects on cardiovascular morbidity and mortality or long term maintenance or weight loss.
- There was moderate evidence showing that more patients on lorcaserin 10mg twice daily achieved ≥5% weight loss than placebo at 52 weeks in obese patients (RR 2.1, 95% CI 2.0-2.3) but did not demonstrate a difference in mean weight loss of ≥5% compared to placebo, meeting only one of the two FDA efficacy criteria.
- There is low evidence that lorcaserin does not cause FDA-defined valvulopathy; although the studies lacked large sample sizes and duration to fully detect long-term development and effects on cardiovascular outcomes.
- There is insufficient evidence to compare lorcaserin with other currently available long-term weight loss agents, lifestyle modifications, and surgery options. There are currently no direct head-to-head comparison trials with other weight loss agents

Recommendations for both phentermine/topiramate and lorcaserin:

- Cover for only OHP covered diagnoses
- As the treatment of obesity with medications is an OHP unfunded diagnosis, eliminate current prior authorization for weight loss medications.

Background:

Obesity is a chronic disease that is growing in prevalence in the United States and worldwide each year.[3] In the United States, more than 30% of males and females are considered obese, and in the state of Oregon, 1400 obesity related deaths occur each year, making obesity only second to tobacco as the state's leading cause of preventable death.[4,5] Under the Oregon Health Plan (OHP) medical treatment of obesity is limited to accepted intensive counseling on nutrition and exercise, provided by health care professionals, according to recommendations of the US Preventive Services Task Force. Pharmaceutical agents are not intended to be covered services for the treatment of obesity. Body mass index (BMI), taking into account a patient's height and weight, is considered a simple screening tool to tell if a patient is obese (Table 1). Research shows that waist circumference may be an acceptable alternative to BMI.[4, 6]

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Table 1: BMI Classifications

Classifications for BMI[6]	Body Mass Index (BMI)
Underweight	<18.5 kg/m^2
Normal weight	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obesity (Class 1)	30-34.9 kg/m^2
Obesity (Class 2)	35-39.9 kg/m^2
Extreme obesity (Class 3)	≥40 kg/m^2

Long term consequences that result from obesity include many chronic diseases, such as diabetes, hypertension, high cholesterol, cardiovascular disease, arthritis, and sleep apnea. Mortality rates and risk of cardiovascular disease rise with increasing degrees of overweight and obesity; marked increases in risk of death occur when BMI levels reach 29 to 30 kg/m^2 or greater.[7] The Diabetes Prevention Program demonstrated that lifestyle interventions that can reduce body weight up to 7% lowers the 5-year risk of developing diabetes by 58%.[8] According to the 2007 Food and Drug Administration (FDA) Industry Guidance for Obesity Treatment, a product can be considered effective for weight management after one year of treatment, if either of the following occurs: 1) the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, 2) or if the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.[4] The U.S. Preventative Services Task Force (USPSTF) found adequate evidence that a vigorous weight loss program involving multi-component behavioral interventions can lead to an average weight loss of 4 to 7 kg. This has been shown to improve glucose tolerance and other physiological risk factors for cardiovascular disease. Direct evidence about multiple interventions on reducing hospitalizations and mortality is lacking, and more trials on the long-term effects of weight reduction need to be conducted. Dietary changes, exercise, and behavioral modifications are considered first-line treatment for weight reduction according to the 2006 Canadian guidelines.[9]

The 2006 Canadian guidelines recommend pharmacological therapy when a patient has a BMI ≥30 kg/m^2 or if they have a BMI of 27-30 kg/m^2 with co-morbid conditions.[9] Medications should only be used in combination with lifestyle modifications, such as increased physical activity and dietary changes. Currently, orlistat (an intestinal fat absorption inhibitor) is the only long-term medication approved for obesity (data available for up to four years of treatment). Short-term medication options include phentermine or diethylpropion, but both have potential for abuse and should not be used longer than 12 weeks.[9,10] Attrition rates in studies evaluating weight loss medications are generally high, averaging above 30% according to a recent systematic review , possibly because of a high female representation, lack of weight related co-morbidities, and lack of an adequate lead-in period.[11] Surgery is reserved for patients who fail lifestyle modifications with or without drug therapy and who have a BMI>35 kg/m^2 with co-morbid conditions or a BMI>40 kg/m^2.[2,3]

Phentermine/Topiramate

Clinical Efficacy (evidence table in Appendix 1):

Two double blind, placebo controlled, phase III, randomized controlled trials (EQUIP & CONQUER) and one double blind extension trial of CONQUER (SEQUEL) compared phentermine and topiramate continuous release at varying doses to placebo.[13–15] The majority of the patients included in all three trials were white females in their early forties and fifties. EQUIP included people who were considered severely obese (BMI ≥35) and were taking medications that included lipid lowering and antihypertensive agents. CONQUER and SEQUEL included patients who were overweight and obese (BMI 27-45), with two or more comorbidities

(hypertension, dyslipidemia, diabetes). The SEQUEL extension study included patients who completed the CONQUER study on treatment and complied with protocol requirements.

The EQUIP trial (n=1267) was a 56-week fair-good quality trial (4-weeks post-randomization used for topiramate titration phase) looking at a titration dose of phentermine and topiramate (3.75mg/23mg) and the highest dose of the combination (15mg/92mg) compared to placebo. The co-primary outcomes were achieving weight loss ≥5% of baseline body weight, weight loss of ≥10% of body weight, and mean percent weight loss from baseline. In the intention to treat (ITT) population, significantly more patients in the treatment group achieved ≥5% loss of baseline body weight for both the high dose and titration dose compared to placebo (66.7%, 44.9%, and 17.3%, respectively; p-value<0.0001 for all comparisons),and achieved ≥10% loss (57%, 23.1%, and 11.1%; p-value <0.0001). Mean percent weight loss from baseline was also significantly greater with treatment compared to placebo (-10.9%, -5.1%, and -1.6%; p-value<0.0001) for phentermine/topiramate 15mg/92mg, 3.75mg/23mg versus placebo, respectively. Weight loss in the high dose group was accompanied by small, but statistically significant greater changes in blood pressure, glucose, triglycerides, and cholesterol compared to placebo. Overall attrition was 40%, with more patients in the placebo arm discontinuing drug than in the treatment arms. External validity is low due to majority of subjects being white females without many significant obesity-associated comorbid diseases. Also, the recommended initial maintenance dose of 7.5mg/46mg was not evaluated in this study.

The CONQUER trial (n=2448) was another fair to good quality, 56-week trial comparing a higher dose of phentermine/topiramate 15mg/92mg and lower dose of 7.5mg/46mg to placebo. Approximately 16% of patients had type 2 diabetes, 36% had hypertriglyceridemia, and 52% had hypertension, however those with significant cardiovascular disease were still excluded from the study. Both doses showed greater efficacy than placebo for each primary outcome. The mean percentage change in bodyweight between drug and placebo was statistically significant in both the 15mg/92mg group (-8.6%; 95% CI -9.3 to -8.0, p<0.001) and the 7.5mg/46mg group (-6.6%; 95% CI -7.4 to -5.8, p<0.0001). More patients in the treatment groups achieved a weight loss of at least 5% (RR 2.98; 95% CI 2.59, 3.41) and 10% (RR 5.07; 95% CI 3.94, 6.57) compared to placebo (p-value<0.0001 for all comparisons to placebo). Although there were few patients ≥65 years and few black patients, there was no significant difference in efficacy based on a subgroup analysis of sex, age, and race; although conclusions should not be drawn from this. The CONQUER trial lacks generalizability to the overall population.

SEQUEL was a 1-year extension of the CONQUER trial (108 weeks), using the patients who completed the CONQUER study on treatment, complied with protocol requirements, and agreed to continue as further participation was optional. Due to significant selection bias, results should be interpreted with caution, as the potential bias toward inclusion of only subjects with positive outcomes from CONQUER. A greater proportion of subjects in the 15mg/92mg treatment arm (85.5%) agreed to continue than both the 7.5mg/46mg arm (79.4%) and the placebo group (69.4%). There continued to be a significantly greater mean percentage change from baseline in body weight for the phentermine/topiramate 15mg/92mg and 7.5mg/46mg groups compared to placebo,(-10.5%, -9.3%, and -1.8%, respectively p-value<0.0001 for all comparisons). The number of patients achieving weight loss of at least 5% (RR 2.51; 95% CI 2.02, 3.07; low dose vs. placebo) and 10% (RR 2.31; 95% CI 1.51, 3.59; low dose vs. placebo) of body weight continued to be more for both treatment groups compared to placebo.

Clinical Safety:

In EQUIP, there was no statistically significant difference in severe adverse events (10.2%, 10.4%, and 8.0%; p-value=0.27) between phentermine 15mg/92mg (RR 1.27; 95% CI 0.85, 1.92), 3.75mg/23mg compared to placebo, respectively. Severe adverse events included cholelithiasis and myelogenous leukemia. There was a significant difference in withdrawals due to adverse events between the high dose of phentermine/topiramate 15mg/92mg and placebo (16% vs. 8.4%; p-value<0.001). The most common events included paresthesia, dry mouth, constipation, dysgeusia, depression, insomnia and irritability (p-values<0.0001).

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

The CONQUER trial reported no statistically significant difference in serious adverse events including nephrolithiasis and paresthesia (5% for phentermine/topiramate 15mg/92mg vs. 4% placebo; p-value=0.31), but did report a statistically significant difference in withdrawal rates (19% vs. 9% for 15mg/92mg vs placebo; p-value<0.0001, RR 2.16; 95% CI 1.70, 2.78). Dose related trends were noted for rates of dry mouth, constipation, dysgeusia, paraesthesia, insomnia, dizziness, anxiety, irritability, and disturbance in attention.

There were also no statistically significant differences in serious adverse events between the phentermine/topiramate 15mg/92mg and placebo in the SEQUEL trial (RR 1.03; 95% CI 0.41, 2.61, p=0.96) or in withdrawals due to adverse events (RR 1.41; 95% CI 0.54, 3.86; p=0.45). The most commonly reported adverse events were upper respiratory tract infection, constipation, paraesthesia, sinusitis, and dry mouth. The incidence of individual adverse events was lower in the second year (weeks 56-108) than in the first year (weeks 0-56).

Lorcaserin

Clinical Efficacy (Evidence table in Appendix 2):

FDA approval of lorcaserin was based on three fair quality phase III, double-blind, randomized, placebo-controlled trials (BLOOM, BLOOM-DM, and BLOSSOM).[16-18] BLOOM and BLOOSOM looked at lorcaserin in the non-diabetic population, while BLOOM-DM was conducted in the diabetic patients. The majority of the subjects for all of the trials were white women in their mid-40's to 50's that were relatively healthy. All patients in the trials were asked to participate in a standardized behavioral weight management program that recommended patients participate in 30 minutes of exercise daily and reduce their caloric intake by 600 kcal daily along with medication treatment. All studies had an overall high attrition rate and the primary data analysis was intention-to-treat (ITT) with last-observation-carried-forward (LOCF) imputation, which could yield misleading results if patients regained weight after withdrawing from the study. None of the studies met the first FDA efficacy criteria of achieving a difference in mean weight loss between drug and placebo of at least 5%, however the second criteria was met (percentage of subjects who lost at least 5 percent of body weight is at least 35%).

The Behavioral Modification and Lorcaserin for Overweight and Obesity Management trial (BLOOM) was a fair quality, 1-year trial that compared lorcaserin 10 mg twice daily versus placebo. Patients who remained in the trial were eligible to continue for a second year. Patients who were on placebo continued to receive it, while patients who had been receiving lorcaserin were randomized again in a 2:1 ratio to lorcaserin or placebo (not reported in evidence table). Endpoints at 52 weeks were analyzed using a modified intention-to-treat (MITT) with last observation carried forward (LOCF) imputation. There was a statistically significant difference between lorcaserin and placebo for all three co-primary endpoints: change in weight from baseline at year 1 (5.9+/-0.2kg vs. 2.2+/-0.1kg; p<0.0001), percent of subjects achieving ≥5% weight loss at week 52 (47.5% vs 20.3%; p-value<0.001), and percent of subjects achieving ≥10% weight loss at week 52 (22.6% vs. 7.7%; p-value<0.001). Although there was weight regain in all groups in year two, loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year two than those reassigned to receive placebo (67.9% vs. 50.3%, p<0.001).

The Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) study was a fair quality, 1-year trial comparing lorcaserin 10 mg BID and lorcaserin 10 mg QD to placebo in a randomized 2:1:2 ratio (n=4008). The co-primary outcomes included percent change in weight from baseline and proportion of participants achieving a weight loss ≥5% over one year. The percent change in weight at year 1 was -5.6%, -4.6%, and -2.7% for lorcaserin 10mg BID, lorcaserin 10mg QD, and placebo respectively (reported<0.001). The difference in mean weight loss between lorcaserin 10mg twice daily and placebo was 3%. The percentage of subjects achieving ≥5% weight loss was 47%, 42%, and 24% (p-value<0.001) for lorcaserin 10mg BID, lorcaserin 10mg QD, and placebo respectively. Although underrepresented, significant weight loss occurred in men, across BMI subgroups, and across racial subgroups. Study limitations included

an unclear method for appropriate allocation concealment and unclear method for patient and caregiver blinding, and exclusion of many preexisting conditions and serotonergic medications.

The Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) was a fair quality, 1-year trial that compared lorcaserin 10mg twice daily and lorcaserin 10mg daily with placebo in patients with type 2 diabetes. BLOOM-DM (n=524) enrolled patients that had ar HbA1c ranging from 7-10% and were currently taking metformin, a sulfonylurea, or both. The change in weight from baseline (-4.7kg vs. -1.6kg; p-value<0.001, mean difference 3%), number of patients with loss of ≥5% of body weight (37.5% vs.16.1%; p-value<0.001), and number with ≥10% of body weight (16.3% vs. 4.4%; p-value<0.001) were statistically significant comparing lorcaserin twice daily to placebo, respectively. Limitations of this study included unclear treatment randomization, unclear allocation concealment, and unclear blinding of outcome assessors.

Clinical Safety:

In the BLOOM trial, there was no statistically significant difference in FDA-defined valvulopathy between lorcaserin and placebo (2.7% vs 2.3% respectively; p-value=0.70, RR 1.1; 95% CI 0.69-1.85). There was also no significant difference in withdrawals due to adverse effects between the two groups (7.1% vs 6.7%; RR 1.06; 95% CI 0.82, 1.37). The most common adverse events reported in both trials were headache, upper respiratory infection, nasopharyngitis, dizziness, and nausea, and there were two patients that experienced serious cardiac disorders in the lorcaserin group (<1%). The BLOSSOM trial also did not demonstrate significant differences in rates of FDA-defined valvulopathy with percentages being 2.0%, 1.4%, and 2.0% for lorcaserin BID, QD, and placebo respectively. However, the statistical power of the echocardiographic safety analysis was limited. Discontinuations due to adverse events were similar between lorcaserin given twice daily and placebo (7.2%, vs. 4.6%).

In the BLOOM-DM trial, rates of hypoglycemia were more frequent in the lorcaserin groups compared to placebo (7.4% BID, 10.5% QD, and 6.3% placebo) and were higher among patients taking sulfonylureas over metformin. At 52 weeks, one patient in the placebo group (0.5%), two in the lorcaserin daily group (2.5%; p=0.187), and six in the lorcaserin twice daily group (2.9%; p=0.122) had echocardiographic FDA-defined valvulopathy that was not present at baseline, but the trial itself enrolled too few patients to provide a statistically significant population analysis specifically for the FDA-defined valvulopathy safety analysis. The most common adverse events in the lorcaserin group compared to placebo were headache, back pain, nasopharyngitis, and nausea.

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

References:

1. Qsymia Prescribing Information. QsymiaPI.pdf. Available at: http://www.vivus.com/docs/QsymiaPI.pdf. Accessed August 23, 2012.
2. Belviq Prescribing Information. BelviqPI.pdf. 2012. Available at: http://us.eisai.com/package_inserts/BelviqPI.pdf. Accessed August 14, 2012.
3. Bray GA. Overview of therapy for obesity in adults. Available at: http://www.uptodate.com/contents/overview-of-therapy-for-obesity-in-adults?source=search_result&search=obesity&selectedTitle=3%7E150#H1. Accessed August 14, 2012.
4. Moyer V. Annals of Internal Medicine | Screening for and Management of Obesity in Adults: U.S. Preventive Services Task Force Recommendation Statement. Available at: http://annals.org/article.aspx?articleid=1200996. Accessed August 14, 2012.
5. Buelow V, Ngo D. Oregon Overweight, Obesity, Physical Activity and Nutrition Facts. *Oregon Health Authority: Health Promotion and Chronic Disease Section*. 2012. Available at: http://public.health.oregon.gov/PreventionWellness/ PhysicalActivity/Pages/pubs.aspx. Accessed August 14, 2012.
6. Initiative NOE, Heart N, Lung, et al. *The Practical guide: identification, evaluation, and treatment of overweight and obesity in adults*. National Heart, Lung, and Blood Institute; 2002.
7. Padwal RS, Rucker D, Li SK, Curioni C, Lau DC. Long-term pharmacotherapy for obesity and overweight. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004094.pub2/abstract. Accessed August 17, 2012.
8. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 2002;346(6):393–403.
9. Lau DCW, Douketis JD, Morrison KM, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *Canadian Medical Association Journal*. 2007;176(8):S1–S13.
10. National Guideline Clearinghouse. National Guideline Clearinghouse | World Gastroenterology Organisation Global Guideline: obesity. Available at: http://guideline.gov/content.aspx?id=15230&search=obesity. Accessed August 14, 2012.
11. Fabricatore AN, Wadden TA, Moore RH, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. *Obes Rev*. 2009;10(3):333–341.
12. FDA News Release. Press Announcements - FDA approves Belviq to treat some overweight or obese adults. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm. Accessed August 14, 2012.
13. Allison DB, Gadde KM, Garvey WT, et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). *Obesity*. 2012;20(2):330–342.
14. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341–1352.
15. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am. J. Clin. Nutr.* 2012;95(2):297–308.
16. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N. Engl. J. Med.* 2010;363(3):245–256.
17. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study. *Obesity (Silver Spring)*. 2012;20(7):1426–1436.
18. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J. Clin. Endocrinol. Metab.* 2011;96(10):3067–3077.

Appendix 1: COMPARATIVE CLINICAL EFFICACY FOR PHENTERMINE/TOPIRAMATE

Relevant Endpoints:

1) Reduction in morbidity and mortality due to cardiovascular events
2) Reduction of Type 2 diabetes
4) Withdrawals due to adverse events

Primary Study Endpoint:

1) Percent of body weight loss
2) Lost ≥5% of baseline body weight
3) Lost ≥10% of baseline body weight

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Ref./Study Design[a]	Drug Regimens	Patient Population	N	Outcomes/ Efficacy Results	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Allison D, et al.[13] RCT, DB, PC, PG, Phase III (EQUIP)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 3.75mg/23mg 3. Placebo 56-week (4-week postrandomization titration period) Randomized in a 2:1:2 ratio	Demographics: Age ~42.7; female 83%; BMI 42.0kg/m^2; white ~80%; black 16-18%; weight 115kg Inclusion Criteria: Age 18-70; BMI≥35kg/m^2(no upper limit); TG≤200mg/dL with treatment of 0-1 lipid lowering med; BP≤140/90mmg/Hg with treatment of 0-2 antihypertensive medications; fasting BG≤110mg/dL Exclusion Criteria: Weight gain/loss >5 kg ≤3 months; history of eating disorders; bariatric surgery, thyroid dysfunction; chronic oral glucocorticoid therapy; bipolar disorder or psychosis; current moderate to severe depression, history of suicidal behavior or ideation, or antidepressant use that had not been stable for ≤3 months; stroke, myocardial infarction, unstable angina, congestive heart failure, or cardiac valvulopathy;	1. 512 2. 241 3. 514	Lost≥5% of baseline body weight (ITT/MI): 1. 381 (74.4%) 2. 123 (51.1%) 3. 127 (24.8%) 1 vs. 3: RR 3.01; 95% CI (2.60, 3.49) p-value<0.0001 2 vs. 3: RR 2.07; 95% CI (1.69, 2.51) p-value<0.0001 Lost≥10% of baseline body weight (ITT/MI): 1. 291 (57.0%) 2. 56 (23.1%) 3. 57 (11.1%) p-value<0.0001 1 vs. 3: RR 5.13; 95% CI (3.98, 6.66) p-value<0.0001 2 vs. 3: RR 2.09; 95% CI (1.47, 2.98) p-value<0.0001 Mean percent weight loss from baseline (ITT/MI): 1. -12.20% (-11.2 to -13.2) 2. -5.25% (-3.9 to -6.6) 3. -1.24% (-0.2 to -2.3) p-value <0.0001	ARR: 50% NNT: 2 ARR: 26% NNT: 4 ARR: 46% NNT: 2 ARR: 12% NNT: 8 N/A	Severe Adverse Events: 1. 52 (10.2%) 2. 25 (10.4%) 3. 41 (8.0%) 1 vs. 3: RR 1.27; 95% CI (0.85, 1.92) p-value=0.22 Withdrawal due to adverse events: 1. 82 (16.0%) 2. 27 (11.3%) 3. 43 (8.4%) 1 vs. 3: RR 1.91; 95% CI (1.33, 2.76) p-value<0.001 No deaths were reported	NS ARR: 8% NNH: 13	**Quality Rating: Fair-Good** **Internal Validity: RoB** Selection: Adequate randomization technique Unclear allocation concealment; groups similar at baseline Performance: Patients and caregivers blinded Study drug and placebo were visually indistinguishable Detection: All study participants, study physicians, site staff, and sponsor representatives were blinded; the independent data and safety monitoring board were unblinded Attrition: High attrition (~40% average), but comparable to previous weight loss trials and similar between arms; used six different analyses to adjust for high attrition rates; results were all showing similar effects of weight loss **External Validity:** Recruitment: Not reported; study conducted at 91 U.S. sites (clinical practices, clinical trial sites, and academic centers) Patient Characteristics: Mostly white females in their 40's; about 13% were using antidepressant; also were taking lipid lowering agents and antihypertensive medications Setting: All patients were provided with standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null Outcomes: Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

2. Gadde K, et al.[14] RCT, DB, PC, Phase III (CONQUER)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 7.5mg/46mg 3. Placebo 56-week (4-week postrandomization titration period) Randomized in a 2:1:2 ratio	Demographics: Age~51; Female 70%; White 86%; African 11%; Weight ~102kg; BMI~36; BP ~128/80; HTN ~52%; Hypertriglyceridaemia ~36%; Type 2 DM ~68%; Three or more co-morbidities ~52% Inclusion Criteria: Patients age 18-70; BMI 27-45 kg/m^2; Systolic BP 130-160 Diastolic BP 85-100; taking at least 2 antihypertensive medications; concentration of triglycerides 2*26-4*52 mmol/L or using at least 2 lipid-lowering drugs; fasting BG ≥5*55 mmol/L, BG≥7*77 mmol/L at 2 hours after oral glucose load during oral glucose tolerance test, or diagnosed type 2 DM managed with lifestyle changes or metformin monotherapy Exclusion Criteria: BP≥160/100 mmHg; type 1 DM; use of antidiabetic drug other than metformin history of nephrolithiasis, major depression; suicidal behavior with intention to act; current substantial depressive symptoms; No tricyclic antidepressants or monoamine oxidase inhibitors	1. 994 2. 498 3. 993	Lost≥5% of baseline body weight (ITT/LOCF): 1. 687 (70%) 2. 303 (62%) 3. 204 (21%) 1 vs. 3: RR 3.36; 95% CI (2.98, 3.80) p-value<0.0001 2 vs. 3: RR 2.98; 95% CI (2.59, 3.41) p-value<0.0001 Lost≥10% of baseline body weight (ITT/LOCF): 1. 467 (48%) 2. 182 (37%) 3. 72 (7%) 1 vs. 3: RR 6.47; 95% CI (5.14, 8.13) p-value<0.0001 2 vs. 3: RR 5.07; 95% CI (3.94, 6.57) p-value<0.0001 Mean percentage weight loss from baseline (ITT/LOCF): 1. Absolute change -10.2 kg (LSM: -9.8%) 95% CI (-10.4, -9.3); p-value<0.0001 2. -8.1kg (LSM: -7.8%) 95% CI (-8.5, -7.1); p-value<0.0001 3. -1.4kg (LSM: -1.2%) 95% CI (-1.8, -0.7)	ARR: 49% NNT: 2 ARR: 41% NNT: 2 ARR: 40% NNT: 2 ARR: 30% NNT: 3 N/A	Serious Adverse Events: 1. 50 (5%) 2. 15 (3%) 3. 40 (4%) 1 vs. 3: RR 1.25; 95% CI (0.82, 1.92) p-value=0.28 Withdrawal due to adverse events: 1. 191 (19%) 2. 58 (12%) 3. 88 (9%) 1 vs. 3: RR 2.16; 95% CI (1.70, 2.78) p-value<0.0001 One placebo-treated patient died as a result of cardiopulmonary arrest	NS ARR: 10% NNH: 10	**Quality Rating: Fair -Good** **Internal Validity: RoB** Selection: Adequate randomization assignment (computer generated algorithm implemented through an interactive voice response system to assign patients according to random allocation sequence); adequate allocation sequence; groups similar at baseline Performance: Investigators (physicians)* and patients were blinded. Detection:; unclear if outcome assessors were blinded Attrition: High attrition rate (overall 38%), but similar to previous weight loss trials and more in placebo arm. **External Validity:** Recruitment: Not reported; conducted at 93 centers in the U.S. Patient Characteristics: Patients were mostly white females with an average weight of 102 kg; they had more co-morbidities to start (over 50% with three or more) and were on one or more medications to control the co-morbidities; not used in advanced DM (controlled with metformin only) Setting: All patients were provided with standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null Outcomes: Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

3. Garvey W, et al.[15] RCT, DB, PC, Phase III extension of CONQUER (SEQUEL)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 7.5mg/46mg 3. Placebo 52-week extension Randomized in a 2:1:2 ratio	Demographics: Age~51; Female ~65%; White ~85%; African ~12% Weight ~102kg; BMI~36; BP ~128/80; HTN ~52%; Hypertriglyceridaemia ~35%; Type 2 DM ~20%; Metabolic syndrome ~67% Inclusion Criteria: Patients age 18-70; BMI 27-45 kg/m^2 as well as ≥2 weight-related co-morbidities, as previously described in CONQUER; female subjects of childbearing potential were required to continue contraception (double-barrier method, stable hormonal contraception + single barrier, or tubal ligation) Exclusion Criteria: BMI≤22 at CONQUER completion; not taking study drug continuously for >4weeks at the end of CONQUER; developing a condition during CONQUER that would interfere with compliance or attainment of study measures, or participating in another formal weight-loss program	1. 295 2. 154 3. 227	Lost≥5% of baseline body weight (ITT/LOCF/MI): 1. 235 (79.7%) 2. 114 (74.3%) 3. 67 (28.9%) 1 vs. 3: RR 2.70; 95% CI (2.22, 3.27) p-value<0.0001 2 vs. 3: RR 2.51; 95% CI (2.02, 3.07) p-value<0.0001 Lost≥10% of baseline body weight (ITT/LOCF/MI): 1. 156 (53%) 2. 78 (50.6%) 3. 26 (11.6%) 1 vs. 3: RR 4.61; 95% CI (3.17, 6.90) p-value<0.0001 2 vs. 3: RR 2.31; 95% CI (1.51, 3.59) p-value<0.0001 Mean percentage change from baseline in body weight (least-square mean using multiple imputation; 95% CI): 1. -11.2% (-12.2, -10.3) 2. -10.3% (-11.6, -9.0) 3. -2.5% (-3.4, -1.6) p-value<0.0001 compared with placebo for all comparisons	ARR: 50% NNT: 2 ARR: 45% NNT: 2 ARR: 41% NNT: 2 ARR: 15% NNT: 7 N/A	Serious Adverse Events: 1. 12 (4.1%) 2. 4 (2.6%) 3. 9 (4.0%) 1 vs. 3: RR 1.03; 95% CI (0.41, 2.61) p-value=0.95 Withdrawal due to adverse events: 1. 13 (4.4%) 2. 7 (4.5%) 3. 7 (3.1%) 1 vs. 3: RR 1.43; 95% CI (0.54, 3.91) p-value=0.43 No deaths reported	NS NS	**Quality Rating: Poor-Fair** **Internal Validity: RoB** Selection: Patients included who consented from CONQUER; those who completed and complied with previous study (may introduce bias away from the null). Performance: Investigators (physicians)* and patients were blinded Detection: Unclear if outcome assessors were blinded Attrition: Lower overall attrition compared to previous studies (average ~15%); potentially due to compliant patients from CONQUER and similar between all arms. **External Validity:** Recruitment: Patients from the CONQUER study were chosen to continue in the SEQUEL study; 36 sites from the CONQUER study were selected for the extension study based on their high initial enrollment numbers and rates of retention Patient Characteristics: Same as the CONQUER study (see above), but considered more compliant individuals overall; smaller sample size Setting: All patients continued to receive standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null Outcomes: Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

RCT: Randomized Controlled Trial; DB: Double-blind; PC: Placebo Controlled; PG: Parallel Group; PHEN/TPM CR: controlled-release phentermine/topiramate; HTN: Hypertension; BP: Blood pressure; BG: Blood glucose; DM: Diabetes mellitus; MITT: Modified-intention-to-treat; LOCF: last-observation-carried-forward; MI: multiple imputation; *Vivus medical information was contacted to clarify what was meant by investigators; they consider investigators (physicians) to be care givers

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Appendix 2:COMPARATIVE CLINICAL EFFICACY FOR LORCASERIN

Relevant Endpoints:

1) Reduction in morbidity and mortality due to cardiovascular events
2) Reduction in incidence of type 2 diabetes
3) FDA-defined valvulopathy
4) Withdrawals due to adverse events
5) Long term maintenance of weight loss

Primary Study Endpoint:

4) Percent change in weight from baseline at 1 year
5) Percent of subjects achieving ≥5% weight loss at week 52
6) Percent of subjects achieving ≥10% weight loss at week 52

Ref./Study Design[a]	Drug Regimens	Patient Population	N	Outcomes/ Efficacy Results	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Smith S, et al. RCT, DB, PC[16] (BLOOM) 2-year study; patients re-randomized in the second year in a 2:1 ratio	1. Lorcaserin (L) 10 mg BID 2. Placebo (P) BID Year 1: 1:1 ratio	Demographics: White 67.9%; Black 18.7%; Hispanic 11.4%; Female 82.9% Mean Age: 43.8±0.3 Weight: 100.4±0.4 kg BMI: 36.2 BP: ~120/76 Total Cholesterol (mg/dL): ~195 HbA1c%: 5.66±0.01 Inclusion Criteria: Age 18 to 65 years; BMI of 30 to 45 or of 27 to 45 with 1+ co-existing condition (HTN, dyslipidemia, CV disease, impaired glucose tolerance, or sleep apnea) Exclusion Criteria: Moderate or more severe mitral regurgitation or aortic regurgitation (i.e. valvulopathy), DM, >140mmHg systolic BP, >90mmHg diastolic BP, depression or other psychiatric disease within the past 2 years, pregnanc and lactation	L: 1593 P: 1584 MITT1: L: 1538 P: 1499	% of subjects achieving ≥5% weight loss at week 52 (MITT): L: 731 (47.5%) P: 304 (20.3%) RR 2.3, 95% CI (2.09, 2.62) p-value<0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): L: 347 (22.6%) P: 115 (7.7%) RR 3.0, 95% CI (2.8, 4.4) p-value<0.001 Weight as a % change from baseline body weight at Year 1 L: -5.9±0.2 kg P: -2.2±0.1 kg Mean Difference: -3.7; 95% CI (-4.1, -3.3); p-value<0.0001	ARR: 27% NNT: 4 ARR: 15% NNT: 7 N/A	Outcome: FDA-defined Valvulopathy at week 52* L: (34/1278) 2.7% P: (28/1191) 2.3% RR 1.1, 95% CI (0.69, 1.85 p-value 0.70 Withdrawal due to adverse events: L: 113 (7.1%) P: 106 (6.7%) RR 1.06; 95% CI (0.82, 1.37); p-value=0.68	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Adequate generation of randomizatic sequence; adequate allocation concealment (treatment kits with randomization numbers we used); groups were similar at baseline; sample s was adequate Performance: Patients and investigators blinded Detection: Unclear if outcome assessors blinded Attrition: High overall attrition (lorcaserin 37.2% and placebo 40.6%): large percentage of withdrawal was from subject decision; used MI analysis with LOCF(potential bias away from the null) **External Validity:** Recruitment: Not reported; conducted at 98 academic and private trial sites Patient Characteristics: Mostly healthy, white, obese females in their 40's Setting: All patients enrolled in a standardized behavioral weight management program Outcomes: 1-year duration with high attrition a LOCF (bias weight reduction over gain); all surrogate endpoints measured as outcomes, nc clinically relevant long-term outcomes

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

3. Fidler M, et al. RCT, DB, PC PG[18] (BLOSSOM)	1. Lorcaserin 10 mg BID 2. Lorcaserin 10 mg QD 3. Placebo 52-week study randomized in a 2:1:2 ratio	Demographics: Age ~43; Female ~80%; White ~67%; Black ~20%; Hispanic ~10%; Weight 100kg; BMI ~35; HTN 23%; Dyslipidemia 27% Inclusion Criteria: Age 18-65 year olds; BMI between 30-45 kg/m2 or between 27 and 29.9 kg/m2 with co-morbidity (HTN, dyslipidemia, CV disease, impaired glucose tolerance, or sleep apnea, and ability to participate in exercise program) Exclusion Criteria: Recent CV events; major surgeries; medical conditions that would prevent food or exercise change; DM; BP>150/95mm/Hg; TG>499mg/dL; SSRI within 1 year; previous bariatric surgery; recent weight-loss drugs (within 1 month for OTC, 3 months for prescription) or low calorie diet; or change in weight o at least 5 kg within 3 months. *Did not exclude patients based on echocardiographic results	1. 1602 2. 801 3. 1601 MITT: 1. 1561 2. 771 3. 1541	% of subjects achieving ≥5% weight loss at week 52 (MITT): 1. 737 (46%) 2. 296 (37%) 3. 384 (24%) 1 vs. 3*: RR 1.91; 95% CI (1.73, 2.12); p-value<0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): 1. 353 (22.6%) 2. 134 (17.4%) 3. 150 (9.7%) p-value<0.001 1 vs. 3*: RR 2.32; 95% CI (1.95, 2.77) Co-Primary End-point ITT with LOCF: Weight as a % change from baseline body weight at Year 1: 1. -5.6% (-5.9 to -5.3%) 2. -4.6% (-5.0 to -4.1%) 3. -2.7% (-3.1 to -2.4%) No p-values were reported *RR not reported for group 2, as it is not an approved dose.	ARR: 22% NNT: 5 ARR: 13% NNT: 8 N/A	Outcome: FDA-defined Valvulopathy that was no present at baseline at week 52* 1. 24/1208 (2.0%) 2. 8/622 (1.4%) 3. 23/1153 (2.0%) Withdrawal due to adverse events: 1. 115 (7.2%) 2. 50 (6.2%) 3. 73 (4.6%) 1 vs. 3*: RR 1.57; 95% CI (1.18, 2.09) Serious adverse events 1. 49 (3.1%) 2. 27 (3.4%) 3. 36 (2.2%) 1 vs. 3*: RR 1.36; 95% CI (0.8-2.12) 1 death in placebo group due to asthma attack *RR not reported for group 2, as it is not an approved dose.	NS ARR: 3% NNH: 38 NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: unclear treatment allocation concealment, adequate randomization techniq (randomization code generated programmatica by statistician not directly involved with study) Performance: Stated double-blinding, but did n specifically mention care giver and patient blinc or use of matching placebo for daily dosing grou Detection: outcome assessors blinded for echocardiography analysis Attrition: High attrition rates (>40%), but simila other weight loss trials; high number of patient requesting to withdraw from study, use of LOCF **External Validity:** Recruitment: Not reported; study was conducte 97 U.S. research centers Patient Characteristics: Majority were women (~80%); white (~67%); included patients with H (BP<150/95), dyslipidemia, CV disease, impaire glucose tolerance, and sleep apnea Setting: All patients were instructed to reduce caloric intake by 600 kcal and participate in 30 minutes of exercise daily; Returned at 2 and 4 weeks post-randomization, then on a monthly b Outcomes: 1-year study with high attrition and LOCF imputation; only reported true IIT for % weight change and ≥5% weight loss; reported MITT for ≥10% weight loss; mostly surrogate endpoints; no morbidity/mortality data or reduction in hospitalizations

2. O'Neil P, et al. RCT, DB, PC[17] (BLOOM-DM)	1.Lorcaserin 10 mg BID 2. Lorcaserin 10 mg QD 3. Placebo 52-week study randomized in a 1:1:1 ratio	Demographics: Age ~53; women 54%; weight ~104kg; BMI ~36; white 58.7%; African Americans 22.3%; HbA1c 8.1%; Metformin 92%; Sulfonylurea 50%; both medications 42% Inclusion Criteria: Type 2 DM treated with metformin, a SFU, or both; HbA1c at visit between 7-10%; 18-65 years old with BMI 27-45 kg/m^2; were able to participate in moderate intensity exercise program Exclusion Criteria: Use of insulin, exenatide o pramlintide (body weight effects); prior bariatric surgery; depression or other psychiatric disorder; cardiopulmonary problems (stroke, MI, unstable angina); TSH or T4 abnormalities; TG>499mg/dL; LDL>160mg/dL; SCr>1.5 times upper limit of norma	1. 256 2. 95 3. 252 MITT: 1. 251 2. 94 3. 248	% of subjects achieving ≥5% weight loss at week 52 (MITT): 1. 94 (37.5%) 2. 42 (44.7%) 3. 40 (16.1%) 1 vs. 3* RR 2.32; 95% CI (1.67, 3.22) p-value <0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): 1. 41 (16.3%) 2. 17 (18.1%) 3. 11 (4.4%) 1 vs. 3*: RR 3.68; 95% CI (1.94, 7.0) p-value <0.001 Weight as a % change from baseline body weight at Year 1 1. -4.5±0.4 2. -5.0±0.5 3. -1.5±0.4 p-value<0.001 *RR not reported for group 2, as it is not an approved dose	ARR: 21% NNT: 5 ARR: 12% NNT: 8 N/A	FDA-defined Valvulopathy that was not present at baseline at week 52* 1. 6 (2.9%) 2. 2 (2.5%) 3. 1 (0.5%) p=0.06 1 vs. 3: RR 5.97; 95% CI (0.72, 49.17) Withdrawal due to adverse events: 1. 22 (8.6%) 2. 6 (6.3%) 3. 11 (4.3%) 1 vs. 3: RR 1.97; 95% CI (0.97, 3.97) Hypoglycemia 1. 19 (7.4%) 2. 10 (10.5%) 3. 16 (6.3%) 1 vs. 3: RR 1.16; 95% CI (0.58, 2.32); p-value=0.66 Serious adverse events 1. 16 (6.3%) 2. 8 (8.4%) 3. 17 (6.7%) 1 vs. 3: RR 0.93; 95% CI (0.46, 1.90); p-value=0.83 No deaths occurred	NS NS NS NS	**Quality Rating: Fair (-)** **Internal Validity: RoB** Selection: Unclear randomization techniques; unclear allocation concealment; groups were similar at baseline Performance: Patients and investigators blinded Detection: Unclear if outcome assessors were blinded Attrition: Included MITT analysis with LOCF; in t study, a smaller population was used compare t the previous study, so small changes in data wil have a large effect on the outcome (bias potent away from the null); had high attrition rates (21 37%) with more patients in the placebo group t treatment arms. **External Validity:** Recruitment: Not reported; conducted in 58 academic and private research sites in U.S. Patient Characteristics: Diabetes population wit HbA1c between 7-10% and only either metform or sulfonylurea or both (no insulin which could potentially increase hypoglycemia side effect); women comprised just over half of the populati small sample size; older (~54 years old) Setting: All patients enrolled in a standardized behavioral weight management program; Retu at 2 and 4 weeks post-randomization, then on a monthly basis Outcomes: 1-year duration with high attrition a LOCF (bias weight reduction over gain); all surrogate endpoints; no clinically relevant long-term outcomes (reported weight loss, cholester blood pressure, etc.)

RCT: Randomized Controlled Trial; DB: Double-blind; PC: Placebo Controlled; PG: Parallel Group; HTN: Hypertension; CV: Cardiovascular; BP: Blood pressure; DM: Diabetes mellitus; TG: Triglycerides; SSRI: Selective serotonin reuptake inhibitor; OTC: over-the-counter, MITT: Modified-intention-to-treat; LOCF: last-observation-carried-forward

*Echocardiographic analyses used all patients with an echocardiogram at baseline and at least one post-baseline time point, with LOCF imputation

Appendix 3: Specific Drug Information for phentermine/topiramate

CLINICAL PHARMACOLOGY[1]

The mechanism of action for both drugs is not fully known. Phentermine is a sympathomimetic amine and is thought to stimulate increased hypothalamic release of norepinephrine, resulting in reduced appetite and decreased food consumption. Topiramate, a fructose monosaccharide derivative, is thought to have a combined pharmacologic effect, including augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase. In combination, it can help suppress appetite and enhance satiety.

PHARMACOKINETICS[1]

Parameter	Result (Phentermine)	Result (Topiramate)
Oral Bioavailability	Not reported	Not reported
Elimination	70-80% in urine unchanged	70% in urine unchanged
Half-Life	~20 hours	~65 hours
Metabolism	P-hydroxylation; N-oxidation CYP3A4 metabolism	Hydroxylation; hydrolysis; glucuronidation

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE FORM:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Titration Doses: 3.75 mg/ 23 mg 11.25mg/ 69mg	Oral	QD morning	Capsule	Moderate CrCl<50mL/min Severe CrCl<30mL/min NTE: 7.5mg/46mg once daily	Moderate hepatic impairment (Child-Pugh score 7 - 9) NTE: 7.5 mg/46 mg once daily	Not recommended under 18 years of age	Use caution (minimal data over age 65)	-With or without food -Start with low dose for 14 days, then increase to recommended doses (either 7.5mg/46mg or 15mg/92mg depending titration phase) -Used for titration purposes
Normal Doses: 7.5mg/ 46mg 15mg/ 92mg	Oral	QD morning	Capsule	Moderate CrCl<50mL/min Severe CrCl<30mL/min NTE: 7.5mg/46mg once daily	Moderate hepatic impairment (Child-Pugh score 7 - 9) NTE: 7.5 mg/46 mg once daily	Not recommended under 18 years of age	Use caution (minimal data over age 65)	-With or without food -Evaluate weight loss after 12 weeks with the 7.5mg/46mg dose (patient should lo at least 3% of body weight to continue o escalate dose) -Patient should lose at least 5% of body weight after 12 weeks at high dose (15mg/92mg) or else discontinue treatm

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Discontinue medication by taking a dose every other day for at least 1 week prior to stopping treatment altogether (potential of precipitating a seizure in norma subjects if abrupt withdrawal)

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

- Risk Evaluation and Mitigation Strategy (REMS) requirement put in place to inform prescribers and female patients of reproductive potential about:
    - The increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to phentermine/topiramate during the first trimeste of pregnancy
    - The importance of pregnancy prevention for females of reproductive potential receiving phentermine/topiramate
    - The need to discontinue phentermine/topiramate immediately if pregnancy occurs
- Requirements: dispense medication guide with prescription; prescriber training required; dispensed by certified pharmacies

Contraindications:

- Pregnancy (topiramate shown to increase risk of oral clefts in first trimester of pregnancy; category X)
- Glaucoma (topiramate has been reported to cause acute myopia and secondary angle closure glaucoma)
- Hyperthyroidism
- During or within 14 days following administration of monoamine oxidase inhibitors
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines

Warnings and Precautions:

- Fetal Toxicity: Phentermine/topiramate can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate).

- Increase in heart rate: A higher percentage of phentermine/topiramate-treated overweight and obese adults experienced heart rate increases from baseline of more than 5, 10, 15, and 20 beats per minute (bpm) compared to placebo-treated overweight and obese adults. Regular monitoring of resting heart rate is recommended while on phentermine/topiramate. Clinical significance of a heart rate elevation with phentermine/topiramate treatment is unclear, especially for patients with cardiac and cerebrovascular disease (such as patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure).

- Suicidal behavior and ideation: Antiepileptic drugs (AEDs), including topiramate, a component of phentermine/topiramate, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue phentermine/topiramate in patients who experience suicidal thoughts or behaviors.

- Acute myopia and secondary angle closure glaucoma: Has been reported in patients treated with topiramate. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure, possible mydriasis; symptoms can occur within the first month

of initiating treatment or anytime during therapy. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. The primary treatment to reverse symptoms is immediate discontinuation of phentermine/topiramate.

- Mood and sleep disorders: Patients with a history of depression may be at increased risk of recurrent depression or other mood disorders while taking phentermine/topiramate. The majority of these mood and sleep disorders resolved spontaneously, or resolved upon discontinuation of dosing.

- Cognitive impairment: Rapid titration or high initial doses of phentermine/topiramate may be associated with higher rates of cognitive events such as attention, memory and language/word-finding difficulties. Since phentermine/topiramate has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain phentermine/topiramate therapy does not affect them adversely. If cognitive dysfunction persists consider dose reduction or withdrawal of phentermine/topiramate for symptoms that are moderate to severe, bothersome, or those which fail to resolve with dose reduction.

- Metabolic acidosis: Hyperchloremic, non-anion gap, metabolic acidosis (decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) has been reported in patients treated with phentermine/topiramate. Conditions or therapies that predispose to acidosis (i.e., renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery or ketogenic diet) may be additive to the bicarbonate lowering effects of topiramate. Concomitant use of phentermine/topiramate and a carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. The effect of phentermine/topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Measurement of electrolytes including serum bicarbonate prior to starting phentermine/topiramate and during treatment is recommended. In clinical trials, the peak reduction in serum bicarbonate occurred by week 4 and in most subjects there was a correction of bicarbonate by week 56, without any change to study drug. However, if persistent metabolic acidosis develops while taking phentermine/topiramate, reduce the dose or discontinue the medication.

- Elevation in creatinine: Peak increases in serum creatinine were observed after 4 to 8 weeks of treatment. On average, serum creatinine gradually declined but remained elevated over baseline creatinine values. Elevations in serum creatinine often signify a decrease in renal function, but the cause for phentermine/topiramate -associated changes in serum creatinine has not been definitively established. Therefore, measurement of serum creatinine prior to starting phentermine/topiramate and during treatment is recommended. If persistent elevations in creatinine occur while taking phentermine/topiramate, reduce the dose or discontinue the medication.

- Potential risk of hypoglycemia in patients with Type 2 Diabetes and on an anti-diabetic medication: Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Phentermine/topiramate has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting and during treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are nonglucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting phentermine/topiramate, appropriate changes should be made to the antidiabetic drug regimen.

- Potential risk of hypotension in patients treated with antihypertensive medications: In hypertensive patients being treated with antihypertensive medications, weight loss may increase the risk of hypotension, and associated symptoms including dizziness, lightheadedness, and syncope. Measurement o blood pressure prior to starting phentermine/topiramate and during treatment is recommended in patients being treated for hypertension. If a patient

develops symptoms associated with low blood pressure after starting phentermine/topiramate, appropriate changes should be made to the antihypertensive drug regimen.

- CNS depression with concomitant CNS depressants including alcohol: Avoid concomitant use of phentermine/topiramate with alcohol because it can potential CNS depression or other centrally mediated effects such as dizziness, drowsiness, light-headedness, impaired coordination, and somnolence.

- Potential seizures with abrupt withdrawal of phentermine/topiramate: It has been shown in patients taking topiramate that abrupt withdrawal can increase the risk for seizures in individuals without a history of seizures or epilepsy. If the medication is immediately terminated, appropriate monitoring is recommended. Patients who are discontinuing the 15mg/92mg dose of phentermine/topiramate, gradual tapering is recommended to alleviate seizure risk.

- Patients with renal impairment: Both phentermine and topiramate are renally cleared, so exposure increases with moderate or severe renal impairment. It has not been studied in patients in end-stage renal disease on dialysis, and the medication should be avoided.

- Patients with hepatic impairment: In patients with mild or moderate hepatic impairment, exposure compared to healthy volunteers was higher, and the dose should be adjusted accordingly. It has not been studied in patient with severe hepatic impairment and should be avoided.

- Kidney stones: Topiramate inhibits carbonic anhydrase activity and promotes kidney stone formation by reducing urinary citrate excretion and increasing urine pH. Avoid the use of the medication with other drugs that inhibit carbonic anhydrase. Also, the use of topiramate by patients on a ketogenic diet may result in a physiological environment that increases the likelihood of kidney stone formation. Increase in fluid intake is recommended.

- Oligohydrosis and Hyperthermia: Topiramate has been shown to decrease sweating and increase body temperature. Patients treated with phentermine/topiramate should be advised to monitor for decreased sweating and increased body temperature during physical activity, especially in hot weather. Caution should be used when it is prescribed with other drugs that predispose patients to heat-related disorders, which include carbonic anhydrase inhibitors and anticholinergic activity.

- Hypokalemia: Mechanism is through carbonic anhydrase activity inhibition, and monitoring potassium levels should be done, especially if used in combination with non-potassium-sparing diuretics.

- LABS: Bicarbonate, creatinine, potassium, and glucose labs should be collected at baseline and periodically during treatment.

Table 1:[1] Adverse Reactions Reported in Greater than or Equal to 2% of Patients and More Frequently with than Placebo During 1-Year Treatment-Overall Study Population				
System Organ Class Preferred Term	Placebo (N=1561) %	Phentermine/topiramate 3.75mg/23mg (N=240) %	Phentermine/topiramate 7.5mg/46mg (N=498) %	Phentermine/topiramate 15mg/92mg (N=1580) %

Nervous System Disorders				
Paresthesia	1.9	4.2	13.7	19.9
Headache	9.3	10.4	7.0	10.6
Dizziness	3.4	2.9	7.2	8.6
Dysgeusia	1.1	1.3	7.4	9.4
Psychiatric Disorders				
Insomnia	4.7	5.0	5.8	9.4
Gastrointestinal Disorders				
Constipation	6.1	7.9	15.1	16.1
Dry Mouth	2.8	6.7	13.5	19.1
Nausea	4.4	5.8	3.6	7.2
Metabolism and Nutrition Disorders				
Hypokalemia	0.4	0.4	1.4	2.5
Infections and Infestations				
Upper Respiratory Tract Infection	12.8	15.8	12.2	13.5
Nasopharyngitis	8.0	12.5	10.6	9.4
Urinary Tract Infection	3.6	3.3	5.2	5.2

Potential Drug Interactions:

- Monoamine oxidase inhibitors
- Oral contraceptives
- CNS depressants including alcohol
- Non-potassium sparing diuretics
- Antiepileptic drugs
- Carbonic Anhydrase Inhibitors

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Appendix 4: Specific Drug Information for lorcaserin

CLINICAL PHARMACOLOGY[2]

Lorcaserin hydrochloride is a selective serotonin 2C receptor agonist for oral administration used for chronic weight management. Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT2C receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The exact mechanism of action is not known. Lorcaserin at the recommended daily dose selectivity interacts with 5-HT2C receptors as compared to 5-HT2A and 5-HT2B receptors, other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites.

PHARMACOKINETICS[2]

Parameter	Result
Oral Bioavailability	Peak plasma 1.5-2 hours after oral dose; unknown absolute bioavailability in humans
Elimination	Urine ~92.3%; feces ~2.2%
Half-Life	~11 hours; ss=3 days (BID dosing); accumulation ~70%
Metabolism	Extensive liver metabolism

DOSE & AVAILABILITY[2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg	Orally	Twice daily	20 mg/day Tablets	No adjustment needed; not recommended in severe renal dysfunction (CrCl<30mL/min) or ESRD	No adjustment needed in mild to moderate impairment; use caution in severe impairment	Not established	No change unless renally impaired	-Can be taken with or without food -Evaluate response to therapy in 12 weeks and if patient has not lost at lea 5% of body weight, discontinue medication

DRUG SAFETY[2]

Serious (REMS, Black Box Warnings, Contraindications):

- Contraindication: Pregnancy (category X)

Warnings and Precautions:

- Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions
  - Possible when given with concomitant medications that can increase serotonin
  - Has not been shown to cause serotonin syndrome or NMS

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

- Valvular heart disease
  - Has not been studied in congestive heart failure or hemodynamically-significant valvular heart disease
- Cognitive impairment possible
- Psychiatric disorders
  - Events of euphoria, hallucination, and dissociation seen at supratherapeutic doses
  - Possible abuse/dependence potential
- Potential risk of hypoglycemia in patients with type 2 diabetes mellitus on antidiabetic therapy
  - Shown to increase hypoglycemic events in patients on sulfonylurea in clinical trial (BLOOM-DM)
  - Has not been studied in patients on insulin yet
- Priapism
  - Has not been proven, but use caution due to the 5-HT_{2c} receptor agonism
- Heart Rate Decreases
  - Use caution in patients with history of bradycardia or heart block greater than first degree
- Laboratory Changes:
  - Hematological Changes: decrease in white blood cell count seen
  - Prolactin Elevation
  - Pulmonary Hypertension: not proven

Allergies/Interactions:

- Drug-Interactions:
  - Other serotonergic neurotransmitter system medications (SSRIs, MAOIs, SNRIs, triptans, TCAs, dextromethorphan, tramadol, etc.);
  - Medications that use CYP2D6 metabolism (lorcaserin is a CYP2D6 inhibitor)
- Food-Drug: None known

Common Adverse Events in Clinical Trials (>5% compared to placebo):

BLOOM and BLOSSOM combined data	Number of patients (%)	
Adverse Events (Non-diabetic patients)	Belviq 10mg BID (N=3195)	Placebo (N=3185)
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Fatigue	229 (7.2)	114 (3.6)
Nausea	264 (8.3)	170 (5.3)
Dry Mouth	169 (5.3)	74 (2.3)
Constipation	186 (5.8)	125 (3.9)

BLOOM-DM data	Number of patients (%)	
Adverse Events (Diabetic patients)	Belviq 10mg BID (N=256)	Placebo (N=252)
Hypoglycemia	75 (29.3)	53 (21)
Headache	37 (14.5)	18 (7.1)
Back pain	30 (11.7)	20 (7.9)
Cough	21 (8.2)	11 (4.4)
Fatigue	19 (7.4)	10 (4.0)

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

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: Benign Prostatic Hyperplasia (BPH)

Month/Year of Review: November 2012
PDL Classes: Benign Prostatic Hyperplasia

Date of Last Review: September 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents:
  - Alpha-Blockers: DOXXAZOSIN, TAMSULOSIN HCL, TERAZOSIN HCL
  - 5-Alpha Reductase Inhibitors: FINASTERIDE
- Non Preferred Agents:
  - Alpha-Blockers: ALFUZOSIN (UROXATRAL®), SILODOSIN (RAPAFLO®), PRAZOSIN (MINIPRESS®), DOXAZOSIN ER (CARDURA XL®), PHENOXYBENZAMINE (DIBENZYLINE®), INDORAMIN (BARATOL®)
  - 5-Alpha Reductase Inhibitors: DUTASTERIDE (AVODART®)
  - Combination: DUTASTERIDE/TAMSULOSIN (JALYN ®)

Research Questions:

- Is there any new evidence of superiority in efficacy or safety of one agent for BPH over another?
- Is there any new relevant evidence to change current policy?

Conclusions:

- There is no new evidence suggesting superiority of one of the newer alpha-blockers or 5-alpha reductase inhibitors over another in efficacy or safety.
- Tadalafil demonstrated improvements in urinary symptoms compared to placebo in patients with lower urinary tract symptoms, but demonstrated no difference in post void residual volume or urinary flow rate.
- Tadalafil is also indicated for patients with concurrent BPH and erectile dysfunction (ED). ED is not a covered diagnosis under the Oregon Health Plan.
- There is insufficient evidence to demonstrate superiority of tadalafil over standard treatment (alpha-blockers).

Recommendations:

- Maintain at least one alpha-blocker and one 5-alpha reductase inhibitor as preferred on the PDL.
- Recommend making tadalafil non-preferred for the treatment of BPH. Because medications to treat impotency or erectile dysfunction are not covered by the Oregon Health Plan, update PA criteria for indication of tadalafil for the simultaneous occurrence of BPH and erectile dysfunction.
- Continue to require prior authorization in accordance with the Oregon Health Plan list of prioritized health services and to limit cosmetic use.

Previous Recommendations:

- Previous evidence does not support a difference in efficacy or effectiveness between different BPH medications.
- According to prior evidence, no differences were found between medications in terms of harms and adverse events.
- It is recommended that at least one Alpha-blocker and one 5-Alpha Reductase Inhibitor be included on the preferred drug list (PDL).
- Consider prior authorization criteria to limit cosmetic use.

Background:

In BPH, the enlarged gland contributes to lower urinary tract symptoms (LUTS) through direct bladder outlet obstruction and increased smooth muscle tone and resistance.[1] The main causes of LUTS include abnormalities of the bladder, prostate, urethra, or sphincters.[2] The primary treatment goal has been to alleviate inconvenient LUTS and more recently to address the prevention of disease progression. LUTS includes storage and/or voiding disturbances common in aging men due to structural or functional abnormalities. [1] The American Urological Association (AUA) guidelines on the management of BPH recommend alpha-blockers for patients with bothersome, moderate to severe LUTS and they have equal clinical effectiveness with slight differences in adverse event profiles. [1] The combination of an alpha-blocker with a 5-alpha-reductase inhibitor is recommended when the LUTS is associated with prostatic enlargement and 5-alpha reductase inhibitors should not be used when BPH is not associated with prostate enlargement. [1] Guidelines from the National Institute for Health and Clinical Excellence recommend an alpha blocker (afluzosin, doxazosin, tamsulosin, or terazosin) to men with moderate to severe LUTS, an anticholinergic to men with the symptoms of overactive bladder, and a 5-alpha reductase inhibitor to men who have prostates to be larger than 30g or a PSA level greater than 1.4ng/ml and who are considered to be at high risk for progression. [2] The Oregon Health Plan (OHP) only covers BPH with urinary obstruction when post void residuals are at least 150 cc's and unspecified urinary obstruction and BPH with obstruction is an unfunded diagnosis.[3] Current prior authorization criteria for the BPH medications are found in Appendix 1.

Methods:

A MEDLINE OVID search was conducted using all included drugs with benign prostatic hyperplasia and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. The Cochrane Collection, PubMed Health, DynaMed, the Canadian Agency for Drug and Technologies in Health (CADTH), and the Centre for Reviews and Dissemination (DARE) 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) and the American Urological Association (AUA) were searched for updated and recent evidence-based guidelines.

New Trials:

A total of 43 citations resulted from the initial MEDLINE search and after review for inclusion, 15 potentially relevant clinical trials were identified (Appendix 2). The other trials were excluded due to lack of relevant outcomes, comparisons to other non-pharmacological treatments and/or no head-to-head studies. These trials are briefly described in Table 1.

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Karadag, et al.[4] Randomized crossover comparison study	Tamsulosin(10mg) to Alfuzosin(0.4mg) vs. Alf to Tam	Men with BPH admitted with lower urinary tract symptoms (LUTS)	Effectiveness of switching alpha blockers based on improvement in IPSS, QoL, average flow rate and voided urine volume.	Before switch(Success rate) After switch(Improvement) Tam to Alf: 42% Tam 27.5% Alf Alf to Tam: 47% Alf 14% Tam Tam and Alf showed equal effectiveness in the treatment of BPH. If a BPH patient does not respond to one alpha-blocker, then switching to a different alpha-blocker may provide benefit for 25–27.5% of patients. (P<0.001)
Chung, et al.[5] Multicentre, prospective, randomized study	Doxazosin-gastrointestinal therapeutic system GITS 4mg vs. Tamsulosin 0.2mg	Male ambulatory patients over 50 years of age with LUTS.	Comparison of early onset (over a 12 week period) efficacy between the two drugs using IPSS scores.	Improvement in total IPSS score from baseline Visit / Doxazosin-GITS / Tamsulosin / p value Week 1: (-7.62),-37.5% / (-5.02),-27.5% / 0.021 Week4: (-8.56),-42.2% / (-6.34),-34.8% / 0.030 Week 12: (-9.27),-45.6% / (-5.48),-27.3% / 0.0005
Yu, et al.[6] RCT, double-blind, multicentre	Silodosin 4mg bid vs. tamsulosin 0.2mg qam + placebo qpm	Men with BPH aged ≥40 years with an IPSS of ≥13	Mean change from baseline to endpoint in IPSS.	Decrease in IPSS (≥25%) / Mean difference in IPSS change S: 86.2% / -0.60, 95% CI (-2.15,0.95) T: 81.9% P=0.53
Zhang, et al.[7] Prospective, multicenter, randomized, open, parallel study	Doxazosin-GITS 4mg vs. Tasmulosin 0.2mg	Chinese men aged ≥50 years with LUTS/BPH.	Change from baseline in self-reported nocturia according to the IPSS and FVC, quality of sleep and quality of life.	Reduction from baseline in mean nocturia (FVC/IPSS) Week 4: D: 1.7, T: 1.3(P=0.001) / D: 1.5, T: 1.1(P=0.001) Week 8: D: 2.1, T: 1.7(P=0.001) / D: 2.0, T: 1.6(P<0.001) Percentage reported improved sleep Week 4: D: 43.6%, T: 27.4% (P=0.020) Week 8: D: 81.9%, T: 67.4% (P=0.022) Improvement in quality of life(Lower number=better QoL) Week 4: D: 2.5, T: 2.8 (P=0.001) Week 8: D: 2.1, T: 2.5 (P<0.001)
Nickel, et al.[8] RCT, double-blind, double-dummy, multicentre	Dutasteride 0.5mg vs. Finasteride 5mg	Men aged >50 years with a clinical diagnosis of BPH	Change in prostate volume	Mean percent reduction in prostate volume 3 months: F: 18.5%, D: 18.3% (P=0.76) 12 months: F: 26.7%, D: 26.3% (P=0.65, CI 1.4-2.3) Reduction in prostate volume at 12 months ≥40cm^3 baseline: F: 27.7%, D: 27.6% (P=0.90) <40cm^3 baseline: F: 24.2%, D: 22.6% (P=0.37)

Watanabe, et al.[9] RCT, crossover, comparative, open-label	Tamsulosin (0.2mg) to Silodosin (4mg) vs. Silo to Tam	Untreated Japanese men diagnosed with LUTS/BPH and an IPSS ≥8 and IPSS-QoL score ≥2	Patient-reported preferred drug for treatment continuation at 8 weeks	Patient preferred Drug Tamsulosin: 59/84 (70.2%) Silodosin: 18/84 (21.4%) P=NS
Montorsi, et al.[10] post hoc analysis	Dutasteride 0.5mg vs Tamsulosin 0.4mg vs. combination	Men ≥50 years with moderate-to-severe LUTS due to BPH at risk of disease progression	Mean changes from baseline in IPSS.	Mean changes from baseline in IPSS at 4 years Combination: -6.3 Dutasteride: -5.3 Tamsulosin: -3.8 P<0.001
Roehrborn, et al.[11] Post hoc analysis	Dutasteride 0.5mg vs. tamsulosin 0.4mg vs. combined therapy	Men aged ≥50 years with diagnosis of BPH	Time to first AUR or BPH-related surgery	Combined therapy (dutasteride + tamsulosin) was statistically better than tamsulosin alone in reducing the risk of AUR or BPH-related surgery (P≤0.001). The incidence of surgery was higher with tamsulosin than in dutasteride or combined therapy (P≤0.001).
Miyakita, et al.[12] RCT, crossover	Silodosin (4mg) to Tamsulosin (0.2mg) vs. Tam to Sil	BPH patients complaining of LUTS	Change in total IPSS from baseline	Change in IPSS total score after first drug S: -7.7 ± 5.9, T: -4.6 ± 5.4 (P<0.05) Change in IPSS after crossover S: -2.6 ± 3.8, T: 0.3 ± 4.3 (P<0.01)
Montorsi, et al.[13] Post hoc analysis	Dutasteride 0.5mg vs. tamsulosin 0.4mg vs. combined therapy	Men age ≥50 years with moderate-to-severe symptoms of BPH	Change from baseline in IPSS and BII scores with combination vs. monotherapy	Mean change in IPSS from baseline Combo: -1.5, D: -1.3, T: -1.1 (P<0.001) Mean change from baseline in BII scores Combo: -2.2, D: -1.8, T: -1.2 (P<0.001)
Yanqun, et al.[14] RCT, DB, parallel group, placebo controlled with an open label extension	Dutasteride (D/D) 0.5mg vs. placebo (6 months) to dutasteride (P/D)	Chinese men aged ≥50 years with diagnosis of BPH	Percentage change in total prostate volume (TPV) from baseline at 6 months	Mean reduction in TPV at 6 months D/D: 17.14% P/D: 3.71% P<0.05
Shin, et al.[15] Retrospective study	Alpha blocker vs. combination (alpha blocker + 5-alpha reductase inhibitor)	Patients ≥40 years with an IPSS of ≤7 and previously treated for BPH without AUR or BPH-related surgery.	Difference in incidences of AUR and BPH-related surgeries between the two groups	Incidence in AUR Alpha blocker: 50/368 (13.6%) Combination: 7/252 (2.8%) P<0.001 Incidence of BPH-related surgeries Alpha blocker: 31/368 (8.4%) Combination: 8/252 (3.2%) P=0.008
Kruep, et al.[16] Retrospective study	5-alpha reductase inhibitor early (within 30 days of	Men ≥50 years of age with BPH or an enlarged prostate	AUR, prostate surgery, and clinical progression (combination of the two	Percentage of patients with AUR Early: 10.2%, Late: 13.8% P<0.0001

	starting an alpha blocker) vs. delayed therapy (30-180 days after starting alpha blocker)		above)	Percentage of patients who underwent surgery Early: 5%, Late: 7% P=0.0002 Percentage of patients with clinical progression Early: 12.8%, Late:17.4% P<0.0001
Madani, et al.[17] RCT, double-blinded	Standard treatment + tadalafil 10mg vs. standard treatment alone (placebo)	Patients with obstructive and irritative urinary tract symptoms due to BPH, IPSS≥8	Differences in IPSS, Qmax and QoL after 3 months between groups	Mean values after treatment of the two groups Placebo / Drug / P-value IPSS 11.37±3.64 / 7.66±3.99 / 0.001 QoL 2.19±0.53 / 1.8±0.98 / 0.036 Qmax 8.73±2.22 / 9.99±4.76 / 0.066
Oelke, et al.[18] RCT, double-blinded	Tadalafil 5mg vs. Tamsulosin 0.4mg vs. placebo	Men ≥45 years of age with LUTS/BPH	Efficacy based on IPSS and BPH Impact Index (BII)	IPSS mean difference from placebo Tadalafil: -2.1 (95%CI -3.3 to -0.8, p=0.001) Tamsulosin: -1.5 (95%CI -2.8 to -0.2, p=0.023) BII mean difference from placebo Tadalafil: -0.8 (95%CI -1.3 to -0.3, p=0.003) Tamsulosin: -0.6 (95%CI -1.1 to -0.1, p=0.026)

IPSS= International Prostate Symptom Score; FVC= frequency volume chart; AUR= Acute urinary retention; QoL=quality of life

New drugs:

The FDA approved tadalafil (Cialis®) in October of 2011 to treat the signs and symptoms of BPH and for the treatment of simultaneous occurrence of BPH and erectile dysfunction. [17,18] In two clinical trials, men with BPH on standard treatment (alpha-blockers) were compared to standard treatment in addition to 5 mg of tadalafil on reduction of symptoms. The mean change in the International Prostate Symptom Score (IPSS) from baseline to endpoint for tadalafil versus placebo was -5.00 versus -2.67. According to the AUA guidelines, a 3-point improvement in IPSS was suggested as the minimum perceived by patients.[19] However, it failed to show a significant improvement in maximal urinary flow rate (Qmax) or post void residual urine volume. There was no significant difference in serious adverse events. A recent systematic review found that tadalafil or other phosphodiesterase-5 inhibitors could significantly improve symptoms in patients with comorbid BPH and ED, however in those without ED there was no sufficient data to prove superiority to alpha-blockers for first-line treatment.[19]

New Combination Products:

The FDA approved the combination of dutasteride and tamsulosin hydrochloride (Jalyn) in June 2010 for the treatment of BPH. The labeling has then been revised to include the risk of high-grade prostate cancer due to dutasteride, its effects on serum prostate specific antigen, and information regarding male breast cancer.[16,17]

New Formulations/Indications:

The FDA approved generic alfuzosin hydrochloride 10mg extended-release tablets in July of 2011. The Division of Bioequivalence has determined that the 10mg dose is therapeutically equivalent to Uroxatral 10mg extended-release tablets.

The FDA also approved generic dutasteride capsules 0.5mg in December 2010. The Division of Bioequivalence determined that the 0.5mg dutasteride capsule is therapeutically equivalent and bioequivalent to Avodart capsules 0.5mg.

New FDA safety alerts:
There was a new FDA drug safety communication in June of 2011 regarding the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer) with the use of 5-alpha reductase inhibitors. The risk appears to be low, but healthcare professionals should weigh the known benefits against the potential risk when deciding to start or continue treatment with these agents in men.[18]

New Systematic Reviews (Appendix 3):
Two recent systematic reviews were published evaluating the new indication of phosphodiesterase-5 (PDE-5) inhibitors for BPH as monotherapy and combination.

A review by Liu et al., included a total of 5 studies (2054 participants) and assessed the efficacy and safety of PDE-5 inhibitors for treating LUTS secondary to BPH.[19] The primary outcomes included changes in the IPSS and maximal urinary flow rate (Qmax) after treatment with PDE-5 inhibitors. Three of the 5 studies investigated tadalafil versus placebo (1499 patients with BPH alone), and vardenafil and sildenafil were evaluated in the other two studies. Their pooled mean change in IPSS from baseline was -5.24 for PDE-5 inhibitors vs. -2.64 for placebo, which demonstrated a statistically significant difference in favor of the PDE-5 inhibitor (95% CI -3.12,-2.07; P<0.00001). The 5 studies then investigated the change in the Qmax from baseline and found that the PDE-5 inhibitors and placebo had a similar effect (95% CI -0.21, 0.64; P=0.32). Even though PDE-5 inhibitors showed an improvement in IPSS, they failed to result in significant improvement in Qmax.[19]The study did not mention a protocol and even though it stated the publication bias was evaluated using a funnel plot, it did not show or discuss the results. Overall, this was a good systematic review and its results can be extrapolated due to the thorough discussion of the studies limitations and that all other data was reported.

In the review by Gacci et al., 12 studies were assessed which looked at use of PDE5-inhibitors alone or in combination with alpha blockers in patients with LUTS/BPH.[20] Studies comparing the effect of PDE5-inhibitors alone vs. placebo included a total of 3,214 patients. These studies found that PDE-5 inhibitors significantly improve IPSS (-2.8; p <0.0001), but not Qmax when compared with placebo (-0.00; p=not significant). These studies also found that 16% of men taking the PDE-5 inhibitor had adverse effects versus 6% of men taking placebo. The studies that compared the effect of alpha blockers alone vs. the combination of alpha blockers and PDE-5 inhibitors included 216 patients. The combination of the two medications significantly improved IPSS (-1.8; p=0.05) and IIEF score (+3.6; p<0.0001) as well as Qmax (+1.5; p<0.0001) when compared to alpha blockers alone. The reported adverse events in the combination therapy group were 6.8% and 5.1% in the group treated with alpha blocker alone.[20] This was a well done systematic review with proper data and results provided, but it lacked the principal summary measures and risk of bias across each study.

References:

1. Allison DB, Gadde KM, Garvey WT, et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). *Obesity*. 2011;20(2):330–342.

2. Jones C, Hill J, Chapple C, on behalf of the Guideline Development Group. Management of lower urinary tract symptoms in men: summary of NICE guidance. *BMJ*. 2010;340(may19 2):c2354–c2354.

3. Oregon Heatlh Authority. Oregon Health Plan Prioritized List of Health Services. *Oregon Health Policy and Research*. 2012. Available at: http://www.oregon.gov/OHA/OHPR/HERC/docs/L/Apr12List.pdf. Accessed May 1, 2012.

4. Karadag E, Oner S, Budak Y, Atahan O. Randomized crossover comparison of tamsulosin and alfuzosin in patients with urinary disturbances caused by benign prostatic hyperplasia. *International Urology & Nephrology*. 2011;43(4):949–54.

5. Chung M, Lee S, Park K, Yoo S, Chung B. Comparative rapid onset of efficacy between doxazosin gastrointestinal therapeutic system and tamsulosin in patients with lower urinary tract symptoms from benign prostatic hyperplasia: a multicentre, prospective, randomized study. *Journal of Clinical Practice*. 2011;65(11):1193–9.

6. Yu H, Lin A, Yang S, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). *BJU International*. 2011;108(11):1843–8.

7. Zhang K, Yu W, Jin J, et al. Effect of doxazosin gastrointestinal therapeutic system 4 mg vs tamsulosin 0.2 mg on nocturia in Chinese men with lower urinary tract symptoms: a prospective, multicenter, randomized, open, parallel study. *Urology*. 2011;78(3):636–40.

8. Nickel J, Gilling P, Tammela T, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU International*. 2011;108(3):388–94.

9. Watanabe T, Ozono S, Kageyama S. A randomized crossover study comparing patient preference for tamsulosin and silodosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia.[Erratum appears in J Int Med Res. 2011;39(3):1122]. *Journal of International Medical Research*. 2011;39(1):129–42.

10. Montorsi F, Roehrborn C, Garcia-Penit J, et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study. *BJU International*. 2011;107(9):1426–31.

11. Roehrborn C, Barkin J, Siami P, et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. *BJU International*. 2011;107(6):946–54.

12. Miyakita H, Yokoyama E, Onodera Y, et al. Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Journal of Urology*. 2010;17(10):869–75.

13. Montorsi F, Henkel T, Geboers A, et al. Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study. *Journal of Clinical Practice*. 2010;64(8):1042–51.

14. Na Y, Ye Z, Zhang S. Efficacy and safety of dutasteride in Chinese adults with symptomatic benign prostatic hyperplasia: a randomized, double-blind, parallel-group, placebo-controlled study with an open-label extension. *Clin Drug Investig*. 2012;32(1):29–39.

15. Shin TJ, Kim CI, Park CH, Kim BH, Kwon YK. α-Blocker Monotherapy and α-Blocker Plus 5-Alpha-Reductase Inhibitor Combination Treatment in Benign Prostatic Hyperplasia; 10 Years' Long-Term Results. *Korean J Urol*. 2012;53(4):248–252.

16. Kruep EJ, Hogue SL, Eaddy MT, Chandra MD. Clinical and economic impact of early versus delayed 5-alpha reductase inhibitor therapy in men taking alpha blockers for symptomatic benign prostatic hyperplasia. *P T*. 2011;36(8):493–507.

17. Madani AH, Afsharimoghaddam A, Roushani A, et al. Evaluation of Tadalafil effect on lower urinary tract symptoms of benign prostatic hyperplasia in patients treated with standard medication. *Int Braz J Urol*. 2012;38(1):33–39.

18. Oelke M, Giuliano F, Mirone V, et al. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917–925.

19. Liu L, Zheng S, Han P, Wei Q. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. *Urology*. 2011;77(1):123–129.

Appendix 1: Current PA Criteria

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s): BPH with urinary obstruction treatment is covered by OHP only when post-void residuals are at least 150ml.

- Cosmetic use for baldness is NOT covered.
- Erectile dysfunction is not covered by OHP

* Note: Finasteride is also available as Propecia®, which is FDA-approved for alopecia/male pattern baldness. Alopecia and male pattern baldness are not approvable diagnoses for 5-Alpha Reductase (5AR) Inhibitors.

Length of Authorization: 1 year

Preferred Alternatives: All preferred alternatives on PDL list: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Non-preferred drugs

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code.	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource 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/dl.shtml.	**No**: Go to #3
3. Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-599.89)	**Yes:** Go to #4	**No:** Go to #5
4. Has the client tried and failed a 2-month trial of a covered alternative	**Yes:** Approve an alpha	**No:** Deny until

alpha blocker (terazosin, doxazosin, prazosin, tamsulosin)?	blocker only for 1 year	client has tried and failed a covered alternative
5. Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	**Yes:** Approve for the shorter of 1 year or length of the prescription	**No:** Go to #6
6. Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? **(599.6, 600.00, 600.10, 600.20, and 600.90**)	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP)	**No:** Pass to RPH; Go to #7

7. RPH Notes only - All other indications need to be evaluated to see if they are above or below the line:

Above the line covered diagnoses related to prostate may be approved for 1 year

Below the line diagnoses (e.g. Hair growth, erectile dysfunction) should be denied (Not Covered by the OHP).

Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size.

97

- 788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve.

Refer questions of coverage to DMAP.

Renewal Therapy		
1. Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-599.89)	**Yes:** Go to #2	**No:** Go to #3

2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	**Yes:** Recommend against combination therapy exceeding 1 year	**No:** Approve for the shorter of 1 year or length of the prescription
3. Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	**Yes:** Approve for 1 year	**No:** Go to #4
4. Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? **(599.6, 600.00, 600.10, 600.20, and 600.90**)	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP)	**No:** Pass to RPH; Go to #5
5. RPH only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis. • Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size. • 788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve.	**If above the line or clinic provides supporting literature:** approve for one year.	**If below the line:** Deny, (Not Covered by the OHP).

86

DUR Board Action: 9/16/10 (KS), 3/18/10(KK), 5-22-08, 2-23-06
Revision(s): 1/1/11, 4/20/10, 5-22-08 (Aebi), 7-1-06, 9-30-05
Effective: 10-14-04 (previously excluded)

Appendix 2: New Trial Abstracts

1. **Karadag E, Oner S, Budak Y, Atahan O. Randomized crossover comparison of tamsulosin and alfuzosin in patients with urinary disturbances caused by benign prostatic hyperplasia. *International Urology & Nephrology*. 2011;43(4):949–54.**

OBJECTIVE: To compare the efficacy and safety of alfuzosin (Alf) and tamsulosin (Tam) in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). METHODS: One hundred men were enrolled in this randomized cross-over study. During enrollment, a detailed medical history was recorded, and International Prostate Symptom Score (IPSS), digital rectal exam, urinary ultrasound, prostate specific antigen (PSA) level, and uroflowmetry were determined. Those with IPSS greater than 8 and a maximum urinary flow rate (Qmax) lower than 15ml/s were randomly divided into either Alf-Tam group or Tam-Alf group (taking each medication for 8 weeks) with no washout period between switching drugs. RESULTS: During the first 8 weeks, each drug significantly improved IPSS and Qmax. After the crossover, both groups continued to have improvement in IPSS and Qmax. Both drugs significantly lowered IPSS and increase Qmax from baseline (P<0.001). Neither drug affected the serum PSA levels. CONCLUSION: Similar favorable outcomes were associated with Tam and Alf. When one alpha blocker does not provide a desired effect in the treatment of BPH, switching to another in the class seems to be beneficial.

2. **Chung M, Lee S, Park K, Yoo S, Chung B. Comparative rapid onset of efficacy between doxazosin gastrointestinal therapeutic system and tamsulosin in patients with lower urinary tract symptoms from benign prostatic hyperplasia: a multicentre, prospective, randomised study. *Journal of Clinical Practice*. 2011;65(11):1193–9.**

OBJECTIVE: To compare the rapidity of improvement in lower urinary tract symptoms (LUTS) for the doxazosin gastrointestinal therapeutic system (GITS) and tamsulosin in BPH patients. METHODS: There were 207 patients randomized for a 12-week daily treatment with either doxazosin-GITS 4 mg or tamsulosin 0.2mg. The primary outcome was to compare the early onsets of efficacy between the two drugs. This was done by analyzing the changes from baseline IPSS. The secondary outcomes included comparing improvements in obstructive/irritative subcore and quality of life (QoL) between the groups, and to evaluate adverse events with the drugs. RESULTS: Both groups showed significant improvements in IPSS scores after the 12 weeks of treatment (p<0.0001). The doxazosin-GITS group showed significantly greater improvements in total IPSS and obstructive subscore than the tamsulosin group during the beginning of the trial (p<0.05). Improvments in irritative subscore and QoL socre did not show significant differences between the two groups. The groups had similar adverse events incidences. CONCLUSION: Doxazosin-GITS showed significantly more rapid onset of efficacy and similar adverse events when compared with tamsulosin. This may help improve patient compliance. Further studies need to be conducted with a larger population and longer follow-up period to confirm the findings of this study.

3. **Yu H, Lin A, Yang S, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). *BJU International*. 2011;108(11):1843–8.**

OBJECTIVE: To test the hypothesis that the efficacy of silodosin would not be inferior to tamsulosin in treating patients with LUTS/BPH. METHODS: The study was conducted at 9 medical centres with a total of 209 patients with an IPSS of ≥13. The patients were randomized to either silodosin 4mg twice daily or tamsulosin 0.2mg once daily for 12 weeks. The primary outcome was the mean change in IPSS from baseline to endpoint. The secondary outcomes measured change in Qmax and QoL score. RESULTS: Of the patients who completed the study 86.2% taking silodosin vs. 81.9% taking tamsulosin achieved a ≥25% decrease in IPSS (P=0.53). The mean difference in IPSS change from baseline was -0.60 (95%CI -2.15, 0.95),

inferring non-inferiority of silodosin to tamsulosin. The mean changes in the Qmax and QoL socre from baseline were comparable between groups (P>0.05). CONCLUSION: This study shows the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2mg once daily in patients with BPH.

4. **Zhang K, Yu W, Jin J, et al. Effect of doxazosin gastrointestinal therapeutic system 4 mg vs tamsulosin 0.2 mg on nocturia in Chinese men with lower urinary tract symptoms: a prospective, multicenter, randomized, open, parallel study. *Urology*. 2011;78(3):636–40.**

OBJECTIVE: To compare the efficacy of doxazosin-GITS 4mg and tamsulosin 0.2mg on nocturia in Chinese men with LUTS/BPH. METHODS: The study is a prospective, multicenter, randomized, open, parallel study of Chinese men aged 50-84 years with LUTS/BPH. Two hundred paitents were randomized to receive either 4mg doxazosin-GITS or 0.2mg tamsulosin for 8 weeks. The IPSS-question 7 and frequency volume chart (FVC) were used to assess nocturia at weeks 4 and 8. Patients also self-reported quality of sleep and quality of life. RESULTS: The reduction in mean nocturia from baseline was greater with doxazosin-GITS than tamsulosin by the FVC (P=0.001) and IPSS-question 7 (P<0.001). There were more patients on doxazosin-GITS who reported improved quality of sleep than patients taking tamsulosin (P=0.020 at 4 weeks; P=0.022 at 8 weeks) and similar results were seen with reports of QoL (P=0.001 at 4 weeks; P<0.001 at 8 weeks). CONCLUSION: Chinese men with LUTS/BPH have shown a slightly better response in reduction of frequency of nocturia with doxazosin-GITS than tamsulosin.

5. **Nickel J, Gilling P, Tammela T, Morrill B, Wilson T, Rittmaster R. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU International*. 2011;108(3):388–94.**

OBJECTIVE: To assess the efficacy and safety of dutasteride compared with finasteride in treating men with symptomatic BPH for 12 months. METHODS: The study was a multicenter, randomized, double-blind, 12-month, parallel group study. The participants were men aged ≥50 years with a clinical diagnosis of BPH. The participants either received once-daily treatment with dutasteride 0.5mg or finasteride 5 mg. Patients underwent a 4-week placebo run-in period and then were randomized to one of the two groups for 48 weeks, followed by an optional 24 month, open-label phase where the patients received dutasteride 0.5mg once daily. The primary outcome was change in prostate volume. The secondary endpoints include improvement in Qmax, symptom scores, and safety in the 24 month open-label phase. RESULTS: Both dutasteride and finasteride were effective at reducing prostate volume with no significant difference between the two. Similar percentage of adverse events was experienced in both treatment groups. CONCLUSION: For the 12 months that dutasteride and finasteride were administered, they showed similar effectiveness in reducing prostate volume and improving Qmax and urinary symptoms.

6. **Watanabe T, Ozono S, Kageyama S. A randomized crossover study comparing patient preference for tamsulosin and silodosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia.[Erratum appears in J Int Med Res. 2011;39(3):1122]. *Journal of International Medical Research*. 2011;39(1):129–42.**

OBJECTIVE: To compare patient preference for tamsulosin and silodosin in patient with LUTS/BPH. METHODS: The study was a randomized, crossover, comparative, open-label study. The study included Japanese patients with LUTS associated with BPH and had an IPSS ≥8 and a QoL score ≥2. They randomly assigned the patients to either a Tam-Sil or Sil-Tam for a total of 8 weeks. The primary outcome was the preferred drug for treatment continuation at 8 weeks, according to the patient-report questionnaire. RESULTS: There were a total of 102 patients who enrolled in the study and 82 completed the 8 weeks. There was a significant difference between the patients who preferred tamsulosin (59/84; 70.2%) and those

that preferred silodosin (18/84; 21.4%). Incidence of adverse effects was significantly lower with tamsulosin (3/91; 3.3%) than with silodosin (25/88). CONCLUSION: The findings of the study indicate that tamsulosin is very effective for BPH, has few adverse effects and is patient-preferred.

7. **Montorsi F, Roehrborn C, Garcia-Penit J, et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study. *BJU International*. 2011;107(9):1426–31.**

OBJECTIVE: To assess the effects of combination therapy with dutasteride and tamsulosin on voiding and storage symptoms with those of dutasteride or tamsulosin alone. METHODS: The study included men aged ≥50 years with moder-to-severe LUTS due to BPH, a prostate volume of >30mL, and a PSA of 1.50-10ng/mL. This was a post hoc analysis of a multicenter, double-blind, parallel group study. Patients received either oral dutasteride 0.5mg or tamsulosin 0.4mg alone or in combination for 4 years. The outcomes analyzed included mean changes form baseline in storage and voiding symptoms at 4 years, which were assessed using the IPSS. RESULTS: The mean reduction in the storage subscore was significantly greater in the combined group versus the dutasteride and tamsulosin monotherapy groups (P<0.001). The mean reduction in the voiding subscore was significantly greater in the combination group versus the dutasteride and tamsulosin monotherapy group (P<0.001). CONCLUSION: It appeared that combined therapy with dutasteride plus tamsulosin provided better long-term control of storage and voiding compared to tamsulosin monotherapy in men with a prostate volume of ≥30mL. Combined therapy was also better than dutasteride monotherapy in men with prostate volumes of ≥30 and <58mL, but not in men with a prostate volume of ≥58mL.

8. **Roehrborn C, Barkin J, Siami P, et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. *BJU International*. 2011;107(6):946–54.**

101

OBJECTIVE: To investigate the influence of baseline variables on the acute urinary retention (AUR), BPH-related surgery and overall clinical progression over a 4-year period in men treated with tamsulosin, dutasteride, or combination therapy. METHODS: A post hoc analysis of a multicenter, randomized, double-blind, parallel group study in men aged ≥50 years with symptomatic BPH. The primary endpoint was time to first AUR or BPH-related surgery. The secondary endpoints included clinical progression of BPH and symptoms. Baseline prostate volumes (PV) and prostate specific antigen (PSA) levels were measured. RESULTS: There were 4844 men participating in the study. Combined therapy was statistically better than tamsulosin alone in reducing the risk of AUR or BPH-related surgery in subgroups of baseline PV≥42mL and in all subgroups of baseline PSA levels (P<0.001). Combined therapy reduced the relative risk (RR) of clinical progression compared with tamsulosin alone across all baseline subgroups. CONCLUSION: Men with baseline PV of >40mL and any baseline PSA level of >1.5ng/mL had greater reductions in the RR of AUR or BPH-related surgery and greater reduction in the RR of clinical progression and symptom deterioration on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy. This supports the long-term use of combined therapy with dutasteride plus tamsulosin in moderate-to-severe BPH.

9. **Miyakita H, Yokoyama E, Onodera Y, et al. Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Journal of Urology*. 2010;17(10):869–75.**

OBJECTIVE: To compare the efficacy and safety of silodosin and tamsulosin in patients with LUTS/BPH. METHODS: This randomized crossover study analyzes BPH students with the complaint of LUTS. The patients are randomly divided into either a silodosin-preceding group (4 weeks of twice daily silodosin 4mg) followed by 4 weeks of once daily tamsulosin at 0.2mg or a tamsulosin preceding group followed by a silodosin group. No drug withdrawal period occurred when switching the drugs. RESULTS: Both drugs significantly improved the IPSS score, but the improvement by silodosin was significantly superior to that by tamsulosin. After the crossover treatment, significant improvement was observed only with silodosin treatment. Silodosin also significantly improved QoL score in both treatment periods, while tamsulosin only significantly improved QoL score in the first treatment period. CONCLUSION: Silodosin exhibits better efficacy in improving subjective symptoms in both initial and crossover treatment, and it appears to improve the QoL of patients than tamsulosin.

10. **Montorsi F, Henkel T, Geboers A, et al. Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study. *Journal of Clinical Practice*. 2010;64(8):1042–51.**

OBJECTIVE: To investigate the effects of combination therapy (dutasteride plus tamsulosin) compared with each monotherapy in men with moderate-to-severe LUTS due to BPH. METHODS: Subjects were randomized to receive either dutasteride 0.5mg, tamsulosin 0.4mg or a combination of the two for 4 years. The primary outcome at 4 years was the time to event and proportion of subjects with acute urinary retention or BPH-related surgery. Secondary endpoints measures BPH Impact Index (BII), IPSS question 8, and Patient Perception of Study Medication (PPSM) questionnaire. RESULTS: Combination therapy resulted in significantly superior improvements from baseline in BII and IPSS question 8 than either monotherapy. The PPSM questionnaire showed that a significantly higher proportion of patients were satisfied and requested the combination therapy for treatment compared to either monotherapy. CONCLUSION: Combinatioin therapy provides significantly superior improvements in patient-reported QoL and treatment satisfaction than either monotherapy at 4 years in men with moderate-to-severe BPH symptoms.

102

11. **Na Y, Ye Z, Zhang S. Efficacy and safety of dutasteride in Chinese adults with symptomatic benign prostatic hyperplasia: a randomized, double-blind, parallel-group, placebo-controlled study with an open-label extension. *Clin Drug Investig*. 2012;32(1):29–39.**

OBJECTIVE: To evaluate the efficacy and safety of dutasteride in Chinese adults with symptomatic BPH. METHODS: This was a randomized, double-blind, parallel-group, placebo-controlled study which took place over 6 months and was followed by an open-label extension of 12 months. Patients were randomized to receive either dutasteride 0.5mg/day orally or matching placebo treatment. After 6 months, eligible participants enter the open-label extension all receiving dutasterdie 0.5mg/day orally. The changes in total prostate volume (TPV), Qmax, and American Urology Association Symptom Index (AUA-SI) were evaluated. RESULTS: Dutasteride significantly reduced mean TPV compared with placebo at 3 and 6 months ($P<0.05$). Higher improvements in Qmax and AUA-SI were observed in the dutasteride group, but no statistical significance between groups was found. CONCLUSION: Dutasteride was effective compared with placebo in the treatment of symptomatic BPH among Chinese men.

12. **Shin TJ, Kim CI, Park CH, Kim BH, Kwon YK. α-Blocker Monotherapy and α-Blocker Plus 5-Alpha-Reductase Inhibitor Combination Treatment in Benign Prostatic Hyperplasia; 10 Years' Long-Term Results. *Korean J Urol*. 2012;53(4):248–252.**

OBJECTIVE: To compare the effects of alpha blocker monotherapy with combination therapy containing an alpha blocker and 5-alpha reductase inhibitor on BPH progression for over 10 years. METHODS: A total of 520 patients received alpha blocker monotherapy or combination therapy as their initial treatment. The incidences of acute urinary retention (AUR) and BPH-related surgery were compared between groups. RESULTS: The incidence of AUR was 13.6% in the alpha blocker group and 2.8% in the combination group (P<0.001). A total of 8.4% and 3.2% of patients underwent BPH-related surgery in the alpha blocker and combination groups, respectively (P=0.008). CONCLUSION: Long-term combination therapy with alpha blocker and 5-alpha reductase inhibitor can suppress the progression of BPH more efficiently than alpha blocker monotherapy (which showed the better effects in patients with PSA>2ng/mL or PV>35mL).

13. **Kruep EJ, Hogue SL, Eaddy MT, Chandra MD. Clinical and economic impact of early versus delayed 5-alpha reductase inhibitor therapy in men taking alpha blockers for symptomatic benign prostatic hyperplasia. *P T*. 2011;36(8):493–507.**

OBJECTIVE: To assess the clinical and economic impact of early versus delayed 5-alpha reductase inhibitor (5-ARI) therapy in patients treated with alpha blocker for BPH. METHODS: This is a retrospective database analysis that included men ≥50 years of age who were treated with BPH. The primary outcome was to evaluate patients using 5-ARI early (within 30 days of starting an alpha blocker) compared with those using delayed 5-ARI therapy (between 30 and 180 days starting the alpha blocker). Acute urinary retention (AUR) and BPH-related surgery were assessed (clinical progression). RESULTS: Patients who started 5-ARI early were less likely than those receiving delayed treatment (12.8% vs. 17.4%, p<0.0001) to have clinical progression, AUR (10.2% vs. 13.8%, p<0.0001), and prostate surgery (5% vs. 7%, p=0.0002). The early group also acquired lower BPH-related medical costs ($572 vs. $730, p<0.0001). CONCLUSION: The results suggest that early 5-ARI therapy for men with symptomatic BPH who are receiving an alpha blocker may significantly reduce the risk of clinical progression over the next 12 months as well as lower BPH-related costs.

14. **Madani AH, Afsharimoghaddam A, Roushani A, Farzan A, Asadollahzade A, Shakiba M. Evaluation of Tadalafil effect on lower urinary tract symptoms of benign prostatic hyperplasia in patients treated with standard medication. *Int Braz J Urol*. 2012;38(1):33–39.**

OBJECTIVE: To evaluate safety and efficacy of tadalafil on lower urinary tract symptoms related to benign prostatic hyperplasia. METHODS: This is a case-controlled randomized clinical trial, from November 2008 to August 2009. The study selected 132 patients with obstructive and irritative urinary tract symptoms due to BPH, IPSS≥8, no indication for surgical intervention and that reached plateau levels of response to treatment. The treatment group received standard treatment of BPH and tadalafil 10mg nightly and the placebo group received only standard treatment of BPH. The primary outcome assessed IPSS, maximum urinary flow rate (Qmax) and quality of life before and after a 3-month period of study. RESULTS: Before treatment, mean IPSS, Qmax and QoL values in the treatment and placebo groups were 13.06±4.37 and 13.66±4.25, 8.92±2.96 mL/s and 9.09±2.91, 2.93±0.86 and 2.66±0.78 mL/s, respectively. After treatment, mean IPSS, Qmax, and QoL values in treatment group were 7.66±3.99, 9.99±4.76 and 1.80±0.98 mL/s, respectively. These findings were compared to corresponding values of the placebo group (11.37±3.64, 8.73±2.22 and 2.19±0.53 mL/s, respectively). IPSS and quality of life were significantly different but Qmax didn't show a significant change. CONCLUSION: Tadalafil improves quality of life and urinary symptoms in patients with LUTS suggestive of BPH, but doesn't have any significant effect on Qmax. Therefore, this drug may be effectively used in combination with standard medical therapies for BPH.

15. **Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917–925.**

OBJECTIVE: To assess tadalafil or tamsulsoin versus placebo for LUTS/BPH. METHODS: This is a randomized, double-blind, international, placebo-controlled, parallel-group study assessing men >45 years of age with LUTS/BPH, International Prostate Symptom Score (IPSS) _13, and maximum urinary flow rate (Qmax) ≥4 to ≤15 ml/s. Following screening and washout, if needed, subjects completed a 4-wk placebo run-in before randomization to placebo (n = 172), tadalafil 5 mg (n = 171), or tamsulosin 0.4 mg (n = 168) once daily for 12 wk. The primary outcome assessed efficacy based on IPSS and BPH Impact Index (BII). RESULTS: IPSS significantly improved versus placebo through 12 wk with tadalafil (-2.1; p = 0.001; primary efficacy outcome) and tamsulosin (-1.5; p = 0.023) and as early as 1 wk (tadalafil and tamsulosin both -1.5; p < 0.01). BPH Impact Index significantly improved versus placebo at first assessment (week 4) with tadalafil (-0.8; p < 0.001) and tamsulosin (-0.9; p < 0.001) and through 12 wk (tadalafil -0.8, p = 0.003; tamsulosin -0.6, p = 0.026). Qmax increased significantly versus placebo with both tadalafil (2.4 ml/s; p = 0.009) and tamsulosin (2.2 ml/s; p = 0.014). CONCLUSION: Monotherapy with tadalafil or tamsulosin resulted in significant and numerically similar improvements versus placebo in LUTS/BPH and Qmax.

Appendix 3: Abstracts of systematic reviews

1. **Liu L, Zheng S, Han P, Wei Q. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. *Urology*. 2011;77(1):123–129.**

OBJECTIVE: To evaluate the efficacy and safety of phosphodiesterase-5 (PDE-5) inhibitors for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia. METHODS: Randomized controlled trials were identified and extracted from MEDLINE, Embase, Cochrane Central, and relevant reference lists. The database search, quality assessment, and data extraction were independently performed by 2 reviewers. Heterogeneity was analyzed using the chi-square test and I^2 test. If lacking of heterogeneity, fixed-effects models were used for the meta-analysis, otherwise random-effects models were used. RESULTS: Five studies were identified. PDE-5 inhibitors showed significant improvement in the IPSS (P<0.00001) when compared with placebo. No statistically significant difference was found in maximal urinary flow rate and postvoid residual urine volume. No statistically significant difference was found between the 2 groups in the incidence of serious adverse events. CONCLUSION: PDE-5 inhibitors are effective and safe for LUTS/BPH. It could be considered first line treatment in the future as well as for patient with comorbid BPH and erectile dysfunction.

2. **Gacci M, Corona G, Salvi M, et al. A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *European Urology*. 2012;61(5):994–1003.**

OBJECTIVE: To analyze the available studies on the use of PDE-5 inhibitors alone or in combination with alpha adrenergic blockers in LUT/BPH patients. METHODS: A systematic search was performed using the Medline, Embase, and Cochrane Library databases through September 2011 including the combination of the following terms: *LUTS, BPH, PDE5-Is, sildenafil, tadalafil, vardenafil, udenafil, α-blockers*, and *α1-adrenergic blocker.* The meta-analysis was conducted according to the guidelines for observational studies in epidemiology. RESULTS: The use of PDE-5 inhibitors alone

was associated with a significant improvement of the IPSS (-2.8, p<0.0001), but not Qmax compared to placebo at the end of the study. CONCLUSION: The data suggests that PDE-5 inhibitors can significantly improve LUTS/BPH in men with or without erectile dysfunction.

105

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: Pancreatic Enzyme Replacement Products (PEP)

Month/Year of Review: November 2012

Last Review: September 2010
Source: Provider Synergies

Current Status of PDL Class:
- Preferred Agents: CREON®, ZENPEP®, LIPASE/PROTEASE/AMYLASE
- Non Preferred Agents: VIOKASE®, ULTRESA®, PANCRELIPASE®, PERTZYE®, PANCREAZE®

Research Questions:
- Is pancrelipase effective in the treatment of exocrine pancreatic insufficiency?
- Is pancrelipase safe in the treatment of exocrine pancreatic insufficiency?
- Is there evidence that one pancrelipase product is more effective or safer than another product?

Conclusions:
- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzymes in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change ir CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).[4,5]
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which ca potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Othe side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.

Recommendations:
- Due to no apparent difference in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration issues.
- Evaluate comparative costs in executive session.

Reason for Review: Since the last review, three forms of pancrealipase have gained approval through the FDA mandated new drug application process (Ultresa®, Pertyze®, and Viokase®). This review will evaluate the efficacy and safety of pancreatic enzyme replacement products (PEPs).

Previous HRC Conclusions:

- 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 in this class in accordance with FDA recommendations.

Background/Summary:

A number of chronic conditions can contribute to the ongoing loss of pancreatic tissue, which in turn, interrupts the normal production of exocrine pancreatic enzymes (EPI). EPI is often associated with steatorrhea, bloating, nausea, pain, diabetes mellitus, abnormal gastric motility, decreased absorption of nutrients, and decreased weight.[1] Implications of reduced nutrient absorption include retarded growth and development, impaired immune response, infections, and bleeding tendencies. The most common causes of EPI are cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic trauma. Patients with these conditions often rely on administration of exogenous pancreatic enzyme replacement therapy (PEP).[14]

The porcine pancrelipase products which make up PEPs, contain lipase, protease, and amylase which catalyze the hydrolysis of fats to monoglycerol, glycerol, and fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars, respectively.[14] The site of pharmacologic action is at the duodenum and small intestine, and there is little systemic absorption. This is a life-long therapy for patients who require pancreatic enzyme replacement and these patients may be at risk for fibrosing colonopathy, which is associated with high dose lipase exposure.[14]

Treatment with PEPs has traditionally been an effective method of managing EPI. [1] PEPs were available as over-the-counter products prior to the Federal Food, Drug, and Cosmetic Act of 1938 and the Drug Efficacy Study Implementation amendment in 1962. Thus, PEP manufacturers were not required to prove safety or efficacy of products that were currently on the market. Among the marketed products, there were substantial variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands. The FDA later deemed that PEPs should be available by prescription only since such product variability could adversely affect the safety and effectiveness of the PEPs, and use of these products required continuous physician monitoring of patients.[14]

In 2004, the FDA announced that all PEPs are to be considered new drugs, and that manufacturers who wish to continue to market PEPs must submit New Drug Applications (NDAs). [1,14] In 2006, the Agency released additional guidance to for PEP manufacturers, defining requirements for drug development in this class. A PEP drug development program could rely on a single adequate and well-controlled study to demonstrate safety and efficacy, but patient populations should include at a minimum, an efficacy study in pediatric patients with CF. Meaningful endpoints could be pharmacodynamic measures such as decrease in steatorrhea as evaluated in a 72-hour quantitative stool collection. Study design could be a randomized, two-period, placebo-controlled, crossover study in as few as 10-25 patients with CF, and the duration of the entire trial could be days to 2 to 3 weeks. The primary efficacy endpoint used in most studies included the coefficient of fat absorption (CFA), however two different methods of measuring CFA were used. Creon was the first marketed PEP in the US to be approved under an NDA.[14]

Author: Brandy Fouts, Pharm.D.

Table 1: Available products[7-13]

Drug Products (Manufacturer)	FDA approval and Manufacturer [a]	FDA approved indications	Amylase (Units)	Lipase (Units)	Protease (Units)	Dosage Form	Other Considerations
Creon 3,000	2009 Solvay	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.	15,000	3,000	9,500	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Creon 6,000			30,000	6,000	19,000		
Creon 12,000			60,000	12,000	38,000		
Creon 24,000			120,000	24,000	76,000		
Zenpep 3	2009 Eurand	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis and other conditions	16,000	3,000	10,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Zenpep 5			27,000	5,000	17,000		
Zenpep 10			55,000	10,000	34,000		
Zenpep 15			82,000	15,000	51,000		
Zenpep 20			109,000	20,000	68,000		
Zenpep 25			136,000	25,000	85,000		
Viokace	2012 Aptalis Pharma	Exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy	39,150	10,440	39,150	Tablet	Tablets must be swallowed whole. Do not crush or chew.
Viokace			78,300	20,880	78,300		
Ultresa	2012 Aptalis Pharma	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	27,600	13,800	27,600	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Ultresa			41,400	20,700	41,400		
Ultresa			46,000	23,000	46,000		
Pancrelipase	2009 X-Gen Pharmaceuticals	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions	27,000	5,000	17,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pancrelipase			55,000	10,000	34,000		
Pancrelipase			82,000	15,000	51,000		
Pancrelipase			109,000	20,000	68,000		
Pertzye	2012 Digestive Care	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	30,250	8,000	28,750	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pertzye			60,500	16,000	57,500		
Pancreaze	2010 Janssen Pharmaceuticals	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	17,500	4,200	10,000	Delayed Release Capsule	Capsule can be opened for patients unable to swallow.
Pancreaze			43,750	10,500	25,000		
Pancreaze			70,000	16,800	40,000		
Pancreaze			61,000	21,000	37,000		

Author: Brandy Fouts, Pharm.D.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCT's) comparing PEP's to placebo or other products was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually 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. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. A total of 24 RCTs and 3 systematic reviews resulted from initial search. After further review, five RCT's were included in review. Main reasons for exclusion were non-meaningful study outcomes, inadequate blinding, redundancy in trials, and irrelevant reason for use (feeding tube clogs).

Efficacy Analysis: (Evidence table in Appendix A)
A randomized, multicenter, double-blind, placebo-controlled, poor quality, parallel group trial (n=27) evaluated the effects on steatorrhea of Creon 10 versus placebo in 27 patients with CP. The primary objective of the study was to compare Creon 10 to placebo in the control of steatorrhea after a 2 week washout phase, which was measured using the mean change in CFA from baseline. Secondary objectives were the evaluation of stool parameters and global improvement of symptoms scales. Patients in the Creon 10 group had a higher mean change in CFA compared to placebo (36.7% vs. 12.1% respectively, p=0.0185). Patients in the Creon 10 group had improved stool consistency (p=0.0102) and decreased stool frequency (p=0.0015). The daily fat excretion decreased significantly more in the Creon 10 patients versus placebo (-56.6 g/d vs. -11.4 g/d, p=0.0181). Global disease symptom scores were evaluated by both physicians and patients. Physicians perceived a greater global disease symptom scores in the Creon 10 group versus placebo (p=0.0425) but this was not statistically significant for subject scores (p=0.0634). This study was discontinued early due to slow recruitment.[2]

A double-blind, randomized, placebo-controlled, two-arm, parallel-group trial (n=54) evaluated the efficacy of delayed-release pancrelipase capsules in patients ≥ 18 years old with EPI due to CP or pancreatic surgery (PS). A single-blind placebo run-in period preceded randomization; baseline measurements were recorded at this time. After the placebo run-in, patients were discharged to home for up to 16 days where they could use any pancreatic enzyme replacement regimen. Eligible patients were then randomized to double-blind treatment with either pancrelipase or placebo for 7 days, taken orally with meals. Dieticians worked with study subjects to ensure consumption of ≥80 g of fat each day. The primary outcome was the change in CFA from baseline to the end of the double-blind treatment period. Two patients did not complete the trial and were excluded from analysis. The mean change from baseline in CFA was 32.1% ± 18.5 for patients treated with pancrelipase, compared to 8.8%±12.5 for patients in the placebo group (p<0.0001). Patients in the pancrelipase group also experienced a greater change in CNA from baseline [97.7±82.3 for the pancrelipase group vs. 24.4±101 for the placebo group (p=0.0013)]. There were few treatment emergent adverse events (TEAEs) recorded for both groups. Five (20%) patients in the pancrelipase group and 6 (20.7%) patients in the placebo group reported at least one TEAE, consisting mainly of GI events (abnormal feces, flatulence, abdominal pain/discomfort). There were no discontinuations due to adverse events or deaths reported during this study.[3]

A double, blind, randomized, placebo-controlled, two-period crossover study (n=32) of Creon 24 versus placebo was conducted in patients with CF and EPI. The primary outcome was the CFA and secondary outcomes were coefficient of nitrogen absorption (CNA), symptoms, and safety. Prior to study initiation, patients

were given an individualized diet by a dietitian that contained at least 100 g/day of fat and included 40% of total calories from fat. Subjects were then randomized 1:1 to one of two crossover treatment sequences: Creon then placebo or placebo then Creon. The Creon 24 capsules were dosed to achieve 4,000 lipase units/g fat. The CFA [least squares (LS) mean] was 88.6% in the Creon group compared to 49.6% in the placebo group ($p<0.001$). Similar results were observed for LS mean of the CNA, with 85.1% in the Creon group compared to 49.9% in the placebo group ($p<0.001$). The LS mean for stool fat, stool nitrogen, and stool weight were all found to favor the Creon group versus placebo ($p<0.001$ for all). There were fewer adverse effects in the Creon group. Adverse effects seen in both the Creon and placebo groups were flatulence, abdominal pain, weight loss, and headache. The only adverse effects seen in Creon subjects and not the placebo group were dizziness and cough.[4]

A double-blind, placebo-controlled study evaluated the efficacy and tolerability of pancrelipase delayed-release 12,000-lipase unit capsules in patients aged 7 to 11 years old with EPI due to CF. This study was a 2-period cross-over trial that was designed to evaluate the difference in the mean change from baseline in CFA compared to placebo (n=17). Each patient received an individualized, prospectively designed diet containing ≥40% of calories derived from fat. Patients eligible for the study received pancreatic enzyme replacement therapy (PERT) for 2 weeks, and then were randomized to treatment or placebo for another two weeks and a baseline measurement was taken. Patients received placebo or treatment for 5 days before crossing-over to the alternative treatment. After a washout period of 14 days, in which patients received their usual PERT, patients entered a second crossover period in which procedures were identical to the first cross-over period. The primary efficacy outcome, overall CFA, was measured on the 2nd and 5th day of each cross-over period. Results show that patients who were treated with this formulation of pancrelipase had significantly increased CFA compared to those treated with placebo [treatment difference=35.4% ($p<0.001$)]. Absorption of nitrogen, measured as a secondary endpoint, was also statistically greater in patients receiving pancrelipase compared to placebo [treatment difference = 35.3% ($p<0.001$)]. TEAEs were reported in 5 patients (29.4%) during pancrelipase treatment and in 9 patients (56.3%) during receipt of placebo. Gastrointestinal adverse events were more prevalent during the receipt of placebo [4 patients (25%)] and there were no TEAEs considered to be related to pancrelipase treatment. No serious TEAEs or discontinuations were reported in this study.[5]

A double-blind, randomized, placebo-controlled, withdrawal study investigated the efficacy and safety of Pancreaze in CF patients aged 7 to 60 with established EPI. The study started with a 7-day screening phase, followed by ≤ 14-day open-label run-in phase, and was followed by a 4-7 day placebo-controlled, double-blind, withdrawal phase. During the screening phase and after laboratory assessments, patients stopped taking their current pancreatic enzyme regimen, and started on a high fat diet (100 ± 15g fat/day or 3 g/kg/day), and Pancreaze was administered based on lipase requirement during the previous 3 days. Forty-eight participants were initially enrolled. Only patients with a CFA>80% (n=40) continued the study and were randomized to continue Pancreaze (n=20) or switch to placebo (n=20). The primary efficacy endpoint was change in percent CFA between 72-hour stool collections at the end of open-label phase and double-blind phase, which favored the Pancreaze group (-1.5%± 5.9) compared to placebo (-34.1%± 23; $p<0.001$). Results were similar between adults and pediatric patients. Similar results were found for protein absorption. TEAs were similar between placebo and Pancreaze. The most common adverse events were abdominal pain and bloating.[6]

Safety/tolerability:

In general, common adverse effects to pancreatic enzymes include nausea, vomiting, bloating, cramping and constipation or diarrhea. Hyperuricosuria and hyperuricemia have been associated with higher doses. Caution should be used in patients with gout, hyperuricemia, or renal impairment.[7-13] Case reports of

colonic strictures have been reported with high-strength preparations (lipase content over 20,000 units per tablet/capsule). Caution is recommended when doses exceed 2500 units/kg/meal or 10,000 units/kg/day.[1]

Creon- The most common adverse effects were hyperglycemia (8%), hypoglycemia (4%), abdominal pain (4%), abnormal feces (4%), flatulence (4%), frequent bowl movements (4%), and nasopharyngitis (4%) which were slightly more common than placebo.[7]

Zenpep- The most common adverse effects were abdominal pain (18%), flatulence (6%), headache (15%), contusion (6%), weight decreased (6%), cough (6%), and early satiety (6%), which were slightly more common than placebo.[8]

Viokace- The most common adverse effects were anemia (3%), anal pruritus (7%), abdominal pain (3%), ascites (3%), flatulence (3%), edema peripheral (3%), biliary tract stones (7%), hydrocholecystis (3%), viral infection (3%), headache (3%), renal cyst (3%), and rash (3%), which did not occur in the placebo group.[9]

Ultresa- The most common adverse effects were headache (7%), pharyngolaryngeal pain (7%), and epistaxis (7%) which were slightly more common than placebo.[10]

Pancrelipase – The most common adverse effects were abdominal pain (18%), flatulence (6%), headache (15%), contusion (6%), decreased weight (6%), which were all less common than placebo.[11]

Pertzye- The most common adverse effects were diarrhea (10%), dyspepsia (10%), and cough (10%), which were slightly more common than placebo.[12]

Pancreaze – The most common adverse effects were abdominal pain (10%) and flatulence (5%), which were all less common than placebo.[13]

High quality Systematic Reviews:

No meta-analyses or high quality systemic reviews have been performed on pancreatic enzyme products.

Pharmacology:[7-13]
Pancreatic enzyme products contain amylase, lipase, and protease, which act as replacements for digestive enzymes secreted by the pancreas. These enzymes are beneficial in patients with inadequate pancreatic secretions (e.g. cystic fibrosis) who require assistance in the digestion of proteins, starches, and fats in the duodenum and proximal small intestines.

Pharmacokinetics:[7-13]
Pancreatic enzyme products are not interchangeable due to the differences in their contents and release mechanisms. None of the pancreatic enzyme products are absorbed from the gastrointestinal tract in appreciable amounts, but exert their action locally in the GI tract. Pancreatic enzymes are excreted in the feces.

Author: Brandy Fouts, Pharm.D.

Pancrelipase, Pancreaze, Creon, Ultresa, Pertzye, Zenpep - Enteric-coated to minimize destruction or inactivation in gastric acid. The capsule is designed to release most enzymes at a pH greater than 5.5.

Contraindications/warnings:[7-13]

- Fibrosing colonopathy is associated with high-dose use of pancreatic enzyme replacement. Exercise caution when doses of pancreatic enzymes exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).
- Use in caution in patients with gout due to the potential increase in uric acid levels. Consider monitoring uric acid levels in patients with hyperuricemia, gout, or renal impairment.
- There is theoretical risk of viral transmission with all pancreatic enzyme products.
- Exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.
- Due not chew pancreatic enzyme capsules do avoid irritation of oral mucosa.

Author: Brandy Fouts, Pharm.D.

References

1. Giuliano, CA, ML Dohoorne-Smith, PB Kale-Pradhan. Pancreatic enzyme products: digesting the changes. Ann Pharmacother 2011;45:658-66.
2. Safdi M, PK Bekal, S Martin, ZA Saeed, F Burton, PP Toskes. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006;33:156-62.
3. Whitcomb DC, GA Lehman, G Vasileva, et al. Pancrelipase delayed-release capsules (Creon) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. Am J Gastroenterol 2010;105:2276-86.
4. Trapnell BC, K Maguiness, GR Graff, D Boyd, K Beckmann, S Caras. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370-7.
5. Graff GR, K Maguiness, J McNamara, R Morton, D Boyd, K Beckmann, D Bennett. Efficacy and tolerability of new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010;32(1):89-103.
6. Trapnell BC, SD Stausbaugh, MS Woo, et al. Efficacy and safety of Pancreaze for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2011;10:350-6.
7. Creon prescribing information. Abbott Laboratories. 5/2011.
8. Zenpep prescribing information. Eurand Pharmaceuticals, Inc. 7/2011.
9. Viokace prescribing information. Aptalis Pharma US, Inc. 3/2012.
10. Ultresa prescribing information. Aptalis Pharma US, Inc. 3/2012.
11. Pancrelipase prescribing information. Eurand Pharmaceuticals, Inc. 4/2010.
12. Pertzye prescribing information. Digestive Care Inc. 5/2012.
13. PANCREAZE prescribing information. Janssen Pharmaceuticals Inc. 9/2011.
14. Center for Drug Evaluation and Research. FDA Summary Review: Application 20-725. Accessed 5/15/2012 at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Author: Brandy Fouts, Pharm.D.

Appendix A:

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
2. Safdi et a 2006 DB, RCT, PC N =27	1. Creon 10: 4 capsules with meals and 2 capsules with snacks. 2. Placebo	Adults >18 years old with chronic pancreatitis and a 12-month history of pancreatic exocrine insufficiency (EPI)	2 week washout followed by a 14 day trial	<u>Mean Δ in coefficient of fat absorption (CFA) from run-in to double –blind phase:</u> Creon 10: 36.7% 95% CI (17.6-55.8) Placebo: 12.1% 95% CI (1.3, 22.9) (p=0.0185) <u>Stool frequency (# of stools)</u> Creon 10: 10.8 to 5.2 Placebo: 14.0 to 14.6 P=0.0015 <u>Daily mean fat excretion in stool (g/day)</u> Creon 10: -56.6 (95% CI -94.8,-18.2) Placebo: -11.4 (95% CI -26.7,3.9) p= 0.0181	N/A	<u>Number of subjects with at least 1 adverse event:</u> Creon 10: 3 (23%) Placebo: 5 (36%) p-value: not reported	N/A	Quality rating: Poor Study was stopped early due to slow recruitment Patients had high fat diets of at least 100g fat/day Most common side effects in patients using Creon were asthenia, cholestatic jaundice, nausea, myalgia, and tremor. The most common side effects in patients using placebo were abdominal pain, neck pain, back pain, anorexia, rectal disorder, pathological fracture, bronchitis, skin disorder, and nephrosclerosis.

3. Whitcomb 2011 MC, RCT, PC, DB n=54	• Pancrelipase: 72,000 lipase units per main meal, 36,000 lipase units per snack x 7 days with meals •Placebo x 7 days with meals	• Patients ≥ 18 years old with confirmed CP or total or partial pancreatect-omy >180 days before enrollment, and severe EPI. Severe EPI was identified by fecal fat ≥40g/day and/or CFA <80%).		<u>Mean Δ in CFA from baseline:</u> Pancrealipase: 32.1%±18.5 Placebo: 8.8%±12.5 p<0.0001 <u>Mean Δ in CNA from baseline:</u> Pancrealipase: 97.7%±82.3 Placebo: 24.4%±101 p<0.0013	N/A	<u>TEAEs:</u> Pancrelipase: 5 (20%) Placebo: 6 (20.7%) p-value: not reported	N/A	Quality rating: Fair The pancrelipase group contained a greater proportion of PS patients (36%) compared to the placebo group (17.2%). The dose of PERT that patients were using at baseline was not standard, thus some patients may have been undertreated prior to randomization. Fat content of diets may have also changed during the measurement period. Patients enrolled in this study will be entered into an open-label extension trial.
4. Trapnell 2009 DB, RCT, PC N=32	1. Creon 24,000/placebo x 5 days each 2. Placebo /Creon 24,000 x 5 days each Creon was dosed to achieve a dose of 4000 lipase units/g fat	Patients with cystic fibrosis <u>≥</u>12 years with exocrine pancreatic insufficiency.	Two 5 day sequences	<u>Least squares CFA</u> Creon: 88.6% (2.3) Placebo: 49.6% (2.3) P<0.001 <u>Least squares mean coefficient of nitrogen absorption (CNA):</u> Creon: 85.1% (1.9) Placebo: 49.9% (1.9) P<0.001	N/A	<u>Any adverse effect:</u> Creon: 14 (44%) Placebo: 20 (65%) p-value: not reported <u>Discontinue due to adverse effects</u>: Creon: 1 (3.1%) Placebo: 0 (0%) p-value: not reported	N/A	Quality rating: Fair Patients had to have been on a stable pancreatic enzyme regimen for <u>≥</u> 3 months Only 31 patients finished the entire study

5. Graff et al. 2010 MC, RCT, PC, DB, XO n=17	1. Pancrelipase x 5 days then placebo x 5 days, 2 week washout, then repeat. 2. Placebo x 5 days and then pancrelipase x 5 days, 2 week washout, then repeat. Pancrelipase 12,000 unit lipase caps were used. Target dose: lipase units/g of dietary fat intake x 5 days and then placebo.	Patients 7-11 years with CF and EPI. EPI = CFA<70% without supplementation or as human fecal elastase <50mcg/g stool in the past 12 months. Patients must have been at a stable dose of pancreatic enzyme replacement therapy for > 3 months and clinically stable (bodyweight, respiratory disease).	Two 5 day phases separated by a two week washout.	<u>Mean CFA</u>: Pancrelipase: 82.8% (77, 88.6) Placebo: 47.4% (41.6, 53.2) Difference: 35.4% (27.2, 43.6), p<0.001 <u>Mean CNA:</u> Pancrelipase: 80.3% (73.5, 87.2) Placebo: 45% (38.2, 51.8) Difference: 35.3% (25.7, 45) p<0.001	N/A	<u>TEAEs:</u> Pancrelipase: 5 (29.4%) Placebo: 9 (56.3%) p-value: not reported	N/A	Quality rating: Fair There were some discrepancies in the balance of patient characteristics between treatment groups. The treatment/placebo group was 55.6% male, and the placebo/treatment group was 87.5% male. Four patients in the treatment/placebo group were using acid-suppressing drugs compared to 0 in the alternative group. The treatment benefit observed in this trial was similar in magnitude to other clinical trials that included the same endpoint.

6. Trapnell 2011 RCT, MC, PC, DB N=40	• Pancreaze 10.5 and 31 capsules • Placebo	• Patients aged 7-60 years old with confirmed CF and CF-related exocrine pancreatic insufficiency	7 day screening phase, followed by an open label ≤14 day run-in phase, followed by a double-blind phase ranging from 4-7 days	Mean CFA (SD): Pancreaze: 86.8% (8.09) Change from baseline: -1.5 (5.9) Placebo: 56.4% (24.9) Change from baseline: -34.1 (23) p<0.001 Mean CNA (SD): Pancreaze: 82.4% (6.0) Change from baseline: 1.3 (4.7) Placebo: 57.9% (19.7) Change from baseline: -26.5 (15.3) p<0.001	N/A	Adverse effects, n (%): Any Placebo: 11 (55) Pancreaze: 4 (20) Pancreaze: 3 abdominal pain, 1 bloating, 1 vomiting Placebo: 6 abdominal pain, 3 bloating, 4 diarrhea, 3 greasy stools, 0 vomiting No serious adverse effects	N/A	Quality rating: Fair Patients were on a stable pancreatic enzyme regimen for ≥1 month prior to study. Included adult and pediatric patients.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction,
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, CGIDS = clinical global impression of disease symptoms scale , CFA coefficient of fat absorption, coefficient of nitrogen absorptio
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

.

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

Oregon Health Authority

Hormone Replacement Therapies

Month/Year of Review: November, 2012
PDL Class: Hormone Replacement Therapy (HRT)
End date of literature search: August, 2012

Date of Last Review: April 2008
Source Document: HRC Report

Current Preferred Agents	Current Non-Preferred Agents
Oral HRT - Estrogen	
Estradiol	Conjugated Estrogens, Synthetic B (Enjuvia®)
Conjugated Estrogens, Synthetic A (Cenestin®)	Esterified Estrogens/methyltestosterone
Estropipate	Esterified estrogens (Menest®)
Norethindrone acetate/Ethinyl Estradiol (Femhrt®)	Estradiol/norethindrone (Activella®)
	Drospirenone/estradiol (Angeliq®)
	Norethindrone acetate/ethinyl estradiol (Jinteli®)
	Estradiol/norethindrone acetate (Mimvey®)
	Estradiol/norgestimate (Prefest®)
	Conjugated estrogens/Medroxyprogesterone (Prempro®, Premphase®)
Topical HRT - Estrogen	
Estradiol patch	Estradiol gel packet (Divigel®)
Estradiol (Alora®) patch	Estradiol gel pump (Elestrin®)
Estradiol (Climara®)	Estradiol patch (Estraderm®)
	Estradiol patch (Estrasorb®)
	Estradiol gel pump (EstroGel®)
	Estradiol spray (Evamist®)
	Estradiol patch (Vivelle-dot®)
	Estradiol/norethindrone acetate patch (Combipatch®)
	Estradiol/levonorgestrel patch (Climara Pro®)
Vaginal HRT - Estrogen	
Estradiol (Estring®) vaginal ring	Estradiol vaginal cream (Estrace®)
Estradiol (Vagifem®) tablet	Estradiol vaginal ring (femring®)
Conjugated Estrogen (Premarin®) cream	

Previous Conclusions:[1]

- Estrogens reduce some menopausal symptoms and have been shown to improve bone density and reduce fracture risk.
- Decreasing doses of conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA) resulted in decreasing preservation of bone density however it is unclear if lower doses of estrogen will sufficiently preserve bone density in a manner to affect outcomes.
- The majority of studies are of estradiol and CEE. For many estrogen preparations, clinical trials are few and evidence is insufficient to conclude they are equal to estrogens that have been studied more extensively.
- For the comparison of the estradiol ring to CEE vaginal cream there was more improvement in pruritus with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets
- CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation).
- There are conflicting results for Breast cancer rates and cardiovascular events.
- At the present time there is no comparative evidence to evaluate estrogen use in subgroup populations of race or ethnicity.
- An increased incidence of probable dementia among participants taking CEE (+/- MPA) starting after 4 years, was positively related to increasing age and lower Mini Mental State exam scores at baseline.

Issues:

- Is there any new comparative evidence of different hormone therapy preparations for reducing symptoms of menopause, preventing low bone density and fractures?
- Is there any new comparative safety evidence of different therapy preparations?
- Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Conclusions:

- Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence.
- Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.
- There are insufficient data to assess the risk of long term hormone therapy use in perimenopausal women or postmenopausal women younger than 50 years of age.
- Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestin to reduce the risk of endometrial hyperplasia.
- There were no consistent differences by age and comorbidities in subgroup analyses.
- Despite of lacking randomized clinical trials evidence for potential favorable thromboembolic risks using transdermal formulation of hormone therapy, several national guidelines recommended transdermal route of administration over oral route.

Recommendation:

- Evaluate price comparisons of individual agents for topical HRT and consider including a topical estrogen plus progestin product.

Methods:

A MEDLINE Ovid search was conducted using hormone replacement therapy (HRT), menopause, estradiol and estrogen. The search was limited to meta-analysis, English language, and to studies conducted in humans since last HRT review. 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 AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Treatment Guidelines

American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause[2] key recommendations (2011 Task force revisions):

- Menopausal hormone therapy (MHT) may be appropriate for the relief of severe menopausal symptoms in selected postmenopausal women, on the basis of an individually determine benefit-versus-risk profile. (Grade A)
- MHT may be prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atropy. (Grade A)
- The use of transdermal route of estrogen administration should be considered in order to avoid the hepatic "first-pass effect," which may theoretically reduce the risk of thromboembolic disease. (Grade B)
- The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption. (Grade B)
- Progestatonal agents should be used for minimum 10 to 14 days per month in women treated with estrogen who have an intact uterus. (Grade A)
- MHT should be used in the lowest dose and for the shortest period necessary to control menopausal symptoms. (Grade A)
- MHT should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-versus-risk analysis of each patient. (Grade A)
- MHT should be prescribed to women in conjunction with a thorough discussion of the possible relationship of MHT to breast cancer. Current evidence suggests that estrogen + progesterone regimens are associated with a possible higher risk of breast cancer than is therapy with estrogen alone. (Grade A)
- Women should be advised that smoking increases the risk of cardiovascular and venous thromboembolic disease when taking estrogen, and aggressive smoking cessation programs should be advised. (Grade A)
- Women should be advised that cerebrovascular accidents occur with increased frequency in patients taking estrogen alone or estrogen +progesterone combination therapies in an age-dependent manner (Grade A)
- Women should be advised that there may be an increase in ovarian epithelial tumors with the use of estrogen for more than 10 years. (Grade B)

- Women may be advised that several studies including the Women's Health Initiative (WHI) have demonstrated a lower risk of colon cancer in women treated with estrogen + progesterone combination. (Grade B)

The 2012 Hormone Therapy Position Statement of the North American Menopause Society (NAMS)[3]

The position statement updated the 2010 evidence-based statement published by the NAMS regarding recommendations for hormone therapy (HT) for postmenopausal women. The 2012 updated statement concluded that recent data support the initiation of HT around the time of menopause to treat menopause -related symptoms and to prevent osteoporosis in women at high risk of fracture. The more favorable benefit-risk ratio for estrogen (ET) allows more flexibility in extending the duration of use compared with combined estrogen-progestogen therapy (EPT), where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years. (See Appendix A for key recommendations)

Venous thromboembolism (VTE) and Hormone Replacement Therapy by NICE[4] **(May 2011)**

This is the 3rd edition of this guideline on VTE risk associated with HRT and treatment recommendations on duration, types of HRT, and preparations of different HRT. (See Appendix A for Key conclusions and recommendations)

Menopause and Osteoporosis Update 2009 by the Society of obstetricians and Gynaecologists of Canada[5] **(SOGC)**

The guidelines provided the updated recommendations on the management of menopause in asymptomatic healthy women as well as in women presenting with vasomotor symptoms or with urogenital, mood, or memory concerns, and on considerations related to cardiovascular disease, breast cancer and bone health, including the diagnosis and clinical management of postmenopausal osteoporosis. Lifestyle interventions, prescription medications, and complementary and alternative therapies are presented according to their efficacy in the treatment of menopausal symptoms. See Appendix A for key HRT related recommendations.

New Systematic Reviews (See Appendix B for Review Abstracts)

Nelson el al.[6] published a systematic review in July 2012 to update the evidence about the effectiveness of hormone therapy in reducing risk of chronic conditions and adverse effects, and to examine whether outcomes vary among women in different subgroups. Randomised placebo-controlled trials of postmenopausal therapy versus placebo for prevention of chronic conditions for postmenopausal women were eligible for inclusion. Women with known thrombotic disorders, hormone sensitive cancer or coronary heart disease were excluded. The review was concerned with primary prevention of new conditions rather than effects on pre-existing conditions. Outcomes of interest were coronary heart disease, stroke, deep vein thrombosis, pulmonary embolism, cancer (breast, colon, lung, endometrium or ovaries), fracture at various sites, cognition and dementia, disease-specific and all-cause mortality and any new findings reported by the trials. Intervention drugs included conjugated equine estrogen with or without medroxyprogesterone acetate, estradiol valerate, 17-beta estradiol plus norethindrone and unopposed transdermal estradiol. The main analysis was based on participants aged 60 to 69. Nine randomized placebo controlled trials were included in the review. The longest follow-up was 11 years (Women's Health Initiative trials). All trials were rated of fair quality. The most common problems across the trials were high attrition and low adherence. The results of review show estrogen plus progestin reduced fractures (HR 0.76, 95% CI 0.69 to 0.83) but increased invasive breast cancer (HR 1.25, 95% CI 1.07 to 1.46), stroke (HR 1.34, 95% CI 1.05 to 1.71),

deep venous thrombosis (HR 1.88, 95% CI 1.38 to 2.55), pulmonary embolism (HR 1.98, 95% CI 1.36 to 2.87), lung cancer death (HR 1.71, 95% CI 1.16 to 2.52), gallbladder disease (HR 1.61, 95% CI 1.30 to 2.00), probable dementia (HR 2.05, 95% CI 1.21 to 3.48) and urinary incontinence (HR 1.39, 95% CI 1.27 to 1.52). There were no statistically significant reductions in colorectal cancer, lung cancer, endometrial, ovarian and cervical cancers, coronary heart disease, pulmonary embolism, all-cause mortality, probable dementia and mild cognitive impairment. Estrogen-only therapy reduced fractures (HR 0.70, 95% CI 0.63 to 0.79), invasive breast cancer incidence (HR 0.77, 95% CI 0.62 to 0.95) and breast cancer death (HR 0.37, 95% CI 0.13 to 0.91) but increased stroke (HR 1.36, 95% CI 1.08 to 1.71), deep venous thrombosis (HR 1.47, 95% CI 1.06 to 2.05), gallbladder disease (HR 1.79, 95% CI 1.44 to 2.22) and urinary incontinence (HR 1.53, 95% CI 1.37 to 1.71). There were no statistically significant reductions in diabetes, colorectal cancer, lung cancer, coronary heart disease, pulmonary embolism, all-cause mortality, probable dementia and mild cognitive impairment. Among the subgroup analyses, there were no consistent differences by age and comorbidities. Other subgroup analyses were not performed due to lack of data.

The review addressed a clear question and was supported by appropriate inclusion criteria. Several relevant data sources were searched. The review was restricted to studies in English (the authors reported that they did not identify any relevant trials from journals in other languages). Study quality was assessed. The authors appropriately highlighted weaknesses in the evidence such as high drop-out rates and differential adherence rates. Two reviewers were involved in study selection, data extraction and quality assessment, which minimized potential for error and bias. The restriction of results to those of the Women's Health Initiative trials appeared justified. The conclusions were based on the evidence presented and appear reliable.

Another recent systematic review by **Marjoribanks et al**[7] assessed the effects of long term HT on mortality cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition and quality of life in perimenopausal and postmenopausal women, both during HT use and after cessation of HT use. Twenty-three studies involving 42,830 women were included. Seventy per cent of the data were derived from two studies (WHI 1998 and Heart and Estrogen/progestin Replacement Study (HERS) 1998 Research Group). Most participants were postmenopausal women with at least some degree of co-morbidity, and the mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (that is generally fit, without overt disease) combined continuous HT significantly increased the risk of a coronary event (after one year's use: AR 4 per 1000, 95% CI 3 to 7), venous thromboembolism (after one year's use: Absolute risk (AR) 7 per 1000, 95% CI 4 to 11), stroke (after three years' use: AR 18 per 1000, 95% CI 14 to 23), breast cancer (after 5.6 years' use: AR 23 per 1000, 95% CI 19 to 29), gallbladder disease (after 5.6 years' use: AR 27 per 1000, 95% CI 21 to 34) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: AR 9 per 1000, 95% CI 6 to 13). Estrogen-only HT significantly increased the risk of venous thromboembolism (after one to two years' use: AR 5 per 1000, 95% CI 2 to 10; after 7 years' use: AR 21 per 1000, 95% CI 16 to 28), stroke (after 7 years' use: AR 32 per 1000, 95% CI 25 to 40) and gallbladder disease (after seven years' use: AR 45 per 1000, 95% CI 36 to 57) but did not significantly increase the risk of breast cancer. Among women aged over 65 years who were relatively healthy and taking continuous combined HT, there was a statistically significant increase in the incidence of dementia (after 4 years' use: AR 18 per 1000, 95% CI 11 to 30). Among women with cardiovascular disease, long term use of combined continuous HT significantly increased the risk of venous thromboembolism (at one year: AR 9 per 1000, 95% CI 3 to 29). Women taking HT had a significantly decreased incidence of fractures with long term use (after 5.6 years of combined HT: AR 86 per 1000, 95% CI 79 to 84; after 7.1 years' use of estrogen-only HT: AR 102 per 1000, 95% CI 91 to 112). Risk of fracture was the only outcome for

which there was strong evidence of clinical benefit from HT. There was no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analyzed subgroups of 2839 relatively healthy 50 to 59 year old women taking combined continuous HT and 1637 taking estrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded as this study was not designed to have the power to detect differences between groups of women within 10 years of the menopause. The authors concluded HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable. There are insufficient data to assess the risk of long term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.

Lin et al[8] conducted a meta-analysis to summarize the relative risks (RR) of colorectal cancer CRC due to estrogen (ET) versus combined estrogen-progestogen therapy (EPT) among peri- or postmenopausal women. From a total of 2,661 articles, four randomized controlled trials, eight cohort and eight case-control studies were included. Variables assessed included study characteristics, duration and recency of menopausal hormone therapy (HT) use, method of assessment of HT use, outcome definition and its ascertainment method. RRs were synthesized by random-effects models. The authors found that EPT ever use was associated with a decreased risk of CRC (RR 0.74, 95% CI 0.68-0.81), and so was ET ever use (RR 0.79, 95% CI 0.69-0.91). While current use of ET was associated with a significantly reduced risk of CRC (RR 0.70, 95% CI 0.57-0.85), former use was not (RR 0.86, 95%CI 0.67-1.11). Recency did not significantly modify the association between EPT and CRC risk. EPT former use was associated with a lower RR of CRC compared to ET former use (p = 0.008) but no such difference was observed between EPT and ET current use (p = 0.12). Overall, authors found consistent evidence supporting the association between EPT and CRC risk reduction, regardless of recency. While literature for the association between ET and CRC risk is heterogeneous, authors' analyses suggest only current use of ET is associated with a decreased CRC risk.

Furness et al[9] conducted a systematic review to assess which hormone therapy regimens provide effective protection against the development of endometrial hyperplasia or carcinoma. The main results of the review indicated that unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low-dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate (NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at two years (1 mg NETA: OR 0.04; 95% confidence interval (CI) 0 to 2.8; 1.5 mg MPA: no hyperplasia events). The authors concluded hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometrial hyperplasia.

References:

1.HRC-2008-04-HRT Update.pdf. Available at: http://cms.oregon.gov/oha/pharmacy/therapeutics/docs/hrc-2008-01-hrt.pdf. Accessed August 28, 2012.

2. National Guideline ClearingHouse. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Available at: http://www.guideline.gov/content.aspx?id=35238&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

3. National Guideline ClearingHouse. The 2012 hormone therapy position statement of The North American Menopause Society. Available at: http://www.guideline.gov/content.aspx?id=36195&search=hormone+replacement+therapy#Section432. Accessed August 29, 2012.

4. National Guideline ClearingHouse. Venous thromboembolism and hormone replacement therapy. Available at: http://www.guideline.gov/content.aspx?id=34965&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

5. National Guideline ClearingHouse. Hormone therapy and breast cancer. In: Menopause and osteoporosis update 2009. Available at: http://www.guideline.gov/content.aspx?id=13611&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

6. Nelson HD, Walker M, Zakher B, Mitchell J. Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventive Services Tas Force Recommendations. *Ann Intern Med*. 2012;157(2):104–113.

7. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. In: *Cochrane Database of Systematic Reviews 2012*. Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004143.pub4/abstract. Accessed August 28, 2012.

8. Lin KJ, Cheung WY, Lai JY-C, Giovannucci EL. The effect of estrogen vs. combined estrogen-progestogen therapy on the risk of colorectal cancer. *International Journal of Cancer*. 2012;130(2):419–430.

9. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. In: *Cochrane Database of Systematic Reviews 2012*. Issue 8. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub4. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000402.pub4/abstract. Accessed August 28, 2012.

10. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian Meta-analysis of Hormone Therapy and Mortality in Younger Postmenopausal Women. *The American Journal of Medicine*. 2009;122(11):1016–1022.e1.

Appendix A

The 2012 Hormone Therapy Position Statement of the North American Menopause Society (NAMS) Conclusions and Recommendations:

- Individualization is of key importance in the decision to use HT and should incorporate the woman's health and quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer.
- The recommendation for duration of therapy differs for EPT and ET. For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3 to 5 years of use; for ET, a more favorable benefit-risk profile was observed during a mean of 7 years of use and 4 years of follow-up, a finding that allows more flexibility in duration of use.
- ET is the most effective treatment of symptoms of vulvar and vaginal atrophy; low-dose, local vaginal ET is advised when only vaginal symptoms are present.
- Women with premature or early menopause who are otherwise appropriate candidates for HT can use HT at least until the median age of natural menopause (age 51 y). Longer duration of treatment can be considered if needed for symptom management.
- Although ET did not increase breast cancer risk in the WHI, there is a lack of safety data supporting the use of ET in breast cancer survivors, and one RCT reported a higher increase in breast cancer recurrence rates.
- Both transdermal and low-dose oral estrogen have been associated with lower risks of VTE and stroke than standard doses of oral estrogen, but RCT evidence is not yet available.

Venous thromboembolism (VTE) and Hormone Replacement Therapy key Conclusions and Recommendations by NICE

- All women commencing HRT should be counseled about the risk of VTE and the signs and symptoms of VTE. All women should be advised to access medical help rapidly if they suspect that they have developed a thrombosis. (Evidence level 1+)
- Women starting or continuing HRT should be counseled with regard to the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies. (Evidence level 1+)
- The risk of VTE may be less with esterfied estrogens compared with conjugated equine estrogen. (Evidence level 2+)
- There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk. (Evidence level 2++)
- There is some evidence that the effect of estrogen therapy may be dose related. Transdermal preparations are associated with a substantially lower risk of VTE than oral preparations. (Evidence level 2+)
- The risk of VTE is highest in the first year of HRT use, with no evidence of continuing risk on stopping HRT. (Evidence level 2++)
- A personal history of thrombosis is a contraindication to oral HRT. If it is considered that quality of life is so severely affected that the benefits of HRT outweigh the risks, a transdermal preparation should be used. (Evidence level 2+)

Menopause and Osteoporosis Update 2009 by the Society of obstetricians and Gynaecologists of Canada key HRT Related Recommendations

- Health care providers should offer HT (estrogen alone or EPT) as the most effective therapy for the medical management of menopausal symptoms. (Evidence level IA)
- Progestins alone or low-dose oral contraceptives can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition. (Evidence level IA)
- HT should be offered to women with premature ovarian failure or early menopause (IA), and it can be recommended until the age of natural menopause. (IIIC)
- Estrogen therapy can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)
- Health care providers should not initiate or continue HT for the sole purpose of preventing coronary artery disease and stroke. (IA)
- Health care providers should abstain from prescribing HT in women at high risk for VTE. (IA)
- Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)
- Health care providers should periodically review the risks and benefits of prescribing HT to a menopausal woman in light the association between duration of use and breast cancer risk. HT may be prescribed for menopausal symptoms in women at increased risk of breast cancer with appropriate counseling and surveillance. (IA)
- Conjugated estrogen cream, and intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vaginal atrophy. (IA)
- Routine progestin cotherapy is not required for endometrial protection in women receiving vaginal estrogen therapy in appropriate dose. (IIIC)
- Estrogen therapy should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence but may be recommended before corrective surgery. (IA)
- Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (IA)
- Usual-dosage HT should be prescribed for symptomatic postmenopausal women as the most effective therapy for menopausal symptom relief (1A) and a reasonable choice for the prevention of bone loss and fracture. (1A)
- Physicians may recommend low- and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (1A) but should inform their patients that despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention (1A), no data are yet available on reduction of fracture risk.
- Estrogen can be prescribed to enhance mood in women with depressive symptoms. The effect appears to be greater for perimenopausal symptomatic women than for postmenopausal women. (IA)
- Estrogen therapy is not currently recommended for reducing the risk of dementia developing in postmenopausal women or for retarding the progression of diagnosed Alzheimer's disease, although limited data suggest that early use of HT in the menopause may be associated with diminished risk of later dementia. (IB)

Appendix B

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendations

Heidi D. Nelson, MD, MPH; Miranda Walker, MA; Bernadette Zakher, MBBS; and Jennifer Mitchell, BA *Ann Intern Med*. 17 July 2012;157(2):104-113

Abstract

Background: Menopausal hormone therapy to prevent chronic conditions is currently not recommended because of its adverse effects.

Purpose: To update evidence about the effectiveness of hormone therapy in reducing risk for chronic conditions and adverse effects, and to examine whether outcomes vary among women in different subgroups.

Data Sources: MEDLINE (January 2002 to November 2011), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 3rd quarter of 2011), Scopus, and reference lists.

Study Selection: Randomized, placebo-controlled trials of menopausal hormone therapy published in English since 2002 that assessed primary prevention of chronic conditions.

Data Extraction: Investigators extracted data on participants, study design, analysis, follow-up, and results; 2 investigators independently rated study quality by using established criteria.

Data Synthesis: 9 fair-quality trials met the inclusion criteria. The Women's Health Initiative reported most of the results, had 11 years of follow-up, and had data most applicable to postmenopausal women in the United States. It showed that estrogen plus progestin therapy reduced fractures (46 fewer per 10 000 woman-years) and increased invasive breast cancer (8 more per 10 000 woman-years), stroke (9 more per 10 000 woman-years), deep venous thrombosis (12 more per 10 000 woman-years), pulmonary embolism (9 more per 10 000 woman-years), lung cancer death (5 more per 10 000 woman-years), gallbladder disease (20 more per 10 000 woman-years), dementia (22 more per 10 000 woman-years), and urinary incontinence (872 more per 10 000 woman-years). Estrogen-only therapy reduced fractures (56 fewer per 10 000 woman-years), invasive breast cancer (8 fewer per 10 000 woman-years), and death (2 fewer per 10 000 woman-years) and increased stroke (11 more per 10 000 woman-years), deep venous thrombosis (7 more per 10 000 woman-years), gallbladder disease (33 more per 10 000 woman-years), and urinary incontinence (1271 more per 10 000 woman-years). Outcomes did not consistently differ by age or comorbid conditions.

Limitation: Limitations of the trials included low adherence, high attrition, inadequate power to detect risks for some outcomes, and evaluation of few regimens.

Conclusion: Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.

Primary Funding Source: Agency for Healthcare Research and Quality.

Long term hormone therapy for perimenopausal and postmenopausal women

Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4.

Abstract

Background: Hormone therapy (HT) is widely used for controlling menopausal symptoms and has also been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005.

Objectives: To assess the effects of long term HT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition and quality of life in perimenopausal and postmenopausal women, both during HT use and after cessation of HT use.

Search methods: We searched the following databases to February 2012: Cochrane Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO.

Selection criteria: We included randomised double-blind studies of HT versus placebo, taken for at least one year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via oral, transdermal, subcutaneous or intranasal routes.

Data collection and analysis: Two authors independently assessed study quality and extracted data. We calculated risk ratios (RRS) for dichotomous data and mean differences (MDs) for continuous data, with 95% confidence intervals (CIs). Where findings were statistically significant, we calculated the absolute risk (AR) in the intervention group (the overall risk of an event in women taking HT).

Main results: Twenty-three studies involving 42,830 women were included. Seventy per cent of the data were derived from two studies (WHI 1998 and HERS 1998). Most participants were postmenopausal American women with at least some degree of co-morbidity, and the mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (that is generally fit, without overt disease) combined continuous HT significantly increased the risk of a coronary event (after one year's use: AR 4 per 1000, 95% CI 3 to 7), venous thrombo-embolism (after one year's use: AR 7 per 1000, 95% CI 4 to 11), stroke (after three years' use: AR 18 per 1000, 95% CI 14 to 23), breast cancer (after 5.6 years' use: AR 23 per 1000, 95% CI 19 to 29), gallbladder disease (after 5.6 years' use: AR 27 per 1000, 95% CI 21 to 34) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: AR 9 per 1000, 95% CI 6 to 13). Oestrogen-only HT significantly increased the risk of venous thrombo-embolism (after one to two years' use: AR 5 per 1000, 95% CI 2 to 10; after 7 years' use: AR 21 per 1000, 95% CI 16 to 28), stroke (after 7 years' use: AR 32 per 1000, 95% CI 25 to 40) and gallbladder disease (after seven years' use: AR 45 per 1000, 95% CI 36 to 57) but did not significantly increase the risk of breast cancer. Among women aged over 65 years who were relatively healthy and taking continuous combined HT, there was a statistically significant increase in the incidence of dementia (after 4 years' use: AR 18 per 1000, 95% CI 11 to 30). Among women with cardiovascular disease, long term use of combined continuous HT significantly increased the risk of venous thrombo-embolism (at one year: AR 9 per 1000, 95% CI 3 to 29). Women taking HT had a significantly decreased incidence of fractures with long term use (after 5.6 years of combined HT: AR 86 per 1000, 95% CI 79 to 84; after 7.1 years' use of oestrogen-only HT: AR 102 per

1000, 95% CI 91 to 112). Risk of fracture was the only outcome for which there was strong evidence of clinical benefit from HT. There was no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analyzed subgroups of 2839 relatively healthy 50 to 59 year old women taking combined continuous HT and 1637 taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thrombo-embolism in women taking combined continuous HT: their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded as this study was not designed to have the power to detect differences between groups of women within 10 years of the menopause.

Authors' conclusions: HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. There are insufficient data to assess the risk of long term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.

The effect of estrogen *vs.* combined estrogen-progestogen therapy on the risk of colorectal cancer

Lin, K. J., Cheung, W. Y., Lai, J. Y.-C. and Giovannucci, E. L. (2012). The effect of estrogen *vs.* combined estrogen-progestogen therapy on the risk of colorectal cancer. Int. J. Cancer, 130: 419–430. doi: 10.1002/ijc.26026

Abstract

Studies suggest that estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) may have different associations with colorectal cancer (CRC) risk, but data are conflicting. Prior meta-analyses did not distinguish between ET and EPT. We conducted a meta-analysis to summarize the relative risks (RR) of CRC due to ET versus EPT among peri- or postmenopausal women. From a total of 2,661 articles, four randomized controlled trials, eight cohort and eight case-control studies were included. Variables assessed included study characteristics, duration and recency of menopausal hormone therapy (HT) use, method of assessment of HT use, outcome definition and its ascertainment method. RRs were synthesized by random-effects models. We found that EPT ever use was associated with a decreased risk of CRC (RR 0.74, 95% CI 0.68-0.81), and so was ET ever use (RR 0.79, 95% CI 0.69-0.91). While current use of ET was associated with a significantly reduced risk of CRC (RR 0.70, 95% CI 0.57-0.85), former use was not (RR 0.86, 95%CI 0.67-1.11). Recency did not significantly modify the association between EPT and CRC risk. EPT former use was associated with a lower RR of CRC compared to ET former use (p = 0.008) but no such difference was observed between EPT and ET current use (p = 0.12). Overall, we found consistent evidence supporting the association between EPT and CRC risk reduction, regardless of recency. While literature for the association between ET and CRC risk is heterogeneous, our analyses suggest only current use of ET is associated with a decreased CRC risk.

Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub4.

Abstract

Background: Reduced circulating estrogen levels around the time of the menopause can induce unacceptable symptoms that affect the health and well-being of women. Hormone therapy (both unopposed estrogen and estrogen/progestogen combinations) is an effective treatment for these symptoms, but is associated with risk of harms.

Guidelines recommend that hormone therapy be given at the lowest effective dose and treatment should be reviewed regularly. The aim of this review is to identify the minimum dose(s) of progestogen required to be added to estrogen so that the rate of endometrial hyperplasia is not increased compared to placebo.

Objectives: The objective of this review is to assess which hormone therapy regimens provide effective protection against the development of endometrial hyperplasia or carcinoma.

Search methods: We searched the Cochrane Menstrual Disorders and Subfertility Group trials register (searched January 2012), The Cochrane Library (Issue 1, 2012), MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), Current Contents (1993 to May 2008), Biological Abstracts (1969 to 2008), Social Sciences Index (1980 to May 2008), PsycINFO (1972 to January 2012) and CINAHL (1982 to May 2008). Attempts were made to identify trials from citation lists of reviews and studies retrieved, and drug companies were contacted for unpublished data.

Selection criteria: Randomised comparisons of unopposed estrogen therapy, combined continuous estrogen-progestogen therapy, sequential estrogen-progestogen therapy with each other or placebo, administered over a minimum period of 12 months. Incidence of endometrial hyperplasia/carcinoma assessed by a biopsy at the end of treatment was a required outcome. Data on adherence to therapy, rates of additional interventions, and withdrawals owing to adverse events were also extracted.

Data collection and analysis: In this update, 46 studies were included. Odds ratios (ORs) were calculated for dichotomous outcomes. The small numbers of studies in each comparison and the clinical heterogeneity precluded meta-analysis for many outcomes.

Main results: Unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low-dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate (NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at two years (1 mg NETA: OR 0.04; 95% confidence interval (CI) 0 to 2.8; 1.5 mg MPA: no hyperplasia events).

Authors'conclusions: Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometria hyperplasia.

Bayesian Meta-analysis of Hormone Therapy and Mortality in Younger Postmenopausal Women

Shelley R. Salpeter, MD, Ji Cheng, MSc,c Lehana Thabane, PhD, Nicholas S. Buckley,Edwin E. Salpeter, PhD *The American Journal of Medicine* (2009) 122, 1016-1022

Abstract

Background: There is uncertainty over the risks and benefits of hormone therapy. We performed a Bayesian meta-analysis to evaluate the effect of hormone therapy on total mortality in younger postmenopausal women. This analysis synthesizes evidence from different sources, taking into account varying views on the issue.

Methods: A comprehensive search from 1966 through January 2008 identified randomized controlled trials of at least 6 month's duration that evaluated hormone therapy in women with mean age < 60 years and reported at least one death, and prospective observational cohort studies that evaluated the relative risk of mortality associated with hormone therapy after adjustment for confounding variables.

Results: The results were synthesized using a hierarchical random-effects Bayesian meta-analysis. The pooled results from 19 randomized trials, with 16,000 women (mean age 55 years) followed for 83,000 patient-years, showed a mortality relative risk of 0.73 (95% credible interval 0.52-0.96). When data from 8 observational studies were added to the analysis, the resultant relative risk was 0.72 (credible interval 0.62-0.82). The posterior probability that hormone therapy reduces total mortality in younger women is almost 1.

Conclusions: The synthesis of data using Bayesian meta-analysis indicates a reduction in mortality in younger postmenopausal women taking hormone therapy compared with no treatment. This finding should be interpreted taking into account the potential benefits and harms of hormone therapy.

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: November 2012
PDL Classes: Cephalopsorins and Related Antibiotics

Date of Last Review: September 2010
Source Document: Provider Synergies

Current Preferred Agents:	Current Non-Preferred Agents*:
1st Generation Cephalosporin Cephalexin Oral 2nd Generation Cephalosporin Cefprozil Oral Cefprozil (Cefzil®) susp Cefuroxime axetil Oral 3rd Generation Cephalosporin Cefdinir Oral Cefdinir (Omnicef®) Susp Cefpodoxime proxetil Oral Penicillin/Beta-Lactamase Inhibitor Combination Amoxicillin/Clavulanate (Augmentin®)susp Amoxicillin/Clavulanate Chewable Amoxicillin/Clavulanate Oral	1st Generation Cephalosporin Cephradine Cephadroxil (Duricef®) 2nd Generation Cephalosporin Cefaclor (Ceclor®) Loracarbef 3rd Generation Cephalosporin Cefixime (Suprax®) Cefditoren (Spectracef®) Ceftibuten (Cedax®) Penicillin/Beta-Lactamase Inhibitor Combination Amoxicillin/Clavulanate ER (Augmentin XR®)

Previous Recommendations:

1. There is no evidence to support a difference in efficacy or effectiveness.
2. Evidence does not support a difference in adverse effects or harm among each subclass.
3. Based on published studies, there is no evidence that one cephalosporin has a particular advantage or disadvantage over others among each subclass. At least one agent from each subclass (1st, 2nd, 3rd generation cephalosporins and amoxicillin/clavulanate) should be included as well as age appropriate dosage forms.
4. Consider prior authorization criteria to allow bridge therapy of these medications during hospitalization rather than changing medication on discharge.

PA Criteria/QL:
No prior authorization criteria required.

Methods:
A MEDLINE OVID search was conducted using all included drugs with either acute otitis media(AOM), community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), pharyngitis, tonsillitis, gonorrhea, urinary tract infection (UTI), Lyme disease, or impetigo and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. The Cochrane Collection, the Centre for Reviews and Dissemination, (DARE) and PubMed Health 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) and Infectious Diseases Society of America (IDSA) were searched for updated and recent evidence-based guidelines.

New Trials:
A total of eight citations resulted from the initial MEDLINE search and after review of titles and abstracts for inclusion, no relevant head-to-head clinical trials were identified. The trials were excluded due to lack of relevant outcomes and/or comparisons and IV route medication administration.

New drugs:
The FDA approved ceftaroline (Teflaro) in October of 2010 for the indications of acute bacterial skin and skin structure infections and community-acquired pneumonia. Ceftaroline is administered by IV infusion only and is covered through the medical benefit. [1–3]

New Formulations/Indications:
A new formulation of cefixime was FDA approved in June of 2012 as a 400mg capsule and is indicated for uncomplicated UTIs, pharyngitis, tonsillitis, AECB and uncomplicated gonorrhea. The 400 mg capsule is bioequivalent to the 400 mg tablet under fasting conditions. However, food reduces the absorption by 15% following administration of the capsule.[4] There has been no evidence of clinical benefit or advantage over currently available formulations.

New FDA safety alerts:
There have been no new drug safety alerts for oral cephalosporins or amoxicillin/clavulanate. There was a recent drug safety communication regarding IV cefepime due to cases of nonconvulsive status epilepticus associated with its use, primarily in patients with renal impairment who did not receive appropriate dosage adjustments of cefepime.[5]

New Systematic Reviews:
Two recent systematic reviews from the Cochrane Collection were published evaluating the efficacy and adverse events between cephalosporins, as well as cephalosporins to other classes of antibiotics.

Twenty-five studies (2488 participants) assessed the efficacy and possible adverse effects of interventions to treat non-surgically-acquired cellulitis.[6] Three of these trials compared IV cephalosporins with penicillin, 6 trials compared different cephalosporins, and one trial compared a macrolide against a first generation cephalosporin. The 6 trials that compared older cephalosporins to newer cephalosporins focused on symptom reduction or symptom free states at the end of treatment. There was no significant difference in percent of patients symptom free between the two groups (87% in older cephalosporins vs. 86.6% in newer cephalosporins, p=0.97). None of the studies including oral cephalosporins reported severe adverse events. The most commonly reported adverse events were nausea and vomiting. The one study that compared a macrolide to a cephalosporin analyzed cure at end of treatment which showed failure rates of 4.16% for azithromycin and 4.35% for cephalexin. The distribution of response was similar in both groups, but was not found to be statistically significant (p=0.37). [6]

In the other review, seventeen studies (5352 participants) assessed the evidence on the comparative efficacy of different antibiotics in alleviating symptoms, shortening duration of illness, preventing relapse and complications, and adverse effects in the treatment of streptococcal pharyngitis. [7] Cephalosporins were compared to penicillins in 5 trials (two in adults and 3 in children) and they found there were no statistically significant differences when measuring the resolution of symptoms at the end of treatment. In four of the trials, incidence of relapse was evaluated and they found there was a benefit of treatment with cephalosporins over penicillin in the adult trials but not in the trials with children. No difference in adverse events between the treatment groups was found. [7]

Guidelines:
The Gonococcal Infections Treatment Guidelines and the IDSA skin and soft tissue infections, CAP, pharyngitis, and UTI guidelines have been updated since the date of the last review, but there have been no changes in recommendations of cephalosporin use.

Recommendations:
1. No further research or review needed at this time.
2. Further evaluate comparative costs due no difference in effectiveness or safety between agents.
3. Maintain at least one agent from each subclass (1^{st}, 2^{nd}, 3^{rd} generation cephalosporins and amoxicillin/clavulanate) as well as age appropriate dosage forms.

References:

1. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J. Antimicrob. Chemother.* 2010;65 Suppl 4:iv41–51.

2. Wilcox MH, Corey GR, Talbot GH, et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J. Antimicrob. Chemother.* 2010;65 Suppl 4:iv53–iv65.

3. File TM Jr, Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin. Infect. Dis.* 2010;51(12):1395–1405.

4. Faulkner RD, Sia LL, Look ZM, et al. Bioequivalency of solid oral dosage forms of cefixime. *International Journal of Pharmaceutics*. 1988;43(1–2):53–58.

5. FDA Drug Safety Communication. Cefepime and risk of seizure in patients not receiving dosage adjustments for kidney impairment. 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm309661.htm.

6. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev*. 2010;(6):CD004299.

7. Van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev*. 2010;(10):CD004406.

Appendix 1: Abstracts of systematic reviews:

1. **Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev*. 2010;(6):CD004299.**

Background: Cellulitis and erysipelas are usually considered similar manifestations of the same condition which includes a skin infection associated with severe pain and systemic symptoms. The standard treatment for cellulitis is antibiotics, but since there are no current national guidelines in the treatment for these skin infections, a review is required to provide current best evidence and highlight gaps in research.
Objectives: To assess the efficacy and possible adverse effects of interventions to treat non-surgically-acquired cellulitis.
Methods: The Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE (ovid), EMBASE, and the ongoing trials databases were searched on 4th May 2010. We included randomized controlled trials comparing two or more different interventions with the key terms cellulitis or erysipelas. Two authors independently assessed trial quality and extracted data.
Results: Twenty-five studies were included with a total of 2488 participants. No two trials examined the same drugs, therefore similar drug types were grouped together. Macrolides and streptogramins were found to be more effective than penicillins (RR 0.84, 95% CI 0.73 to 0.97). An oral macrolide compared to intravenous penicillin demonstrating that oral therapies can be more effective than iv therapies (RR 0.85, 95% CI 0.73 to 0.98). Studies comparing penicillins with cephalosporins showed no difference in treatment effect (RR 0.99, 95% CI 0.68 to 1.43). Trials that compared different generations of cephalosporin, also showed no difference in treatment effect (RR 1.00, 95% CI 0.94 to1.06).
Conclusion: The best treatment for cellulitis cannot be defined at this time and because most recommendations are made on single trials, more studies may need to be conducted.

2. **Van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev*. 2010;(10):CD004406.**

Background: Pharyngitis is a common upper respiratory tract infection with sore throat as a common symptom. Antibiotics are often prescribed to treat this condition. The review was conducted to determine the best antibiotic to treat sore throats with positive throat swabs for group A beta-hemolytic streptococci (GABHS).
Objectives: To assess the evidence on the comparative efficacy of different antibiotics in alleviating symptoms, shortening duration of illness, preventing relapse, preventing complications, and adverse effects.
Methods: The Cochrane Library, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched. We included randomized, double-blind trials comparing different antibiotics reporting: clinical cure, clinical relapse, complications, or adverse events. Two authors independently screened trials for inclusion and extracted data.
Results: Seventeen trials were included containing a total of 5352 participants. There were no difference in symptom resolution between cephalosporins and penicillin (OR 0.79, 95% CI 0.55 to 1.12). Clinical relapse was lower with cephalosporins (OR 0.55, 95% CI 0.31 to 0.99) with overall number needed to treat to benefit (NNTB) 50. There were no differences between macrolides and penicillin. Carbacephem showed better symptom resolution post-treatment (OR 0.70, 95% CI 0.49 to 0.99; NNTB 14), but only in children. Children experienced more adverse events with macrolides (OR 2.33; 95% CI 1.06 to 5.15).
Conclusion: Evidence is insufficient to differentiate between antibiotics for GABHS tonsillopharyngitis. Limited evidence in adults suggests cephalosporins are more effective than penicillin for relapse, but the NNTB is high. Limited evidence in children suggests carbacephem is more effective for symptom resolution. Based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as first choice.

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

Opthalmic Antibiotic-Steroid Combination Agents

Month/Year of Review: November 2012
Date of Last Review: March 2010
PDL Class: Opthalmic Antibiotics-steroids combination
Source Document: Provider Synergies (PS)

Current Preferred Agents	Current Non-Preferred Agents
Neo/polymyx B sulf/dexamethasone drops	Fluometholone/sulfacetamide (FML-S Liquifilm®) drops
Neomy sulf/bacitrac/poly/HC ointment	Gentamicin/prednisolone (Pred-G®) 0.3%/1% drops and 0.3%/0.6% ointment
Sulfacetm NA/prednisol AC (Belphamide S. O. P®) ointment	Loprednol/tobromycin (Zylert®) drops
Sulfacetm NA/prednisol AC (Blephamide®) drops	
Tobramycin sulf/dexamethasone drops	
Tobramycin sulf/dexamethasone (Tobradex®) Ointment	

Previous Recommendations:

1. There is no difference in efficacy/effectiveness or in safety between agents. (Strength of recommendation: C)
2. There is insufficient evidence to make a specific recommendation.

PA Criteria/QL: None

Recommendations:
No further research or review needed at this time.

Background:
The use of a combination drug with anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will present in the eye.

Methods:
A MEDLINE OVID search was conducted using all ophthalmic antibiotics-steroid combination agents 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, 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 36 citations resulted and after review for inclusions, two potentially relevant clinical trials were identified (Appendix 1). These trials are briefly described in Table 1.

Table 1: Potential Relevant New Trials

Study	Comparison	Population	Primary Outcome	Results
Blair J[1], 2011 RCT	Dexamethasone + gatifloxacin compared with gatifloxacin + Placebo	Over the age of 12 years with bacterial corneal ulcer confirmed by culture.	Residual ulcer size at 10 weeks based on digital photographs.	All subjects (n = 30) demonstrated a reduction in ulcer size over the study period. There was no significant difference between the 2 groups in terms of the primary outcome.
Torkildsen GL[2], 2011 RCT, MC, investigator-masked	Tobramycin/dexamethasone (ST) compared to azithromycin	Patients with moderate to severe blepharitis/ blepharoconjunctivitis.	Seven-item global score defined as the total score of lid margin redness, bulbar conjunctival redness, palpebral conjunctival redness, ocular discharge (0-3 scale), and lid swelling, itchy eyelids, and gritty eyes (0-4 scale).	A statistically significant lower mean globa score (p = 0.0002) was observed in subjects treated with ST compared to subjects treated with azithromycin at Day 8. No serious adverse events were reported during the course of the study in either group.

RCT = Randomized control trial; MC = multi-center

New drugs:
None identified.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.

Guidelines:
None identified.

References:

1. Blair J, Hodge W, Al-Ghamdi S, et al. Comparison of antibiotic-only and antibiotic-steroid combination treatment in corneal ulcer patients: double-blinded randomized clinical trial. *Can. J. Ophthalmol.* 2011;46(1):40–45.

2. Torkildsen GL, Cockrum P, Meier E, et al. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Curr Med Res Opin*. 2011;27(1):171–178.

Appendix 1

1. Blair J, Hodge W, Al-Ghamdi S, et al. Comparison of antibiotic-only and antibiotic-steroid combination treatment in corneal ulcer patients: double-blinded randomized clinical trial. Can. J. Ophthalmol. 2011;46(1):40–45.

   Objective: To determine the benefit of early addition of corticosteroids to antibiotics in the treatment of corneal ulcers.

   Participants: Thirty eyes of 30 patients, over the age of 12 years, with bacterial corneal ulcer confirmed by culture.

   Methods: Patients were randomized before enrollment; 15 were treated with gatifloxacin (Zymar) and a masked placebo and the other 15 were treated with gatifloxacin and masked dexamethasone 0.1% (Maxidex). Primary outcome was residual ulcer size at 10 weeks based on digital photographs. Secondary outcomes included residual ulcer area by clinician estimate, visual acuity, VF-14 score, and time to healing.

   Results: All subjects (n = 30) demonstrated a reduction in ulcer size over the study period. There was no significant difference between the 2 groups in terms of the primary outcome. There was a significant difference between the 2 groups in 1 of the secondary outcomes. The mean residual ulcer size compared with the baseline by clinician estimate (slit-lamp) was -0.789 mm2 for the antibiotic-only group and -4.206 mm2 for the antibiotic-steroid group (p = 0.05). Among the other secondary outcomes there were no significant differences between the 2 groups.

   Conclusions: No benefit was demonstrated in our primary outcome for using steroids in combination with antibiotic therapy in treatment of corneal ulcers. This study suggests that the early addition of steroids to the antibiotic treatment of corneal ulcers does not seem to be harmful when employed in a closely monitored clinical setting.

2. Torkildsen GL, Cockrum P, Meier E, et al. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Curr Med Res Opin*. 2011;27(1):171–178.

   Objective: To evaluate the clinical efficacy and safety of tobramycin/dexamethasone (TobraDex ST ; 'ST') ophthalmic suspension 0.3%/0.05% compared to azithromycin (Azasite®) ophthalmic solution (1%) in the treatment of moderate to severe blepharitis/blepharoconjunctivitis.

   Research design and methods: The study was a multicenter, randomized, investigator-masked, and active-controlled, 15-day study. Enrolled in the study were 122 adult subjects (at least 18 years of age) diagnosed with moderate to severe blepharitis/blepharoconjunctivitis, defined by a minimum score of at least '1' for one of the lid signs, one of the conjunctival signs, and one of the symptoms in at least one eye and a minimum global score (total signs and symptoms score) of '5' in the same eye. One group of 61 subjects received ST with instructions to dose 1 drop four times daily (QID) for 14 days. The other group of 61 subjects received azithromycin and dosed with 1 drop twice daily (BID) for 2 days followed by once daily (QD) dosing for 12 days. Visits were conducted at Day 1 (baseline), Day 8 and Day 15. The a priori primary outcome parameter of the study was the seven-item global score defined as the total score of lid margin redness, bulbar conjunctival redness, palpebral conjunctival redness, ocular discharge (0-3 scale), and lid swelling, itchy eyelids, and gritty eyes (0-4 scale). The study utilized standardized, validated photograph control scales developed by Ora, Inc. (Andover, MA). Clinical trial registration: The study was registered at ClinicalTrials.gov under the registry number NCT01102244.

   Results: A statistically significant lower mean global score (p = 0.0002) was observed in subjects treated with ST compared to subjects treated with azithromycin at Day 8. No serious adverse events were reported during the course of the study in either group.

   Conclusion: ST provides a fast and effective treatment of acute blepharitis compared to azithromycin. Initial therapy with the combination of tobramycin/dexamethasone provides faster inflammation relief than azithromycin for moderate to severe blepharitis/blepharoconjunctivitis.