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 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. NEW BUSINESS
- a. Cystic Fibrosis* — M. Herink (OSU)
  1. Hypertonic Saline
  2. Carryover from 8/30 P&T: Dornase Alfa
  3. Public Comment
  4. Discussion of clinical recommendations to OHA
- b. Bone Metabolism Agents* — K. Ketchum (OSU)
  1. Abbreviated Class Update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- c. Colony Stimulating Factors* — A. Burns (OSU)
  1. Abbreviated Class Update
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- d. Intravenous/Sub-Q PAH Agents* — K. Sentena (OSU)
  1. Abbreviated Class Review
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- e. Drug Class Scans* — M. Herink (OSU)
  1. Growth Hormone
  2. Ulcerative Colitis
  3. Ophthalmic Antibiotics
  4. Phosphate Binders
  5. Public Comment
  6. 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)*

II. NEW BUSINESS (continued)

g. Classes Under Consideration for Annual PDL Pricing Review* R. Citron (OSU)

1. Antipsychotics- 2nd Generation
2. ADHD
3. Hepatitis C
4. Hematopoietic Agents
5. Asthma Controllers
6. Insulins
7. Pulmonary Arterial Hypertension
8. Other Lipotropics
9. DPP-4 Inhibitors
10. DRIs, ACE-Is and ARBs
11. DRIs, ACE-Is and ARBs + HCT
12. Otic Antibiotics
13. Topical Antiprasitics
14. Public Comment
15. Discussion of clinical recommendations to OHA

III. EXECUTIVE SESSION

IV. RECONVENE for PUBLIC RECOMMENDATIONS

V. 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, August 30, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

Members Present: Andris Antoniskis, MD, Tracy Klein, PhD, FNP; William Origer, MD; Stacy Ramirez, PharmD
Members Present by Phone: Joshua Bishop, PharmD; David Pass, MD
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Ted Williams, PharmD; Valerie Smith; Richard Holsapple, RPh; Ralph Magrish, MPA; Israel Harden
Staff Present by Phone: Bing-Bing Liang, PharmD; Kathy Sentena, PharmD
Audience: David Bashoum (Genentech); Stacy Daw (Genentech); Amy Burns (OSU); Chelsea Smith (OSU); Lori Howarth (Bayer); Annie Ogostalick (Abbott); Steve Faloon (Otsoka); Paul Bonham (NovoNordisk); Treli Trianlafillon (Viiv Healthcare); Diann Matthews; Amanda Meeker (CareOregon); Yarli (CareOregon); Eric Meyer (Teva); Greg Crepta (Teva); Sherri Van Everen (Genentech); Deborah Wafer (Gilead); Yoona Kim (Gilead); Barry Benson (Merck); Nathan Wood (Merck); Bruce Smith (GSK); Cheryl Fletcher (Abbott); Gene McLauty (Viiv); Jamie Damm (Vertex); Michael Estos (Pfizer); Rajesh Patel (BMS); Debra Edgar; Stephanie Kendall; Richard Kosesan

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. The meeting was called to order at 1pm.
b. Conflict of interest declarations were reviewed and no new conflicts were reported.
c. The committee reviewed the June 28, 2012 minutes.
ACTION: All in favor to approve minutes as is.

II. DUR ACTIVITIES
a. Mr. Magrish presented highlights from the FFY 2011 CMS Annual Report.
b. Mr. Holsapple presented the ProDUR Report and the Committee recommended noticing pharmacies about the importance of identifying prescription fills that were canceled due to ProDUR denials.
c. Dr. Williams presented the RetroDUR Report. d. Mr. Citron presented the Quarterly Utilization Reports.
e. Dr. Sentena presented the Oregon State Drug Review Newsletter titled “Can The Diabetic War Be Fought By Aggressive Blood Pressure Control?”.

III. OLD BUSINESS
a. Dr. Sentena presented on Oral Direct Factor X Inhibitors: Rivaroxaban (Xarelto®) recommending updates to the current prior authorization criteria.

**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)*

***ACTION:** All in favor of criteria updates as is.

b. Dr. Herink presented on Targeted Immune Modulators recommending implementing prior authorization criteria for non-preferred agents only to ensure DMARDs are used first line, initiating quantity limits to prevent doses from exceeding recommendations and making Humira and Enbrel preferred on the PDL with no prior authorization requirements and Remicade and all other drugs in class non-preferred with prior authorization requirements.

***ACTION:** All in favor after Executive Session of proposed PA criteria, PDL status updates and quantity limits.

c. Dr. Herink presented on Antipsoriatics recommending updates to the prior authorization criteria.

***ACTION:** All in favor of proposed PA criteria updates.

d. Dr. Herink presented on Fingolimod (Gilenya®) recommending updates to the prior authorization criteria.

***ACTION:** All in favor of proposed PA criteria updates.

e. Dr. Herink presented on Erythropoiesis Stimulating Agents recommending updates to the prior authorization criteria, make Procrit and Aranesp preferred and Epogen and Peginesatide non-preferred.

***ACTION:** All in favor after Executive Session of proposed PA criteria and PDL status updates.

IV. NEW BUSINESS

a. Dr. Herink presented on Inhaled Antibiotics and Dornase Alfa for Cystic Fibrosis recommending making tobramycin inhaled solution (Tobi) and dornase alfa (Pulmozyme) preferred with quantity limits and aztreonam inhalation solution (Cayston) non-preferred. Yoon Kim with Gilead presented public comment on the class. Expert testimony was submitted in writing by Dr. Jeff Gold, MD with the Department of Pulmonary Medicine at OHSU.

***ACTION:** All in favor after Executive Session of making Tobi preferred with quantity limits, and make Cayston non-preferred with quantity limits. Pulmozyme (Dornase Alpha) was deferred until September's meeting to discuss with hypertonic saline and percentage of patient's tolerance and coverage guidance on vitamins.

b. Dr. Liang presented on ranolazine (Ranexa®) recommending making Ranexa® non-preferred.

***ACTION:** All in favor after Executive Session of PDL status update.

c. Dr. Liang presented on Diuretic Agents Class recommending adding loop, thiazide/thiazide like and potassium sparing diuretics class to the PDL with all multisource agents ≤ $0.25 preferred, except for amiloride, chlorothiazide, chlorthalidone, eplerenone, ethycrinic acide, furosemide solution 40mg/5ml, methyclothiazide, metalozone, triamterent/HCTZ tablets.

***ACTION:** All in favor after Executive Session of PDL status updates.

d. Dr. Herink presented on Ophthalmics: Glaucoma Agents recommending making generic latanoprost preferred and Zioptin®, Alphagan P, apraclonidine HCL and Travatan Z non-preferred. Nathan Wood with Merck presented public comment on Zioptin®.

***ACTION:** All in favor after Executive Session of PDL status updates.

e. Dr. Herink presented on Vascular Endothelial Growth Factors (VEGF) Inhibitors recommending making pegaptanib non-preferred and comparing costs for bevacizumab, ranibizumab and aflibercept.

***ACTION:** All in favor after Executive Session to defer PDL updates until September's meeting with updated pricing information.

V. The meeting adjourned at approximately 4pm.

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

Abbreviated Drug Evaluation: Hypertonic Saline Inhalation for Cystic Fibrosis

Month/Year of Review: September 2012
End date of literature search: August 2012
Generic Name: Hypertonic Saline
PDL Class: None

Research Questions:

- Is there evidence to support the use of inhaled hypertonic saline (HS) in cystic fibrosis (CF)?
- Are there certain subpopulations in which inhaled HS has a clinical advantage in efficacy or safety?

Conclusions:

- Based on fair quality evidence and a moderate estimated benefit (mean change in forced expiratory volume at one second [Fev1] of 3%-7.7%), current guidelines recommend the chronic use of inhaled HS for patients six years of age and older to improve lung function and reduce exacerbations.
- There is moderate quality evidence that treatment with HS in CF patients improves short term lung function, decreases pulmonary exacerbations, and has a small effect on improvement in quality of life.
- There is insufficient evidence to determine the long term improvement in lung function from inhaled HS.
- There is low quality evidence that in infants and young children, there is no difference in the rate of pulmonary exacerbations with HS compared to isotonic saline.
- Inhaled HS is relatively well tolerated with cough and bronchospasm being the most common adverse events.
- There is insufficient evidence to determine the long term effects of HS on mortality in patients with CF.

Recommendations:

- Include inhaled hypertonic saline in the CF medication class.
- Due to evidence of improved short term lung function and reduction in pulmonary exacerbations, make preferred for patients greater than six years of age and evaluate comparative costs within the class.

Background:
Cystic Fibrosis (CF) is characterized by retained dry thick mucus that provides a source for chronic infection. Mucolytics are first-line therapy because the thick mucus is the primary cause for airway obstruction, including both dornase alfa and inhalations of HS.[1] In the lungs, dysfunction of the CF Transmembrane Conductance Regulator (CFTR) gene causes airway surface liquid (ASL) depletion and thickened viscous mucus results in decreased mucociliary clearance (MCC). Inhaled HS induces osmotic flow of water into the mucus layer resulting in improved mucus run, transportability of sputum, and increased hydration of the airway surface. HS has been shown to improve lung function and reduce exacerbation rates in patients with CF.

Twice daily inhalation of has been shown to reduce sputum markers of inflammation, reduce the risk of pulmonary exacerbation, and modestly improve pulmonary function.[2] The primary limitation of HS is poor tolerance due to increased cough and bronchopasm, as well as the time it takes for administration.[2,3] Also, the benefit of HS occurs early and many trials evaluating HS have relatively small numbers and of short duration.[2,3]

Guidelines:
The 2007 Cystic Fibrosis Foundation Pulmonary Guidance outlines the treatment recommendations for chronic maintenance of lung health in CF patients. Using the U.S. Preventive Services Task Force recommendation grades, chronic treatments are given an evidence grade as well as an estimated treatment effect. The guidelines determined the evidence for the use of HS in patients with CF to be of fair quality (two randomized controlled trials, two randomized crossover trials vs. dornase alfa). Studies demonstrated it was well tolerated in general and the most common side effect was cough or bronchospasm. A review of the literature demonstrated that HS therapy resulted in a mean increase in FEV1 of 15% compared with 2.8% in the placebo group (normal saline). Only one study was identified which evaluated HS on pulmonary exacerbations and found that HS demonstrated a 56% reduction in pulmonary exacerbations for patients receiving 7% saline compared with normal saline. The committee concluded that HS provided a net benefit that was moderate. For patients 6 years of age and older with CF , the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).[4]

Clinical Efficacy:
Systematic Reviews
The Cochrane Collaboration conducted a systematic review in 2010 to investigate the effects of treatment with nebulised HS in CF compared to placebo and or other treatments for mucociliary clearance. A total of 19 trials were identified, but only 12 trials met the inclusion criteria with a total of 442 participants (aged 6 years to 46 years).[3] Results demonstrated that while the use of hypertonic saline has been shown to lead to a small improvement in lung function up to four weeks of treatment, this effect was not sustained at 48 weeks. It was shown to reduce the frequency of pulmonary exacerbations and may have a small effect on improvement in quality of life in adults. [3]

Seven trials, including 281 patients, compared hypertonic saline 3% to 7% versus isotonic saline. The data from the trials were pooled and analyzed. There was a significant improvement in mean percent change in FEV1 after 4 weeks of treatment with hypertonic saline 3-7% compared to isotonic saline, (MD 4.15; 95% CI 1.14 to 7.16). There was also a significant improvement in forced vital capacity (FVC) at four weeks (MD 2.75; 95% CI 0.00 to 5.49). There was no significant difference in FEV1 and FVC demonstrated at 48 weeks. The mean number of exacerbations per participant in the control group was 0.89, as compared with 0.39 in the hypertonic saline group (difference, 0.50, 95% CI 0.14 to 0.86; P =0.02). The meta-analysis of the data demonstrated a significant improvement in quality of life, as measured by the Cystic Fibrosis questionnaire; or CFQ (MD 7.77; 95% CI 1.86 to 13.68) with hypertonic saline compared to the control group. [3] Three

trials, including 80 patients, compared hypertonic saline to dornase alfa. After three months one trial found that dornase alfa led to a greater increase in FEV1 compared to hypertonic saline (MD 8.00%; 95%CI 2.00%to 14.00%).[3]

Clinical Trials

Recently, a fair quality, large, randomized, placebo-controlled study evaluated the use of HS (n=158) compared to isotonic saline (n=163) in children less than six years of age with CF over 48 weeks.[5] This is the first clinical trial assessing chronic HS use in patients less than 6 years of age. Results failed to demonstrate a reduction in the rate of pulmonary exacerbations. Mean age of subjects was 2.2 years and the majority of patients were male. Fifteen participants (9%) withdrew from the HS group compared to 14 (7%) in the isotonic saline group. The pulmonary exacerbation rate was 2.3 (95% CI 2.0-2.5) per person-year in those randomized to HS and 2.3 (95% CI 2.1-2.6) per person-year among those randomized to isotonic saline (ratio of HS compared to isotonic saline 0.97; 95% CI 0.83-1.13). [5] The ratio of mean total days of antibiotic days in HS compared to isotonic saline was 1.13 (95% CI 0.91-1.40). [5] There was also no significant difference in any secondary outcomes (height, weight, respiratory rate, oxygen saturation, and cough). The most common serious adverse event in both groups was cough or increased cough (8% HS vs. 10% isotonic saline). Authors noted that using the outcome of pulmonary exacerbation in younger children may pose a challenge because they presumably have less underlying lung disease than older patients and different endpoints should be evaluated in these younger patients.[6]

References:

1. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am. J. Respir. Crit. Care Med.* 2011;183(11):1463–1471.

2. Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. *BMC Med*. 2012;10(1):88.

3. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database of Systematic Reviews*. 2009;(2). Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001506.pub3/abstract. Accessed July 10, 2012.

4. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am. J. Respir. Crit. Care Med.* 2007;176(10):957–969.

5. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA*. 2012;307(21):2269–2277.

6. Dasenbrook EC, Konstan MW. Inhaled hypertonic saline in infants and young children with cystic fibrosis. *JAMA*. 2012;307(21):2316–2317.

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

Abbreviated Class Review: Inhaled Antibiotics and Dornase Alfa for Cystic Fibrosis

Month/Year of Review: August 2012 **End of literature search:** May 2012
Drugs Included: Tobramycin (Tobi®), Aztreonam (Cayston®), Dornase alfa (Pulmozyme®)

Issues:

- What evidence is available for the efficacy and safety of inhaled tobramycin, aztreonam, and dornase alfa for cystic fibrosis (CF)?
- Is there comparative evidence that either inhaled tobramycin or aztreonam is superior in efficacy or safety?
- Are there specific subpopulations or clinical situations in which one inhaled antibiotic provides clear benefit over another?

Conclusions:

- There is insufficient long-term evidence available for all drugs in the class. The longest study for dornase alfa (DA) is 2 years and tobramycin inhalation solution (TIS) is 33 months. There is no evidence for aztreonam lysine for inhalation (AZLI) beyond a 28-day course.
- Efficacy and safety has not been established for use of AZLI in patients <7 years old, TIS < 6 years old, and DA <5 years old.
- There is insufficient comparative evidence for efficacy and safety of TIS and AZLI.
- There is moderate quality evidence that overall, the frequencies of pulmonary exacerbations, hospitalizations, and parenteral antipseudomonal antibiotic use are improved with chronic suppressive therapy with TIS in patients with mild to severe CF.
- There is low to moderate quality short term evidence that AZLI modestly improves lung function as measured by FEV1, improves patient-reported respiratory symptoms, and lengthens the time to use of additional antipseudomonal antibiotics compared to placebo.
- A Cochrane review showed demonstrated low quality evidence that inhaled antibiotics improved lung function in patients with CF and that TIS, specifically, significantly decreased hospitalization among patients.
- AZLI and TIS were well tolerated throughout all clinical trials, with cough being the most frequently reported adverse event. There have been post-marketing reports of hearing loss in patients using TIS.
- The Cystic Fibrosis Foundation evaluated 19 trials of DA in a total of 3140 patients. Long-term studies show a significant improvement over placebo in lung function and improvement in quality of life, while there is conflicting evidence on the effect of DA on the incidence of pulmonary exacerbations. A Cochrane review of DA, including 2469 participants, found no statistical difference in mortality compared to placebo or hypertonic saline. Spirometric lung function was improved in the treatment groups at multiple time frames up to two years.
- The only significant adverse effects found in clinical trials of DA compared to placebo were voice alteration and rash.

Recommendations:

1) Due to more published efficacy and safety data and a demonstrated continued benefit over 2 years and decrease in hospitalizations, make TIS a preferred agent on the PDL with a quantity limit of 56 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
2) Make AZLI a non-preferred agent due to a lack of comparative evidence or demonstrated clinical benefit in efficacy or safety over TIS, and limit to patients with cystic fibrosis with a quantity limit of 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy)
3) Make DA a preferred agent on the PDL with a quantity limit of 30 vials/30 days

Drug Products[1-3]	FDA approval [1-3]	FDA approved indications[1-3]	Usual Dose/Duration[1-3]	Potential Off-label Uses	Other Considerations
Tobramycin inhalation solution (Tobi)	1997	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*	300mg inhaled twice daily (as close to 12 hours apart and not less than 6 hours apart). Tobi should be administered in repeated cycles of 28 days on drug followed by 28 days off drug.	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Inhaled tobramycin is administered using a hand-held PAR LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor.
Aztreonam inhalation solution (Cayston)	2010	Improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*	75mg administered 3 times a day for a 28-day course, followed by 28 days off therapy	Bronchiectasis for patients without cystic fibrosis and chronic bronchial infection with *Pseudomonas aeruginosa*	Patients should use bronchodilator prior to administration of aztreonam. Aztreonam must be administered using an Altera nebulizer system.
Dornase alfa (Pulmozyme)	1993	Management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with cystic fibrosis.	2.5 mg daily using a recommended nebulizer	Non-cystic fibrosis pre-term infants suffering from atelectasis	Patients should use a recommended nebulizer/compressor system.

Methods:
A Medline literature search ending May 2012 for meta-analyses or randomized active-controlled trials (RCT's) comparing all included drugs to each other or to other drugs for the treatment of cystic fibrosis was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources. Results of this search included two RCT's for tobramycin, 3 RCT's for aztreonam, two Cochrane systematic reviews, and one evidence based treatment guideline.

Background:
CF is an inherited chronic disease that affects about 30,000 children and adults in the U.S. and about 70,000 people worldwide. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues.[4] Transport of chloride, sodium, and bicarbonate are disrupted, which may lead to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.[4]

Although multiple organ systems are affected in CF patients, pulmonary disease is the leading cause of morbidity and mortality in patients with CF. The thickened, viscous airway secretions obstruct the airway, resulting in endobronchial infection, and an exaggerated inflammatory response that may lead to development of bronchiectasis and progressive obstructive airways disease.[4,5] There are a number of treatment options for the maintenance of lung health in CF patients, including aerosolized antibiotics, recombinant human deoxyribonuclease (rhDNase), hypertonic saline, and anti-inflammatory agents. Although some of these treatments may be administered by multiple routes (intravenous, oral, inhaled), administration by inhalation is preferred, as this method of delivery promotes high concentrations of the drug in airways and lower concentrations in plasma, minimizing the system toxicity.[6]

Bacterial colonization of the airway secretions with *Pseudomonas aeruginosa, Haemophilus influenza, Staphylococcus aureus or Burkholderia cepacia* may occur in patients with CF. *P. aeruginosa* is the most common pathogen in CF patients, and chronic colonization may cause respiratory insufficiency and eventual respiratory failure.[7] Consequences in this patient population include increased morbidity and mortality. Therefore, therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes. The CF foundation defines clinically meaningful endpoints as time to need for additional antipseudomonal antibiotics and hospitalization. The Cystic Fibrosis Questionnaire-Revised (CFQR) has been validated as a subjective measure to assess multiple domains of patient quality of life and is approved by the FDA as a patient reported outcome measure. The clinical importance is uncertain due to no known correlation to other clinically meaningful endpoints.

There are two inhaled antibiotic agents approved for the management of patients with CF that is complicated by *Pseudomonas aeruginosa,* TIS and AZLI. AZLI is a monobactam antibiotic that was FDA approved in 2010. It is administered via nebulizer at a dose of 75mg three times daily for 28 days, followed by 28 days off therapy. TIS is an aminoglycoside antibiotic that was FDA approved in 1997 and is administered at a dose of 300mg twice daily for 28 days, followed by 28 days off therapy.[1,2] Inhaled antibiotics help reduce exacerbations and improve lung function by reducing *P.aeruginosa* concentrations. Guidelines published by the Cystic Fibrosis Foundation in 2007 (prior to approval AZLI) recommend the routine use of TIS in patients with chronic *P. aeruginosa* infections for asymptomatic and symptomatic CF patients ≥ 6 years old cultures to improve lung function and/or reduce exacerbations. Data from their registry suggests that almost 70% of eligible patients use inhaled tobramycin.[5] AZLI is the only other inhaled antibiotic approved for use in CF patients.[2]

DA is a purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme that assists in the breakdown of DNA which accumulates in cystic fibrosis patients. It treats the thickened secretions in the lungs that facilitate bacterial infection and airway obstruction in CF patients. It works by degrading the excess DNA that accumulates with CF mucus, and promoting airway clearance. DA was approved in 1993 for the management of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with forced vital capacity (FVC) >40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with CF.[3] The Cystic Fibrosis Guidelines recommend use of DA in patients with asymptomatic, mild, moderate, or severe lung disease to improve lung function and reduce exacerbation.[5]

Hypertonic saline (HS) inhalation increases hydration of airways surface liquid in patients with CF, which helps improve mucociliary clearance. For patients 6 years of age and older with C , the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations (fair level of evidence, grade of recommendation B).[5]

Systematic Reviews:

CF GUIDELINES

The Cystic Fibrosis Foundation published treatment guidelines on chronic medications for maintenance of lung health in 2007, prior to the FDA approval of AZLI. The guidelines strongly recommend TIS to improve lung function and reduce exacerbations in patients ≥6 years old, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways. The guidelines also recommend chronic use of TIS to reduce exacerbations in patients ≥6 years old that are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in cultures of the airways.[5]

The recommendations are based on results from a systematic review of 6 trials, with a total of 679 participants. Three of the studies showed that patients taking TIS had a significantly improved forced expiratory volume at one second (FEV_1), with a net benefit in lung function of 7.8 to 12%. The largest study (n=520), reported a 26% reduction in hospitalizations and a 36% reduction in the use of IV anti-pseudomonal antibiotics for those using tobramycin compared to placebo.[5]

The Cystic Fibrosis Foundation recommends the use of DA for CF patients with mild lung disease, and they strongly recommend its use for CF patients with moderate to severe lung disease. DA was studied in 19 trials (n=3140) of varying lengths. Most short-term studies showed a significant improvement in FEV_1 by 11.2-15.4%, and long-term studies uniformly demonstrated improvement in lung function. One study (n=968) found that FEV_1 increased by 5.8% compared to placebo after 24 weeks of treatment with dornase alfa, and another study (n=320), saw a similar improvement in FEV_1 (net benefit 7.3%) in patients with severe CF lung disease who were treated for 12 weeks. DA was well tolerated as there were few adverse events that were increased by DA compared to placebo. The most common adverse event was voice alteration.[5]

INHALED ANTIBIOTIC COCHRANE REVIEW

A 2009 Cochrane review found 19 trials, including 1724 patients from a literature search ending January 2011, which evaluated the effect of any inhaled antibiotic treatment as long-term therapy in people with CF, compared to placebo or usual treatment. Investigators found that inhaled antibiotics improved lung function and reduced the frequency of exacerbations during the study and that the best evidence is for inhaled tobramycin. Further research is necessary to show maintenance of benefits, and to establish a preferred antibiotic therapy and dosage regimen. There was significant heterogeneity among the trials, in terms of design, drug type, dose and delivery, duration of treatment and outcome measures, which complicated interpretation of the results and reduces the validity of pooling the data.[14]

Eight trials, including 1152 patients, compared TIS to usual treatment from 1 to 33 months, with the majority of participants (45%) included in one high quality trial. Three trials reported the mean change in % predicted FEV_1, which was greater for inhaled antibiotics compared to placebo [mean difference: 9.48 (95% CI 5.92, 13.04)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. Three trials reported the change in % predicted FVC, which was greater for inhaled antibiotics compared to placebo [mean difference 8.04 (95% CI 4.24, 11.85)]. Two of these trials (81.9% of the evaluable population) studied the effectiveness of TIS. The largest trial included in the Cochrane review, with 520 participants, reported a mean increase in FEV_1 of 10% in the TIS treated group, compared to a 2% decrease in mean FEV_1 in the control group after 20 weeks ($P<0.001$). The same trial reported a mean increase in FVC of 8% in the TIS treated group, compared to a mean of a 1% decrease in the mean FVC in the control group.[14]

Two trials with a duration of three to 12 months had outcomes for hospital admissions available for analysis. There was a significant risk reduction for one or more hospital admissions [RR 0.72 (95% CI 0.60, 0.86)]. One trial of more than 12 months had a nonsignificant risk reduction for at least

one hospital admission [RR 0.59 (95% CI 0.34, 1.05)]. The longest trial was 32 months and found no significant difference for hospital admissions [RR 0.80 (95% CI 0.39, 1.65)]. All four of these trials were conducted using TIS as the study drug.[14]

Two trials included AZLI. In one trial, Participants were treated with aztreonam lysine for 28 days and followed after this period to measure the time to a pulmonary exacerbation treatment; estimated as 92 days in the aztreonam lysine group and 71 days in the control group (P = 0.007). This study did not utilize intent to treat analysis, had a moderate rate of patient discontinuation, and was of short duration. The second study evaluated CFQR as the primary endpoint but was not included in the analysis because it was classified as "awaiting classification" until more information available.[14]

There was no evidence of clinically important adverse effects during the trials. Overall, patients who used inhaled antibiotics experienced more resistance to antibiotics, tinnitus and change in voice than those in placebo groups. Five trials measured renal function and found no significant evidence of renal impairment. However, one trial found that nine people in the TIS group and the placebo group saw transient increases of 50% or more in the creatinine level. Five trials measured audiometry and found that four stated that no abnormality was found.[14]

DORNASE ALFA COCHRANE REVIEW

A 2010 Cochrane review on DA in CF set out to determine whether DA improved mortality and morbidity compared to placebo or other mucolytics (hypertonic saline, acetylcysteine, and mesna) and to identify adverse effects. The last data search occurred on July 17, 2009. A total of 43 trials were identified, but only trials that were randomized or quasi-randomized which compared DA to placebo, standard therapy, or another mucolytic were included in the analysis. Fifteen trials remained after exclusion criteria were applied, which contained 2469 participants. Of these studies, 12 compared DA to placebo or no DA treatment; one compared daily DA with hypertonic saline and alternate day DA; and two compared daily DA to hypertonic saline. The timeframe of these studies ranged from six days to two years and included patients of all ages.[13]

Outcomes of the review were grouped into the following timeframes: one, three, six, and twelve months and annually thereafter. The primary outcomes were changes in lung function (FEV_1 and FVC) from baseline, change from baseline in quality of life, mean number of exacerbations, and number of deaths. Secondary outcomes were number of days treatment with IV antibiotics, number of days treatment with oral antibiotics, number of days in hospital due to respiratory exacerbations, change in weight from baseline, number of adverse events such as alteration in voice, hemoptysis, bronchospasm, and cost.[13]

Dornase alfa versus placebo or no dornase alfa treatment.
Overall there was no statistical difference in mortality between treatment groups at any time period. For the mean percentage change of FVC in DA treated group versus placebo there was improvement at one month [mean difference 7.52 (95% CI 1.34, 13.69)], three months [mean difference 5.10 (95% CI 1.23, 8.97)], six months [mean difference 3.80 (95% CI 2.62, 4.98)], but not at two years [mean difference 0.70 (95% CI -1.24, 2.64)]. The only identified increased adverse effect was voice alteration and rash. No differences were seen in mean number of days of IV antibiotics at three months [mean difference 2.96 (95% CI -7.29, 1.37), or mean number of inpatient treatment at 3 months [mean difference 0.92 (95% CI -2.19, 4.05)]. For safety outcomes there was no difference in hemoptysis, dyspnea, or pneumothrax. There was an increase in voice alteration at one month in the treatment group [mean difference 4.03 (95% CI 1.29, 12.62), three months [RR 2.87 (95% CI 1.44, 5.71), but not at six months [RR 1.73 (95% CI 0.69, 4.34). There was increase in the incidence of rash at two years [RR 4.63 (95% CI 1.35, 15.89)].[13]

Dornase alfa versus mucolytic
There was a reported 8% (95% CI 2, 14%) increase in FEV1 from baseline in the DA group compared to hypertonic saline. There were no deaths reported in any of the trials. There was no difference in number of inpatient days of treatment when DA was compared to hypertonic saline [mean difference -0.4 (95% CI -2.32, 1.52). The most frequently reported adverse events were increased cough, coryza, throat infection, allergic reaction to antibiotic, wheeze, breathlessness, hemoptysis, chest pain, and oral thrush.[13,15]

Randomized Controlled Trials (Evidence table in Appendix 1).
There are no published head to head trials comparing TIS to AZLI. An open-label, randomized, phase 3 trial, sponsored by Gilead Sciences, has been conducted comparing AZLI to TIS. Preliminary results have been published only in abstract form. 268 patients received 28-day, intermittent, repeating courses of either treatment over 24 weeks. The co-primary endpoints were non-inferiority of AZLI for mean percent change in FEV1 percent predicted at Day 28 compared to baseline and superiority of AZLI for mean actual change in FEV1 percent predicted across three treatment cycles (six months).

<u>TOBRAMYCIN</u>
Pivotal studies evaluating the use of tobramycin have been included in the Cystic Fibrosis Foundation Pulmonary Guidelines published in 2007, as well as a 2009 Cochrane Review of inhaled antibiotics. Since the publication of these reviews, one additional study has been published evaluating the safety and efficacy of TIS.[8]

In the Early Inhaled Tobramycin for Eradication (ELITE) trial, the short and long term efficacy of tobramycin inhalation solution (TIS) 300mg/5ml twice daily was evaluated in CF patients with early onset *P. aeruginosa* infection (n=88). All patients received TIS twice daily for 28 days, at which

point they were randomized to either discontinue TIS (28-day group) or receive an additional 28 days of therapy (56-day group). Patients were excluded from the efficacy analysis if there was no eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications. This trial was rated of poor quality because it was not blinded which may have increased the risk of bias and included a high attrition rate.[8] Of the 88 patients randomized, only 65 were included in the efficacy analysis (74%). [8]

AZTREONAM

The efficacy and safety of AZLI, dosed 75mg two or three times daily, has been studied in two phase III, randomized, placebo-controlled trials (AIR-CF1 and AIR-CF2), and a phase IIIb published study (AIR-CF4). Efficacy endpoints and inclusion/exclusion criteria varied across studies.[6,18]

AIR-CF1 was a fair quality, randomized, double-blind, placebo-controlled, international study (n=164) which evaluated the short-term efficacy and safety of AZLI in patients with cystic fibrosis, *P. aeruginosa* infection, and moderate-to-severe lung function [FEV_1 25%-75% predicted].[9] Patients ≥6 years old with no recent use of anti-pseudomonal antibiotics or azithromycin were treated with 75mg AZLI three times a day for 28 days or placebo and monitored for 14 days after study completion.[9] The primary endpoint was the change in patient-reported respiratory symptoms using the CF-Questionnaire-Revised (CFQ-R) Respiratory Scale. The CFQ-R scale is a validated, disease-specific, health related quality-of-life instrument that meets most of the US FDA guidelines on patient reported outcomes.[6] After 28 days, patients treated with AZLI saw an improved mean CFQ-R respiratory score compared to placebo [9.7 points (95%CI 4.3, 15.1), p<0.001]. Although the scores of both groups declined after treatment, at day 42, the treatment difference was still significant [6.3 points (95% CI 1.2, 11.4), p=0.15). The minimum clinically important difference for clinically stable patients is 5 points for the CFQR. The increase in disease scores was independent of disease severity, although patients treated with AZLI also saw a significant improvement in all secondary endpoints of FEV_1 (10.3% predicted, p<0.001), sputum *P. aeruginosa* density (-1.453 log 10 cfu/g, p<0.001), and non-respiratory CFQ-R scales (e.g. eating, emotional functioning, health perceptions), compared to placebo.[9]

AIR-CF2 was a fair quality, randomized, double-blind, placebo-controlled, multicenter study (n=211) which evaluated maintenance treatment for a *P. aeruginosa* infection in patients with CF. This study included patients ≥6 years old who had a pulmonary *P. aeruginosa* infection requiring ≥3 courses of TIS within the previous year.[6,10] Patients were randomized into one of three treatment groups (placebo, AZLI twice daily or AZLI three times daily) and treated for 28 days and followed up with for an additional 56 days (day 84). The primary efficacy endpoint was the time to need for inhaled or intravenous anti-pseudomonal antibacterials to treat symptoms of pulmonary exacerbations. The median time to need additional inhaled antibiotics in patients treated with AZLI was 21 days longer compared to the placebo group (92 vs 71 days, measured from baseline; p=0.007). Pulmonary function was also improved in AZLI patients compared to placebo. Pooled data for AZLI showed a mean change in FEV_1 of 6.3% [95% CI 2.5, 10.1); p=0.001], and a significant improvement in mean change in CFQ-R score [5.01 points (95% CI 0.81, 9.21); p=0.02].[10] The prespecified statistical plan compared subjects in each treatment regimen to the corresponding placebo regimen, however there was not sufficient power to compare dosage regimens and the data was pooled.[6]

AIR-CF4 is a fair quality phase IIIb trial with a similar study design to AIR-CF1, but extends the efficacy and safety evaluation of AZLI to include patients with CF, *P. aeruginosa* airway infection, and milder impairment of lung function (FEV_1 >75% predicted).[11] Patients were randomized to a 28-day course of AZLI or placebo, administered three times daily. The primary endpoint was the change from baseline at day 28 on the CFQ-R Respiratory Scale. Patients treated with AZLI saw a non-statistically significant improvement in CFQ-R score of 1.80 versus placebo [(95% CI: -2.83, 6.44); p=0.443)]. Statistically significant treatment effects were seen in AZLI-treated patients for several secondary endpoints: change from baseline at day 28 for adjusted mean log 10 PA CFUs in sputum (AZLI -1.4, placebo -0.14; p=0.016), and relative change in FEV_1% predicted (AZLI 0.29%, Placebo -2.5%; p=0.21). This study did not meet its primary endpoint, and authors suggest that the sensitivity of the CFQ-R is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.[11]

Safety/tolerability:

AZTREONAM:

Overall, in clinical trials, AZLI was well tolerated. Most adverse events were mild to moderate in severity, and the most commonly reported adverse events were associated with respiratory symptoms, such as cough, productive cough, nasal congestion, respiratory tract congestion, wheezing and pharyngolaryngeal pain.[6,11] The observed respiratory symptoms are consistent with those generally seen in patients with cystic fibrosis lung disease, and there were no statistically significant differences between treatment groups in drug-related adverse events or serious adverse events.[6]

In AIR-CF1, the only adverse event with a statistically significant difference in incidence between treatment groups was productive cough (12% in AZLI-treated patients vs. 25% in placebo-treated patients; p=0.047).[9] During the study, 5% of AZLI-treated patients were hospitalized, compared to 14% of placebo-treated patients; the difference was not statistically significant (p=0.064).[6] Six AZLI-treated patients and 13 placebo-treated patients discontinued the study due to an adverse event. Sixteen of these patients required treatment with non-study anti-pseudomonal antibiotics and had symptoms indicative of pulmonary exacerbation. There were no deaths or reports of anaphylaxis reported in this study.[9] In AIR-CF2, there were no statistically significant differences between treatment groups in the type and incidence of adverse events. Overall, seven patients were hospitalized during the treatment period for pulmonary exacerbations (AZLI-BID:2, AZLI-TID:4, placebo-1). No deaths were reported during this study period.[10]

The safety profile of AZLI was similar in AIR-CF4. The most common adverse events seen in both treatment groups were cough, productive cough, respiratory tract congestion, fatigue, pulmonary function test decreased, and abdominal pain. Abdominal pain is the only adverse effect that occurred at a higher rate in one group than the other (12.3% placebo, 1.3% AZLI, p=0.01). Serious adverse events occurred in 11.8% of AZLI-treated patients and 3.7% of placebo-treated patients (p=0.073), and all of these adverse events resulted in hospitalizations, but none were considered to be treatment related. There were no deaths in this study.[11]

References:

1) Tobi Prescribing Information. Novartis. 11/2009.
2) Cayston Prescribing Information. Gilead. 2010.
3) Pulmozyme Prescribing Information. Genentech, Inc. 10/2010.
4) Katkin, JP. "Cystic Fibrosis: Clinical Manifestations of Pulmonary Disease." Mar. 2012. Web. 1 Apr. 2012.
5) Flume, P.A. et al. "Cystic Fibrosis Pulmonary Guidelines." *American Journal of Respiratory and Critical Care Medicine* 176.10 (2007): 957–969. Print.
6) Plosker, G.L. "Aztreonam Lysine for Inhalation Solution: In Cystic Fibrosis." *Drugs* 70.14 (2010): 1843–1855. Print.
7) Dipiro, JT et al. "Cystic Fibrosis." *Pharmacotherapy: a Pathophysiologic Approach.* 7th ed. McGraw-Hill, 2008. 535-46. Print.
8) Ratjen, F. et al. "Treatment of Early Pseudomonas Aeruginosa Infection in Patients with Cystic Fibrosis: The ELITE Trial." *Thorax* 65.4 (2010): 286–291. Print.
9) Retsch-Bogart, George Z et al. "Efficacy and Safety of Inhaled Aztreonam Lysine for Airway Pseudomonas in Cystic Fibrosis." *Chest* 135.5 (2009): 1223-1232. Web. 30 Apr. 2012.
10) McCoy, Karen S et al. "Inhaled Aztreonam Lysine for Chronic Airway Pseudomonas Aeruginosa in Cystic Fibrosis." *American Journal of Respiratory and Critical Care Medicine* 178.9 (2008): 921-928. Web. 30 Apr. 2012.
11) Wainwright, C E et al. "Aztreonam for Inhalation Solution (AZLI) in Patients with Cystic Fibrosis, Mild Lung Impairment, and P. Aeruginosa." *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society* 10.4 (2011): 234-242. Web. 30 Apr. 2012.
12) Quan JM, Tiddens HAWM, Sy JP, McKenzie SG, Montgomery MD, Ribinson PJ, et al. A two-year randomized, placebo controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. Journal of Pediatrics 2001;129(6):913-20.
13) Jones, AP, and C. Wallis. "Dornase Alfa for Cystic Fibrosis." *Cochrane Database Syst Rev* 3 (2010): n. pag. Print.
14) Ryan, G., M. Singh, and K. Dwan. "Inhaled Antibiotics for Long-term Therapy in Cystic Fibrosis." *Cochrane Database Syst Rev* 3 (2011): n. pag. Print
15) Suri R, Metcalfe C, Lees B, Grieve R, Flather M, Normand C, et al. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomized trial. Lancet 2001;358(9290):1216-21.
16) Lexicomp Online. "Dornase alfa." Accessed 4/15/2012 at http://www.crlonline.com/lco/action/doc/retrieve/docid/group_f/125928.
17) Lexicomp Online. "Aztreonam lysine." Accessed 4/15/2012 at http://www.crlonline.com/lco/action/doc/retrieve/docid/group_f/126558,
18) Kirkby, S., K. Novak, and K. McCoy. "Aztreonam (for Inhalation Solution) for the Treatment of Chronic Lung Infections in Patients with Cystic Fibrosis: An Evidence-based Review." *Core Evidence* 6 (2011): 59. Print.

Appendix 1:
Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	Efficacy Results[2] (CI, p-values)	ARR / NNT	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1. Ratjen et al. 2010[8]. RCT, OL, MC	1. TIS 300mg/5ml x 28 days n=45 2. TIS 300mg/5ml x 56 days n=43	• ≥ 6 months old • Confirmed CF • First/early PA infection (new detection of PA after negative cultures for ≥ 1 yr and ≥ 4 negative cultures available or up to 2 yrs with 4 negative cultures in the absence of anti-pseudomonal treatment	Median time to recurrence of any strain of PA: 28 day group: 26.12 months 56 day group: 25.82 months HR 0.81; 95% CI 0.37 to 1.75 Difference: 0.3 months 95% CI (0.37,2.75) P=0.593	N/A	Treatment emergent adverse events: 28 day group: 73% 56 day group: 58% Serious adverse events: 28 day group: 14% 56 day group: 12% P-values not reported	N/A	Quality Rating: Poor **Internal Validity: RoB** Selection: The number of subjects analyzed was lower than investigators initially planned. Unclear on generation of randomization sequence. Performance: This was an open-label study, increasing the risk of bias. Good adherence in both groups. The comparato used of TIS for 56 days is not standard treatment or an indicated length of therapy in CF. Detection: Patient's selected in routine clinic visits with positive P. aeruginosa diagnostic test causing possible increased diagnostic interventions. Attrition: Patients who received at least one dose of the study medication were included in the analysis, however, if there was no PA eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications, patients were excluded from analysis. Although 88 patients were randomized, only 65 were included in the efficacy analysis. **External Validity:** Recruitment: Only included patients who regularly attended outpatient clinic appointments. Patient Characteristics: Appropriate Setting: Clinic Setting Outcomes: Microbiological outcome and not clinical outcome used as primary endpoint

2. Retsch-Bogart et al.[9] 2009 (AIR-CF1) Phase 3, RCT, DB, MC	1. AZLI 75mg TID x 28 days n=80 2. Placebo (PBO) n=84	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥25% to ≤75% of predicted • No antipseudomonals within 4 weeks	Δ in CFQ-R score: Day 28 treatment difference: 9.7 points 95% CI (4.3, 5.1) P<0.001 Day 28 mean FEV_1 (% change from baseline) AZLI: 7.9% PBO: -2.4% Diff: 10.3%; 95% CI (6.3-14.3) P<0.001 Hospitalizations AZLI: 5% PBO: 14% P=0.064	N/A N/A N/A	Productive cough: AZLI: 10 (12.5%) PBO: 21 (25%) P=0.047 Incidence of all other adverse events was similar between treatment groups.	ARR: 12.5% NNT: 8	Quality Rating: Fair **Internal Validity: RoB** Selection: Computer generation central randomization schedule, unclear concealment of allocation. Slightly older mean age in placebo group. Performance: Short term efficacy measured (1 cycle of treatment), double-blinded Detection: Unclear blinding of evaluators. Attrition: Efficacy and safety analyses included all randomly assigned patients receiving one or more doses of AZLI/placebo. FEV1 and CFQ-R analyses used the last-observation-carried-forward convention. 84% of patients completed treatment and only 75% of patients completed follow-up **External Validity:** Recruitment: N/A Patient Characteristics: Patients included in this trial were receiving lower doses of maintenance therapy than recommended in clinical guidelines. They had received fewer courses of TIS during the previous year (mean 1.8 compared to 5.3 in previous clinical trials), and fewer patients were using dornase alfa (65% vs 85% in other trials), and none had received azithromycin. This may have impacted patient intolerance to available therapies, lack of clinical response to specific therapies, clinician and patient preferences, or difficulty of obtaining drugs. Setting: International sites; 63% in the US and Canada Outcomes: Treatment difference was larger than the 5 point minimal clinically important difference previously determined, but used primary endpoint that is subjective based on patient ratings.

McCoy et al.[10] 2008 (AIR-CF2) Phase 3, RCT, DB, MC	1. AZLI 75mg BID x 28 days n=69 2. AZLI 75mg TID x 28 days n=66 3. Matching PBO n=76	• ≥6 yrs old • Cystic fibrosis • PA infection requiring ≥3 courses of TIS within the previous year	<u>Median time to need antipseudomonal antibacterials:</u> AZLI: 92 days PBO: 71 days Diff: 21 days P=0.007	NA	Treatment-emergent adverse events were comparable; differences were not statistically significant.	NA	Quality rating: Fair **Internal Validity: RoB** <u>Selection:</u> The proportion of patients younger than 18 years in the placebo group (15.8%) was smaller than that in the AZLI-pooled group (25.2%), adding potential bias as a higher percentage of patients >18 y/o are pseudomonas positive.. Unclear information regarding randomization sequence generation and allocation concealment. <u>Performance:</u> High dosing compliance, double blinded <u>Detection:</u> Unclear blinding of evaluators. <u>Attrition:</u> Efficacy and safety analyses included all randomly assigned patients receiving one or more 1 doses of AZLI/placebo. CFQ-R and FEV1 efficacy analyses used the last observation carried forward convention. **External Validity:** <u>Recruitment: N/A</u> <u>Patient Characteristics:</u> Only patients who had 3 or more courses of tobramycin inhalation solution within the previous year <u>Setting:</u> All study patients completed a course of tobramycin inhalation prior to starting aztreonam inhalation <u>Outcomes:</u> Primary endpoint depended on clinician judgment/patient report of symptoms. The prespecified statistical plan compared subjects who received AZLI with those who didn't, but there was not sufficient power to compare dosage regimens. (DRUGS) Results from treatment and placebo groups were pooled.

4.Wainwright et al.[11] 2011 (AIR-CF4) RCT, DB, MC	1. AZLI 75mg TID n=76 2. PBO n=81 x28 days	• ≥6 yrs old • Cystic fibrosis • Positive for PA on throat swab or sputum culture • FEV_1 ≥75% of predicted • No symptoms of pulmonary exacerbation w/in 7 days of baseline	Δ in CFQ-R score: AZLI: 3.22 PBO: 1.41 Diff: 1.8 points, 95% CI(-2.83,6.44) P=0.443	NA	Serious adverse events: AZLI: 11.8% PBO: 3.7% Difference: 8.1% P=0.073 None were considered treatment-related	NA	Quality rating: Fair **Internal Validity: RoB** Selection: Unclear information regarding randomization sequence generation and allocation concealment. Performance: Double-blinded Detection: Unclear blinding of evaluators. Attrition: low attrition rate, ITT analysis using all patients receiving at least 1 dose of drug **External Validity:** Recruitment: N/A Patient Characteristics: Included patients with milder impairment of lung function than previous trials (FEV1 > 75%). Setting: Appropriate Outcomes: This study did not meet its primary endpoint. Authors suggest that the sensitivity of the CFQ-RSS is not sufficient for patients with modest symptoms at baseline, or the study may not have been adequately powered to detect a change.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, MC=mulitcentre, OL=open label.
[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
[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), RoB=risk of bias

Appendix 2: Drug Information

Pharmacology:

Tobramycin[1]	Aztreonam[2]	Dornase alfa[3]
An aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelop, and eventual cell death.	A beta-lactam antibiotic that exhibits activity *in vitro* against Gram-negative pathogens including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis and death of the cell.	A deoxyribonuclease (DNA) enzyme genetically engineered from Chinese Hamster Ovary cells which selectively cleaves DNA of the viscous mucous in cystic fibrosis patients. This reduces viscosity and improves airflow, potentially decreasing the risk of bacterial infection.

Pharmacokinetics:

Table 1. Pharmacokinetic comparison

Parameters	Tobramycin[1]	Aztreonam[2]	Dornase alpha[3,16]
Protein Binding		56%	
Half-life (h)	2 hrs (for IV administration)	2.1 hrs	Unknown
Metabolism		Hepatic (IM administration, minor)	Unknown
Elimination	Renal/expectorated sputum	Renal (10%)	Unknown
Renal Dose Adjustment	None listed	None	None listed
Hepatic Dose Adjustment	None listed	None	None listed
Food effect on pharmacokinetics	None listed	None	None listed
Mean Sputum Concentration	1237 mcg/g 10 minutes after dose	726mcg/g 10 minutes after dose	3 µg/mL
Mean Plasma Concentration	0.95mcg/mL 1 hour after dose	0.59 mcg/mL 1 hour after dose	
Mean sputum concentration 2 hours following inhalation			0.6 µg/mL
Concentration following bronchoalveolar lavage fluid obtained within 90 minutes of first dose in patient 3 months to 10 years			0.007 to 1.8 µg/mL
Over an average of 14 days of doses, serum DNase concentrations (mean ± SD) increase			Patients 3 months to <5 years: 1.3 ± 1.3 ng/mL Patients 5 to ≤ 10 years 0.8 ±

			1.2 ng/mL

Contraindications/warnings

Tobramycin[1]

- **Contraindication:** Patients with a known hypersensitivity to any aminoglycoside.
- **Warnings:**
  - **General:** Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.
  - **Ototoxicity:** Ototoxicity, as measured by complaints of hearing loss or by audimetric evaluations, did not occur with tobramycin therapy during clinical studies. However, transient tinnitus occurred in eight tobramycin-treated patients versus no placebo patients in the clinical studies. Onset of tinnitus warrants caution. In post-marketing experience, patients receiving tobramycin have reported hearing loss.
  - **Nephrotoxicity:** Nephrotoxicity was not seen in clinical trials with tobramycin but has been associated with aminoglycosides as a class. If nephrotoxicity occurs, tobramycin should be discontinued until serum concentrations fall below 2 mcg/mL.
  - **Muscular Disorders:** Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
  - **Bronchospasm:** Bronchospasm can occur with inhalation of tobramycin. In clinical studies, changes in FEV_1 measured after the inhaled dose were similar in the tobramycin and placebo groups.

Aztreonam[2]

- **Contraindication:** Patients with a known allergy to aztreonam.
- **Warnings:**
  - **Allergic reactions:** Severe allergic reactions have been reported following administration of aztreonam for injection in patients with no known history of exposure to aztreonam. If an allergic reaction occurs, stop administration and initiate treatment as appropriate. Caution is advised when administering aztreonam to patients if they have a history of beta-lactam allergy, although patients with a known beta-lactam allergy have received aztreonam in clinical trials and no severe allergic reactions were reported.
  - **Bronchospasm:** Bronchospasm is a complication associated with nebulized therapies. Reduction of 15% or more in FEV_1 immediately following administration of study medication after pretreatment with a bronchodilator was observed in 3% of patients treated with aztreonam.
  - **Decreases in FEV_1 after 28-day treatment cycle:** In clinical trials, patients with increases in FEV_1 during a 28-day course of aztreonam were sometimes treated for pulmonary exacerbations when FEV_1 declined after the treatment period. Consider a patient's baseline FEV_1 measured prior to aztreonam therapy and the presence of other symptoms when evaluating whether post-treatment changes in FEV_1 are caused by a pulmonary exacerbation.

- **Development of drug-resistant bacteria:** Prescribing aztreonam in the absence of known *Pseudomonas aeruginosa* infection in patients with CF is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.

Dornase alpha[3]

- **Contraindication:** Patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.
- **Warnings:**
  - **Decreased pulmonary function** of less than 40% of normal. It does not significantly reduce the risk of respiratory infections that require intravenous antibiotics. Safety and efficacy studies have not been conducted for daily administration for greater than 1 year.

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

Abbreviated Class Update
Bone Metabolism Agents for Osteoporosis or Paget's Disease

Month/Year of Review: August 2012 **Search End Date:** May 2012 (Week 5)

Current Status of PDL Class:

- Preferred Agents: ALENDRONATE, ALENDRONATE /VITAMIN D3, IBANDRONATE TABLET
- Non Preferred: CALCITONIN INH, CALCITONIN SQ/IM, ETIDRONATE, IBANDRONATE (IV), RISEDRONATE, RISDRONATE DR, TERIPARATIDE SQ, RALOXIFENE, DENOSUMAB (PENDING REVIEW), ZOLEDRONIC ACID IV (PENDING REVIEW), TILUDRONATE (PENDING REVIEW)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of bone metabolism agents?
- Are denosumab (2010), zoledronic acid (2001) or tiludronate (1997) more effective or safer for the treatment of osteoporosis or Paget's Disease than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- The comparative efficacy and safety of treatments has not been assessed for men with osteoporosis.
- There is high strength evidence that specific bisphosphonates (zoledronic acid, risedronate, alendronate) and denosumab reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. No other drugs reduce all three fracture risks.
- There is insufficient or no data to distinguish superiority of any bisphosphonate, or bisphosphonates superior to other drugs for reduction in vertebral fracture risk in postmenopausal women. Evidence for etidronate, ibandronate, pamidronate have not been shown to reduce non-vertebral fractures in post-menopausal women. There is insufficient evidence for tilundronate for osteoporosis treatment.
- There was high strength evidence that the incidence of osteonecrosis of the jaw in patients taking bisphosphonates was low (<1-28 cases in 100,000 person years). Low strength evidence associated bisphosphonate use with atypical femur fractures and insufficient evidence associated bisphosphonate use to esophageal cancer and atrial fibrillation.
- There is high strength evidence of increased risk of infection with denosumab compared to placebo.
- There is high strength evidence that raloxifene increases the odds of pulmonary embolism, thromboembolic events and cerebrovascular accidents compared to placebo.
- Nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate are ibandronate) are considered first-line therapy for Paget's Disease treatment. There is insufficient evidence to distinguish superiority of any nitrogen-containing bisphosphonate.

Recommendations:

- Consider inclusion of denosumab, zoledronic acid, risedronate, alendronate in various routes and dosing schedules for osteoporosis treatment based upon cost.
- Include at least one nitrogen-containing bisphosphonate for Paget's Disease **(**zoledronic acid, pamidronate, risedronate, alendronate or ibandronate).
- Make calcitonin, raloxefene and teriparatide non-preferred due to limited evidence to reduce non-vertebral and hip fracture risk in post-menopausal women. Calcitonin has limited evidence for Paget's Disease.
- Make tiludronate non-preferred as it is only indicated for Paget's, is not a nitrogen containing bisphosphonate and it has insufficient evidence for osteoporosis treatment.
- Consider a RetroDUR intervention of bisphosponates to notify clinicians to re-evaluate patient FRAX score after 5 years of therapy.

Reason for Review:

In May 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the drugs used for osteoporosis. A Provider Synergies Review from January 2010 was the evidence source.[1] The previous review was limited to self-administered drugs with a Food and Drug Administration (FDA) indication for osteoporosis. This review expands to physician administered drugs with indications for osteoporosis or Paget's Disease. It excludes drugs only indicated for oncology related indications (e.g. gallium nitrate & pamidronate).

Previous HRC Conclusions (May 2010):

- Evidence does not support a difference in efficacy/effectiveness but calcitonin is not considered first line treatment.
- Evidence does not support a difference in harms/adverse events but teriparatide (Black box warning) is not considered first line treatment.
- Recommend inclusion of at least one member of the bisphosphonates as primary therapy with accommodation for different dosage regimens to improve compliance.
- Consider prior authorization requirements for calcitonin, raloxifene, and teriparatide.

Background:

Osteoporosis is a skeletal disease of decreasing bone mass resulting in diminished bone strength and increased risk of fractures.[2] Multiple mechanisms are responsible including old age, sex steroid deficiency, lipid oxidation, decreased physical activity and use of glucocorticoids. Throughout life, older bone is resorbed by osteoclasts and replaced with new bone made by osteoblasts.[2] This process is known as remodeling and is orchestrated and targeted to a particular site that is in need for repair by osteocytes.[2] When this system is out of balance, bone loss occurs.[3] In the past decade, the master signals that regulate this process have been defined. The receptor activator of nuclear factor kappa-B ligand (RANKL) is a key signal that increases bone loss and has become a prime target for the treatment of osteoporosis.[4]

Bone mineral density (BMD) assessed with dual x-ray absorptiometry (DXA) is a surrogate marker used to diagnose osteoporosis. A patient is considered to have osteoporosis with a BMD T-score of less than 2.5 standard deviations below the average of a young adult.[4] BMD can be used in conjunction with the World Health Organization fracture-risk assessment tool (FRAX) to estimate an individual's 10-year risk of sustaining a hip

fracture or other osteoporotic fractures.[4] The life-time fracture risk of a patient with osteoporosis is as high as 40% and fractures of the hip, spine or wrist the most common locations.[4] The National Osteoporosis Foundation estimates more than 10 million people have osteoporosis with 50% of Caucasian women with a lifetime risk of fracture and 20% of men.[3] The primary goal of osteoporosis management is to reduce fracture risk.

Drugs to treat osteoporosis fall into two groups, the anti-resorptive drugs, which slow down bone resorption, and anabolic drugs, which stimulate bone formation. The anti-resorptive drugs include bisphosphonates, raloxifene, calcitonin and the new IgG2 monoclonal antibody, denusomab, which suppresses the RANKL pathway. Parathyroid hormone increases bone formation and is the only anabolic drug. All drugs require adequate serum levels of calcium and vitamin D for optimum effect. Bisphosphonates are considered first line[5] therapy but short-term tolerability and potential long-term risk of atypical femur fracture, osteonecrosis of the jaw and esophageal cancer have left patients and clinicians looking for other options.[6]

Paget's Disease is a disorder of bone metabolism that includes an accelerated rate of bone remodeling, resulting in overgrowth of bone at selected sites and impaired integrity of affected bone.[7] It is a fairly common finding in aging bone, with estimates ranging from 2.3 - 9% in older patients within affected populations.[8] Many patients with Paget's Disease are asymptomatic but others exhibit pain and deformities.[7] Fractures, bone tumors, neurologic disease, cardiac disease, and abnormalities in calcium and phosphate balance can also occur.[7] The goals of treatment are to reduce pain, normalize bone remodeling and slow disease progression.[7] The newer nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate and ibandronate) are first-line for the initial treatment of Paget disease.

Methods:

A Medline literature search ending May 2012 Week 5 for meta-analyses or randomized active-controlled trials (RCT's) comparing bisphosphonates to each other or to other osteoporosis drugs for the treatment of osteoporosis or Paget's Disease was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches the following were reviewed: three systematic reviews of osteoporosis treatments;[9 10 11] one systematic review of Paget treatment;[7] two systematic reviews of denosumab; [12] two denosumab monographs; [13 14] one clinical treatment guideline;[15] and FDA safety warnings.[6]

Systematic Reviews:

<u>ARHQ</u>

The AHRQ[9] updated the comparative effectiveness review of treatments to prevent fractures in men and women with osteoporosis in January 2012 with a search end date of March 2011. It compared the effectiveness and safety of bisphosphonates, raloxefene, hormone replacement therapy, teriparatide, calcium, vitamin D, exercise and denosumab for the prevention or treatment of osteoporosis. The population was limited to adults with low bone density or osteoporosis (excluding those with Paget's disease, cancer, other diseases of bone metabolism, or those on drugs causing

osteoporosis). The outcomes of interest were vertebral, hip and/or total fractures unless the study specifically noted lack of power or reported fractures only as an adverse event. Study duration was a minimum of 6 months. Only RCTs were included and were assessed for quality.

The comparative efficacy of treatments has not been assessed among men with osteoporosis.

There was high strength evidence that bisphosphonates and denosumab reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. There was high strength evidence that teriparatide and raloxifene reduce the risk of vertebral fractures in post-menopausal women. Raloxifene was shown to be not effective in reducing the risk of hip or nonvertebral fractures in post-menopausal women. There was moderate evidence that hormone replacement does not prevent fractures in post-menopausal women with established osteoporosis. There was low to moderate evidence that the effect of calcium alone and vitamin D alone on fracture risk is uncertain. Data were insufficient to distinguish superiority of any bisphosphonate. There was insufficient evidence comparing bisphosphonates to calcium, teriparatide or raloxifene.

There was high strength evidence that the incidence of osteonecrosis of the jaw in patients taking bisphosphonates was low (<1-28 cases in 100,000 person years). Low strength evidence associated bisphosphonate use with atypical femur fractures and insufficient evidence associated bisphosphonate use to esophageal cancer and atrial fibrillation. There is high strength evidence that alendronate users have increased risk of mild upper gastrointestinal events compared to denosumab. There is high strength evidence of increased risk of infection with denosumab. There is high strength evidence that raloxifene increases the odds of pulmonary embolism, thromboembolic events and cerebrovascular accidents compared to placebo.

CADTH

CADTH[10] evaluated the clinical effectiveness and harms of denosumab, raloxifene, and zoledronic acid in postmenopausal women with osteoporosis. No active-controlled RCTs were identified. Denosumab, zoledronic acid, and raloxifene were all effective in reducing the risk of vertebral fractures, both clinically and radiographically assessed, after 36 months of treatment compared with placebo. Denosumab and zoledronic acid reduced the risk of multiple vertebral fractures, hip fractures, and non-vertebral fractures. There was limited evidence for raloxifene on these outcomes, suggesting it may not be effective in preventing non-vertebral fractures, including hip fractures. The proportion of patients who died during the trials, as well as the overall incidence of serious adverse events, was not significantly different between each active drug and placebo. However, denosumab was associated with a higher incidence of cellulitis, zoledronic acid with atrial fibrillation, and raloxifene with venous thromboembolism and hot flushes compared with placebo.

Clinical Evidence

Clinical Evidence updated the review *Fracture prevention in postmenopausal women* in September 2010.[11] Key findings were:

- *Alendronate, risedronate, zoledronate, denosumab, and parathyroid hormone reduce vertebral and non-vertebral fractures compared with placebo.*
  - *Etidronate, ibandronate, pamidronate, and raloxifene reduce vertebral fractures, but have not been shown to reduce non-vertebral fractures.*
  - *Raloxifene protects against breast cancer, but increases venous thromboembolic events and stroke compared with placebo.*

- *Calcitonin may reduce vertebral fractures over 1 to 5 years, but has not been shown to reduce non-vertebral fractures.*

- *CAUTION: Hormone replacement therapy may reduce fractures, but it increases the risk of breast cancer and cardiovascular events. The risks of adverse effects of treatment are thought to outweigh the beneficial effects of hormone replacement therapy in prevention of fractures.*
- *Combined calcium plus vitamin D or vitamin D analogues alone may reduce vertebral and non-vertebral fractures, but trials have given inconclusive results.*
- *Monotherapy with calcium or vitamin D has not been shown to reduce fractures, and calcium alone may potentially be associated with an increased risk of cardiovascular adverse effects.*

UpToDate

The nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, risedronate, alendronate are ibandronate) are the primary agents used for the initial treatment of Paget disease. UpToDate[7] summarized the major trials comparing the nitrogen-containing bisphosphonates. Normalization or reduction in serum alkaline phosphatase levels have been the primary end points in clinical trials of antipagetic therapies, as surrogate markers for reduction in increased bone turnover. In two identical, six-month trials involving a total of 357 patients, zoledronic acid patients achieved the primary endpoint more often than risedronate patients (96% versus 74%).[16 17] In a two-year randomized, open label trial of 72 patients, alendronate achieved biochemical remission, defined as both the serum alkaline phosphatase and urine deoxypyridinoline/creatinine ratio being in the normal range, more often than pamidronate (86% versus 56%) after one year.[18] However, the results were affected by whether or not the patients had previously been treated with pamidronate. In the 44 previously untreated patients, the biochemical remission rate of was similar (91% versus 86%). A third trial included 120 patients and at six months, zoledronic acid was associated with higher rates of both the biochemical response (97% versus 45%) and normalization of serum alkaline phosphatase (93% versus 35%) compared to pamidronate.[19] The comparisons were limited by small numbers of patients, short duration or lack of blinding and the use of surrogate endpoints. Calcitonin is the only other FDA approved drug for the treatment of patients with Paget disease who cannot tolerate bisphosphonates. Subcutaneous calcitonin was evaluated in 85 patients and found that serum alkaline phosphatase or urine hydroxyproline excretions were initially reduced by about 50%.[20] However, these parameters returned to pretreatment levels in 26% of patients and almost all of these patients developed high titer anti-calcitonin antibodies.

Lin, et al

Lin, et al reviewed four RCTs[21 22 23 24] comparing denosumab 60mg subcutaneously every six months to alendronate 70mg orally every week. The studies were systematically identified, assessed for quality and data extracted. The review provided low quality evidence there was no significant difference in fracture risk between the denosumab and alendronate at 1 year [3 studies, fixed-effects OR (95% CI): 1.42 (0.84–2.40), p = 0.19, I2 = 0%]. There was low to very low evidence of no differences in total adverse events, serious adverse events, neoplasms or infections.

CADTH

The Common Drug Review[13] systematically reviewed six denosumab RCTs of post-menopausal women with osteoporosis as determined by low BMD. Only the FREEDOM trial included incidence of new vertebral fracture as a primary outcome. The other five relied on the percentage change in BMD, adherence or percentage change in cortical thickness at distal radius. FREEDOM[25] (N=7,808) was a 36-month double-blind double-dummy parallel-group RCT comparing denosumab 60 mg subcutaneousloy every six months with placebo. In the FREEDOM trial, patients having both a

baseline and at least one follow-up spinal radiograph, the 36-month incidence of radiographically confirmed new vertebral fracture was lower for denosumab (2.3%) compared with placebo (7.2%), absolute risk reduction (ARR): 4.8%, 95% confidence interval (CI), 3.9% to 5.8%. None of the active comparator trials were powered to examine fracture. DECIDE[21] and STAND[22] reported fracture incidence as patient reported adverse events and the frequency of fracture was similar between denosumab and alendronate. Mortality, serious adverse events and withdrawal due to adverse events were similar between denosumab and placebo in the FREEDOM trial, and between denosumab and alendronate in the STAND and DECIDE trials. The Canadian Expert Drug Advisory Committee recommended denosumab coverage for women with postmenopausal osteoporosis for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus (e.g., esophageal stricture or achalasia), and have at least two of the following: age >75 years, a prior fragility fracture or a BMD T-score ≤ -2.5.

VA

The VA Pharmacy Benefits Management Services reviewed denosumab for formulary placement in January 2012.[14] Denosumab's FDA labeled indications are: treatment of postmenopausal women with osteoporosis, treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[26 27] The FREEDOM fracture findings were reported. In addition, denosumab was reported to be noninferior to alendronate, across all surrogate measures and superiority with respect to lumbar spine BMD and distal one third radius. Few men have received denosumab. Data is limited to treatment for bone loss resulting from androgen deprivation therapy and glucocorticoids. Denosumab's adverse effect profile includes increased risk serious events: hypocalcemia, infection, osteonecrosis of the jaw, and dermatologic reactions such as cellulitis, rash, and eczema. Unanswered safety concerns include a risk for cancers and pancreatitis. Common adverse events were back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The VA determined denosumab's place in therapy is as an alternative to zoledronic acid and subcutaneous teriparatide for patients who cannot tolerate an oral bisphosphonate, who have not had a satisfactory response to an oral bisphosphonate, or who have a contraindication to a bisphosphonate (e.g., a creatinine clearance less than 30 or 35 mL/min). Denosumab's advantages include twice yearly administration, a rapid onset of action (similar to zoledronic acid), an increase in BMD at the distal ⅓ radius, and use in patients with renal impairment. The VA lists disadvantages as the risk of serious adverse events, and whether the potential for development of neoplasms and pancreatitis is real, a higher cost.

New Guidelines:

NICE published clinical treatment guidance for denosumab for the prevention of osteoporotic fractures in postmenopausal women in October 2010.[15] The recommendations are:

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

- *who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments and*
- *who have a combination of T-score1, age and number of independent clinical risk factors for fracture (see section 1.3) as indicated in the following table.*

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	– [a]	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

[a] Treatment with denosumab is not recommended.

Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

Recent FDA warnings:

Bisphosphonates:

The FDA has monitored the bisphosphonates for several safety issues.[6]

In September 2011 the zoledronic acid label was revised to include a contraindication in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. Kidney failure is a rare, but serious, condition associated with the use of zoledronic acid in patients with a history of or risk factors for renal impairment. Cases of acute renal failure requiring dialysis or having a fatal outcome following zoledronic acid use have been reported to FDA.

In July 2011 the FDA advised that the benefits of oral bisphosphonate drugs in reducing the risk of serious fractures in people with osteoporosis continue to outweigh the potential risks of developing esophageal cancer. There have been conflicting findings from studies evaluating this risk and it is important to note that the risk of this cancer is extremely rare, especially in women.

In October 2010 the FDA clarified recommendations regarding the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis. These fractures are very uncommon (<1% of all hip and femur fractures overall). It is not clear if bisphosphonates are the cause but have been predominantly reported in patients taking bisphosphonates. These atypical fractures may be related to long-term term bisphosphonate use. Specific recommendations are:

- Be aware of the possible risk of atypical subtrochanteric and diaphyseal femur fractures in patients taking bisphosphonates.
- Continue to follow the recommendations in the drug label when prescribing bisphosphonates.
- Discuss the known benefits and potential risks of using bisphosphonates with patients.
- Evaluate any patient who presents with new thigh or groin pain to rule out a femoral fracture.

- Discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.
- Consider periodic reevaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over 5 years.
- Report any adverse events with the use of bisphosphonates to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Denosumab:

Denosumab carries a mandated Risk Management and Mitigation Strategy to inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw, associated with denosumab.

References:

1. Provider Synergies. Bone Resorption Suppression and Related Agents Review. 2010. Available at: http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/ps-2010-01-bone-resorption.pdf. Accessed May 8, 2012.

2. Manolagas SC. Pathogenesis of osteoporosis. 2011. Available at: www.uptodate.com (subscription required). Accessed June 8, 2012.

3. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. *National Osteoporosis Foundation*. 2010. Available at: http://www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf. Accessed May 8, 2012.

4. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. *The Lancet*. 2011;377(9773):1276–1287.

5. The North American Menopause Society. Management of osteoporosis in postmenopausal women. *Menopause*. 2010;17(1):25–54.

6. Research C for DE and. Postmarket Drug Safety Information for Patients and Providers - Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) Information. 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101551.htm. Accessed June 8, 2012.

7. Seton M. Treatment of Paget disease of bone. *Treatment of Paget disease of bon*. 2012. Available at: http:/www.uptodate.com (subscription required). Accessed June 11, 2012.

8. Seton M. Clinical manifestations and diagnosis of Paget disease of bone. *Clinical manifestations and diagnosis of Paget disease of bone*. 2012. Available at: www.uptodate.com (subscription required). Accessed June 12, 2012.

9. Effective Health Care Program. Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. *Agency for Health Research and Quality*. 2012. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/160/1006/CER53_LBD_executivesummary.pdf. Accessed May 8, 2012.

10. Gauthier K, Bai A, Perras C, et al. Denosumab, Raloxifene, and Zoledronic Acid for the Treatment of Postmenopausal Osteoporosis: Clinical Effectiveness and Harms. *Canadian Agency for Drugs and Technologies in Health*. 2012. Available at: http://cadth.ca/media/pdf/tr0001_Osteoporosis_e.pdf. Accessed May 8, 2012.

11. Vestergaard P, Mosekilde L, Langdahl B. Fracture prevention in postmenopausal women. *Clinical Evidence*. 2010. Available at: http://clinicalevidence.bmj.com (subscription required). Accessed May 8, 2012.

12. Lin T, Wang C, Cai X-Z, et al. Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. *International Journal of Clinical Practice*. 2012;66(4):399–408.

13. Canadian Agency for Drugs and Technologies in Health. Common Drug Review - Denosumab. *Canadian Agency for Drugs and Technologies in Health*. 2011. Available at: http://www.cadth.ca/media/cdr/complete/cdr_complete_Prolia_April-1-11.pdf. Accessed May 8, 2012.

14. Semla T. Denosumab (Prolia) Monograph. *US Department of Veterans Affairs*. 2012. Available at: http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Monographs/Denosumab%20(Prolia)%20Monograph.doc. Accessed May 8, 2012.

15. NICE. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. *NHS National Institute for Health and Clinical Excellence*. 2010. Available at: http://www.nice.org.uk/nicemedia/live/13251/51293/51293.pdf. Accessed May 8, 2012.

16. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *New England Journal of Medicine*. 2005;353(9):898–908.

17. Hosking D, Lyles K, Brown JP, et al. Long-Term Control of Bone Turnover in Paget's Disease With Zoledronic Acid and Risedronate. *Journal of Bone and Mineral Research*. 2007;22(1):142–148.

18. Walsh J., Ward L., Stewart G., et al. A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. *Bone*. 2004;34(4):747–754.

19. Merlotti D, Gennari L, Martini G, et al. Comparison of Different Intravenous Bisphosphonate Regimens for Paget's Disease of Bone. *Journal of Bone and Mineral Research*. 2007;22(10):1510–1517. Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1359/jbmr.070704/abstract. Accessed June 11, 2012.

20. Singer FR, Fredericks RS, Minkin C. Salmon calcitonin therapy for paget's disease of bone the problem of acquired clinical resistance. *Arthritis & Rheumatism*. 1980;23(10):1148–1154.

21. Brown JP, Prince RL, Deal C, et al. Comparison of the Effect of Denosumab and Alendronate on BMD and Biochemical Markers of Bone Turnover in Postmenopausal Women With Low Bone Mass: A Randomized, Blinded, Phase 3 Trial. *Journal of Bone and Mineral Research*. 2009;24(1):153–161.

22. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *Journal of Bone and Mineral Research*. 2010;25(1):72–81.

23. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *New England Journal of Medicine*. 2006;354(8):821–831.

24. Seeman E, Delmas P, Hanley D, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *Journal of Bone*. 2010;25(8):1886–94.

25. Cummings SR, San Martin J, McClung MR, et al. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. 2009.

26. Amgen. Prolia Label. *US Food & Drug Administraion*. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125320s5s6lbl.pdf. Accessed May 9, 2012.

27. Amgen. Xgeva Label. *US Food & Drug Administraion*. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125320s0054lbl.pdf. Accessed May 9, 2012.

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 Class Update: Colony Stimulating Factors

Month/Year of Review: September 2012

End date of literature search: July Week 2 2012

Current Status of PDL Class:

- Preferred Agents: FILGRASTIM (NEUPOGEN®), PEGFILGRASTIM (NEULASTA®), SARGRAMOSTIM (LEUKINE®)

Research Questions:

- Does new information change the previous recommendations regarding the efficacy and safety of colony stimulating factors (CSFs)?

Conclusions:

- There is moderate level evidence filgrastim and pegfilgrastim are considered equally efficacious and safe for prophylaxis of febrile neutropenia in patients receiving myelosuppressive chemotherapy for solid or non-myeloid malignancies
- There is moderate level evidence that filgrastim and pegfilgrastim are safe for use for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies
- There is moderate level evidence sargramostim is considered efficacious for prophylaxis of febrile neutropenia in patients receiving chemotherapy receiving myelosuppressive chemotherapy for solid or non-myeloid malignancies, but sargramostim lacks the body of data of other CSFs
- There is insufficient evidence that sargramostim is safe for use for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies
- There is low level evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is efficacious for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy
- There is insufficient evidence that use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is safe for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy
- There is moderate level evidence that use of filgrastim and sargramostim are considered efficacious in speeding engraftment for cancer patients with a peripheral blood stem cell transplant
- There is insufficient evidence that use of pegfilgrastim is considered efficacious in speeding engraftment for cancer patients with a peripheral blood stem cell transplant
- There is insufficient evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) is considered safe in speeding engraftment for cancer patients with a peripheral blood stem cell transplant

- There is low level evidence supporting off-label use of CSFs for hepatitis C treatment-induced neutropenia as more effective than dose reduction in improving sustained virologic response

Recommendations:

- Continue to list all drugs as preferred due to lack of comparative evidence for indications other than for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies.
- Evaluate use of CSFs for hepatitis C and if inappropriate use is noted, bring back recommendation of prior authorization to the committee for consideration

Reason for Review:

In 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness of the CSFs. A December 2009 Provider Synergies Review was used as the evidence source.[1] Since this review, several systematic reviews and randomized controlled trials (RCTs) have been published, as well as updated guidelines from the National Comprehensive Cancer Network (NCCN), the European Organization for Research and Treatment of Cancer (EORTC), the European Association of the Study of the Liver (EAOSL), the Department of Veteran Affairs (VA), and the Canadian Agency for Drugs and Technologies in Health (CADTH).

Previous HRC Conclusions (2010):

- Evidence does not support a difference in efficacy or safety
- Recommend all agents without restriction

Background:

Three CSFs are available in the US: filgrastim, pegfilgrastim, and sargramostim. All are recombinant hematopoietic growth factors[2]; but differ in the cell lines they stimulate. Filgrastim and pegfilgrastim are granulocyte-colony stimulating factors which induce proliferation of neutrophils.[3-4] Sargramostim is a granulocyte macrophage-colony stimulating factor which stimulates the proliferation of neutrophil, monocyte, red-blood cell and platelet precursors.[5] Pegfilgrastim is a pegylated formulation of filgrastim and is dosed subcutaneously (SQ) one time only.[6] Filgrastim and sargramostim are available in SQ and intravenous (IV) formulations and are given once daily for SQ formulations or on multiple days by IV infusion.[7-8] All CSFs promote various responses from their target cells including activation and division, as well as some end-cell functions.[3-5]

Filgrastim is used to prevent and treat febrile neutropenia (FN), typically in patients with lymphomas, myelomas or solid tumors. It is indicated for FN prophylaxis in patients with non-myeloid malignancies undergoing myelosuppressive or myeloablative chemotherapy followed by bone marrow transplantation; and in acute myeloid leukemia (AML) patients receiving chemotherapy. It is used to treat non-cancer related Neutropenic disorder. Filgrastim is also indicated to speed myeloid recovery (engraftment) in harvesting of peripheral blood progenitor cells for transplant.[7] Pegfilgrastim is indicated for FN prophylaxis in patients with non-myeloid malignancies receiving chemotherapy, but is also used off-label for filgrastim's other indications: in AML patients receiving chemotherapy, Neutropenic disorder, and for engraftment after peripheral blood stem cell transplant.[6]

Like filgrastim and pegfilgrastim, sargramostim is most often used in patients with cancer to prevent FN but in a different way. Although it is indicated for use for FN prophylaxis in patients with AML, it is not approved for this use in patients with non-myeloid malignancies. Instead, sargramostim is used primarily to speed engraftment after allogeneic or autologous bone marrow transplantation or following the harvesting of peripheral blood progenitor cells for transplant or

graft.[8] Quick myeloid recovery (engraftment) in patients undergoing a bone marrow or peripheral blood progenitor cell transplant reduces the risk or duration of FN in both situations.[9]

FN can have a dose-limiting effect on chemotherapy, resulting in interruption of therapy, hospitalizations and intensive antibiotics.[9] CSFs are not used prophylactically in all patients due to safety concerns regarding the risk of developing secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).[3] In addition, treating off-label chemotherapy-induced FN in patients with leukemia or MDS is controversial because of the increased risk of stimulating the cancerous cell lines.[9] CSFs are also used off-label for neutropenia induced from Hepatitis C (HCV) treatment or from AIDs, aplastic anemia, and Crohn's disease.[6-8] Please see Appendix 1 for all CSF indications.

Previously, the HRC concluded no difference in effectiveness or safety of filgrastim, pegfilgrastim, and sargramostim. All three were recommended for PDL placement without restriction.

Methods:
A Medline literature search was conducted beginning 2009 and ending July week 2 2012 for new systematic reviews and RCT's comparing filgrastim, pegfilgrastim or sargramostim for the treatment of neutropenia and peripheral blood progenitor cells transplantation. 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. RCTs will be emphasized only if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, five new RCTs and six systematic reviews regarding the use of CSFs in cancer patients were identified; as were one new systematic review and RCT looking at CSF use during HCV treatment. All are included here. Five relevant guidelines from the NCCN, EORTC, EAOSL, VA, and CADTH were updated since the previous HRC review. Recommendations from the guidelines are listed here. Finally, one FDA Safety Alert was released for filgrastim. No new evidence was found regarding use in chronic neutropenic disorder, bone marrow transplant, or non-cancer related peripheral blood progenitor cell transplant, or any off-label indications with the exception of HCV treatment-induced neutropenia. Please see Appendix 1 for all CSF indications.

For use in chemotherapy-induced neutropenia:

Systematic Reviews:
Cooper et al[10] performed a poor-to-fair quality systematic review to look at the effectiveness of CSFs in reducing incidence of FN in adults with lymphoma or solid tumor undergoing myelosuppressive chemotherapy. Twenty studies were included with filgrastim, pegfilgrastim and lenograstim (CSF not available in US) used as prophylaxis compared with each other or placebo to prevent FN. Quality of the individual studies was not addressed. All three medications significantly reduced the risk of FN compared with placebo: pegfilgrastim RR 0.30 (95% CI 0.14-0.65), filgrastim RR 0.57 (95% CI 0.48-0.69). Five studies compared pegfilgrastim vs. filgrastim and demonstrated that pegfilgrastim reduced the risk of FN compared to filgrastim RR 0.66 (95% CI 0.44-0.98). Analysis for safety of CSF use was not included.

A poor-to-fair quality meta-analysis by Kruderer[11] also looked at the effectiveness of CSFs in reducing incidence of FN, infection-related mortality, and early mortality in adults with lymphoma or solid tumor undergoing chemotherapy. Fourteen of the 17 RCTs included in this systematic review were also used in the

above review. Quality assessment of individual trials was performed but not included in the published review. As with Cooper et al, this analysis found that both pegfilgrastim RR 0.077 (95% CI 0.034-0.175) and filgrastim RR 0.614 (95% CI 0.528-0.718) reduced the risk of FN versus placebo. Both medications decreased the risk of early mortality compared to placebo: pegfilgrastim RR 0.359 (95% CI .130-0.988), filgrastim RR 0.603 (95% CI 0.41-0.887). Only filgrastim decreased the risk of infection-related mortality: RR 0.529 (95% CI 0.304-.921). Pegfilgrastim and filgrastim were not compared with one another. Bone pain, the most common CSF side effect was also examined in the review. Bone or musculoskeletal pain was more common in CSF than placebo patients: RR 4.023 (95% CI 1.56-7.52).

Dynamed[3] reported new level-2 (mid-level) evidence that CSFs use was associated with reduced mortality but increased risk of AML or MDS in patients receiving chemotherapy for solid tumor or lymphoma. The fair quality systematic review by Lyman et al[12] analyzed 25 RCTs that used either filgrastim or lenograstim versus placebo in adult patients with lymphoma or solid tumors. Unlike the two reviews discussed above, this analysis included only studies with data on AML/MDS rates after CSFs treatment. The review found that patients treated with CSFs had a higher risk of developing a secondary malignancy: RR 1.92 (95%CI 1.19-3.07). CSF treatment was associated with a decrease in risk, however, for all-cause mortality: RR 0.897 (95% CI 0.857-0.938). Differences between lenograstim and filgrastim were not analyzed.

Heuser et al[13] examined the safety and efficacy of using CSFs agents prophylactically in patients with AML. Fourteen RCTs using filgrastim, pegfilgrastim, or sargramostim were included in this fair quality systematic review. Individual trial quality was uneven and there was significant heterogeneity between trials. Reviewers found using a CSF compared with placebo significantly decreased the time to engraftment (-4.13 days, 95% CI-4.23, -4.04) and length of hospitalization (-2.06 days, 95% CI-2.36, -1.76), but made no difference in infection related mortality. Other outcomes, rates of remission, disease-free and overall survival, were not significantly different between CSF and placebo patients. Analysis of CSF adverse events was not included.

Two new systematic reviews available from the Cochrane Collaboration examined the practice of giving CSFs to patients with leukemia. Sasse et al[14] found children with acute lymphoblastic leukemia (ALL) given prophylactic filgrastim or sargramostim had reduced incidence of FN episodes compared with placebo: RR 0.63 (CI 0.46-0.85). Prophylactic CSFs also significantly reduced the time to engraftment (-3.44 days, 95% CI -4.76, -2.12), length of hospitalization (-1.58 days, 95% CI -3.00, -0.15) and incidence of infections (RR 0.56, 95%CI 0.39-0.80). Although the authors intended to analyze adverse events, they were unable to due to a lack of uniformity in the side effects reported in the trials. This was a good quality review but with the limitation of a small number of heterogeneous studies decreasing the level of evidence.

The second Cochrane review, Gurion et al[15], looked at the safety outcomes of overall survival and all-cause mortality in AML patients given prophylactic filgrastim or sargramostim post-chemotherapy. Secondary outcomes included number of patients achieving complete remission, disease-free survival, incidence of FN and number of fungal and bacterial infections. No difference was found between treatment and placebo groups for any of the outcomes. There were slightly more discontinuations due to adverse events in the CSF vs. placebo groups (RR 1.33, 95% CI 1.00 -1.76). This was a good quality review but with the limitation of inclusion of a large number of studies with a high risk of bias.

A protocol[16] has been published from the Cochrane Collaboration to examine the use of CSFs in MDS. No date is given for expected completion.

New Guidelines:

European Organization for Research and Treatment of Cancer (EORTC) [17] *November 2010*

This guideline does not include sargramostim and is not intended for neutropenia due to leukemia, myelodysplastic syndrome, or HIV. Recommendations were graded based on the level of evidence. Grade A recommendations were taken from level I: evidence obtained from high quality sources (meta analyses, large RCTs). Grade B and C recommendations were consistent (B) or inconsistent (C) with findings from evidence levels II, III and IV: evidence obtained for level II was from at least one well-designed experimental or controlled trial, for level III from non-controlled experimental or well-designed observational studies, and for level IV from comparative, correlation, or case studies. Grade D recommendations have little to no systematic empirical evidence support.

- Patients' risk factors for FN should be considered evaluated prior to chemotherapy (Grade B).
- CSFs should be considered in patients with risk factors and chemotherapy regimens associated with a >10% increased risk of FN (Grade A/B).
- CSFs are recommended in patients with risk factors and chemotherapy regimens associated with a >20% increased risk of FN (Grade A/B).
- In situations where dose-dense /intensive chemotherapy strategies have survival benefits, prophylactic CSFs should be used (Grade A).
- If reductions in chemotherapy dose intensity/density are known to be associated with poor prognosis, primary CSF prophylaxis may be used to maintain chemotherapy (Grade A).
- For patients with solid tumors and ongoing FN, CSFs are indicated only in special situations: these are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infections, such as severe sepsis or septic shock (Grade B).
- Filgrastim and pegfilgrastim have demonstrated clinical efficacy and either of these agents should be used to prevent FN, where indicated. (Grade A).

The National Comprehensive Cancer Network (NCCN) [18] *Updated January 2012*

This guideline covers chemotherapy induced FN in patients with non-myeloid or solid tumors. Recommendations for patients with AML or MDS are covered in separate guidelines.[19-20] Recommendations are categorized as 1,2A, 2B, or 3. Category 1 is based upon high level evidence and uniform NCCN consensus; category 2A is based on lower-level evidence and uniform NCCN consensus; category 2B is based on lower-level evidence and some NCCN consensus; and a category 3 recommendation is based on any type of evidence and NCCN disagreement as the appropriateness of the intervention.

- Filgrastim and pegfilgrastim are considered to have equal efficacy (Category 1 recommendation for use).
- Due to the lack of evidence to support use in patients with non-myeloid or solid tumors, sargramostim is given a category 2b recommendation for use.
- Patients are stratified by a combination of personal risk factors (age, prior FN, or chemo) and chemotherapy regimen.
- Patients with risk of 10-20% of developing FN are considered for CSFs therapy (Category 2A recommendation).
- Patients with a risk of >20% of developing FN are recommended to start prophylactic CSFs (Category 2A recommendation).
- Patients who develop NF while on a CSF should continue the CSF (Category 2A recommendation).
- Patients without prophylactic FN who develop FN should be considered for CSF therapy only if they have risk factors (age, prior FN, severe infection or neutropenia) (Category 2A recommendation).
- CSFs are not recommended for prophylaxis in patients with MDS or AML[19-20] (Category 2A recommendations).

Randomized Controlled Trials:

The following RCTs were published after the systematic reviews included above. They were not rated for quality. RCT results supported the systematic review evidence.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results

Sebban C, et al. Eur J Cancer. 2012;48(5):713–720[21]	Pegfilgrastim vs. filgrastim	Adults with lymphoma or myeloma undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Mean duration of febrile neutropenia; safety and cost outcomes also examined	No difference found between the two for primary clinical and safety outcomes; pegfilgrastim was rated as more cost-effective
Beksac M, et al. Leukemia Research. 2011;35(3):340–345[22]	Filgrastim vs. placebo	Adults with acute myeloid leukemia (AML) undergoing high-dose chemotherapy	Short and long term differences in FN, hospitalization, antibiotic therapy and 3 years overall survival	No difference found between the two groups for any clinical outcome
Gerds A, et al. Biol. Blood Marrow Transplant. 2010;16(5):678–685[23]	Filgrastim vs. pegfilgrastim	Adults with lymphoma, myeloma, or solid tumor undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Time to neutrophils engraftment; NF, hospitalizations, transfusions and death were secondary outcomes	No difference found between the two for primary clinical and safety outcomes; pegfilgrastim was rated as more cost-effective
Ladenstein R, et al. J Clin Oncol. 2010;28(21):3516–3524[24]	Prophylactic filgrastim vs. symptom-triggered filgrastim	Children (ages 3-17) with neuroblastoma	Number of NF episodes; days with fever, in hospital, or on antibiotics were secondary outcomes	Prophylactic filgrastim had significantly ($p<0.05$) less FN episodes, days with fever, hospital and antibiotic days
Rifkin R, et al. Clin Lymph Mye Leuk. 2010;10(3):186–191[25]	Filgrastim vs. pegfilgrastim	Adults with lymphoma undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Time to engraftment	No difference found between the two for the primary outcome
Castagna L, et al. Ann Oncol. 2009;21(7):1482–1485[26]	Filgrastim vs. pegfilgrastim	Adults with lymphoma, myeloma, or solid tumor undergoing high-dose chemotherapy followed by peripheral blood progenitor transplantation	Duration of neutropenia; time to neutrophils engraftment, incidence of fever and infection were secondary outcomes	Pegfilgrastim is noninferior to filgrastim in the primary and secondary outcomes

For use in HCV treatment-induced neutropenia:

Systematic Reviews:

Tandon et al [27] conducted a fair quality systematic review to establish if use of filgrastim or lenograstim for HCV treatment-induced neutropenia impacted sustained virologic response (SVR) rates when compared to standard of care pegylated interferon-alfa PegINF dose reduction. The quality of studies included was poor, the majority of articles included were case series with one RCT, and provided low level evidence to conclude CSF should be used in HCV patients with neutropenia. The rate of SVR was 54.5% for patients given a CSF compared with 26.3% for dose reduction patients. Conclusions were drawn primarily from the

single, small RCT which was underpowered to determine any stastical difference in efficacy. The pooled risk from seven studies of an adverse event from CSF use was 13.1%. The most common adverse events were bone pain, rash, body aches and spleen enlargement; these were considered clinically insignificant.

New Guidelines:
These guidelines cover management and treatment of HCV including recommendations for supportive treatment for adverse events like neutropenia.

European Association of the Study of the Liver (EAOSL) [28] *Updated December 2011*
Recommendations in this guideline were graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of the recommendations are based on the quality of the underlying evidence and classified as high (A), moderate (B) or low (C). The GRADE system then offers two grades of recommendation: strong (1) or weak (2).

- There is no evidence that neutropenia during PegINF and ribavirin therapy is associated with more frequent infection episodes (C1).
- There is no evidence that the use of CSFs reduces the rate of infections and/or improves SVR rates (B1).
- EAOSL recognizes the use of CSFs during HCV treatment when the neutrophil count drops below 750–500/mm^3 is considered standard practice but finds there is insufficient evidence to recommend this practice

The Canadian Agency for Drugs and Technologies in Health (CADTH) [29] *Updated March 2012*
This is technically not a guideline but something CADTH frequently publishes, a Rapid Response Report. These reports provide recommendations based on a summary of the evidence. For this report, after a search including MEDLINE, PubMed, EMBASE, The Cochrane Library and other major international health technology agencies one fair-quality systematic review and one fair/poor quality open label RCT were included for analysis. These reports include an analysis of the quality of the studies and reviews chosen but do not rate or grade their recommendations.

- There is no clear evidence that would suggest an advantage of CSF intervention versus PegINF dose reduction as a strategy for managing neutropenia in patients with chronic hepatitis C infection treated with PegINF and ribavirin.

The Department of Veteran Affairs (VA) [30] *Updated May 2012*
Recommendations are classified by level of evidence: level A evidence is derived from RCTs or meta-analysis, level B from a single randomized or nonrandomized studies, and level C from expert opinion or standard-of-care. From there recommendations are further categorized in classes. For Class I, there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective. Class II recommendations have conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment; for Class IIa the weight of evidence/opinion is in favor of efficacy while for Class IIb efficacy is less well established by evidence/opinion. Class III is the lowest level recommendation for which there is evidence/general agreement that a diagnostic evaluation procedure/treatment is not useful or effective, and in some cases, may be harmful.

- Initial management of HCV treatment-related neutropenia should consist of a PegINF reduction for a neutrophil count <750/mm^3, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Randomized Controlled Trials:

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Talal AH, et al. *J. Acquir.*	Unspecified CSF vs.	HCV patients with comorbid HIV experiencing HCV treatment-	Difference in rate of SVR	No difference found between the two strategies for the primary outcome

Immune Defic. Syndr. 2011; 58(3):261–268[31]	PegINF dose reduction	induced neutropenia		

New Safety Alerts, Indications:

FDA Safety Alert May 2012: "Adverse Reactions" labeling changed to include the finding of decreased bone density and osteoporosis in pediatric SCN patients following post marketing surveillance. [32]

References:

1. Provider Synergies. Colony Stimulating Factors Review. 2009.
2. Sieff CA. Introduction to recombinant hematopoietic growth factors. Available at: http://www.uptodate.com/contents/introduction-to-recombinant-hematopoietic-growth-factors?source=search_result&search=colony+stimulating+factors&selectedTitle=2%7E150#H5. Accessed July 27, 2012.
3. Anon. DynaMed: Filgrastim. Available at: http://web.ebscohost.com/dynamed/detail?vid=3&hid=122&sid=092d93f4-eb19-4052-82ed-0fbf954e09dc%40sessionmgr112&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=233423. Accessed July 27, 2012.
4. Anon. DynaMed: Pegfilgrastim. Available at: http://web.ebscohost.com/dynamed/detail?vid=5&hid=122&sid=092d93f4-eb19-4052-82ed-0fbf954e09dc%40sessionmgr112&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=232864. Accessed July 27, 2012.
5. Anon. DynaMed: Sargramostim. Available at: http://web.ebscohost.com/dynamed/detail?vid=7&hid=122&sid=092d93f4-eb19-4052-82ed-0fbf954e09dc%40sessionmgr112&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=233433. Accessed July 27, 2012.
6. Anon. Pegfilgrastim 360 View Dashboard - MICROMEDEX® 2.0. Available at: http://www.thomsonhc.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch. Accessed July 27, 2012.
7. Anon. Filfgrastim 360 View Dashboard - MICROMEDEX® 2.0. Available at: http://www.thomsonhc.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch. Accessed July 27, 2012.
8. Anon. Sargramostim 360 View Dashboard - MICROMEDEX® 2.0. Available at: http://www.thomsonhc.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch. Accessed July 27, 2012.
9. Larson RA. Use of granulocyte colony stimulating factors in patients with chemotherapy-induced neutropenia. *Up to Date*. Available at: http://www.uptodate.com/contents/use-of-granulocyte-colony-stimulating-factors-in-patients-with-chemotherapy-induced-neutropenia?source=search_result&search=colony+stimulating+factors&selectedTitle=1%7E150. Accessed July 27, 2012.
10. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer*. 2011;11(1):404.
11. Kuderer NM. Meta-Analysis of Randomized Controlled Trials of Granulocyte Colony-Stimulating Factor Prophylaxis in Adult Cancer Patients Receiving Chemotherapy. In: Lyman GH, Dale DC, eds. *Hematopoietic Growth Factors in Oncology*.Vol 157. Boston, MA: Springer US; 2010:127–143. Available at: http://www.springerlink.com/index/10.1007/978-1-4419-7073-2_8. Accessed July 27, 2012.
12. Lyman GH, Dale DC, Wolff DA, et al. Acute Myeloid Leukemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy With Granulocyte Colony-Stimulating Factor: A Systematic Review. *J Clin Oncol*. 2010;28(17):2914–2924.
13. Heuser M, Zapf A, Morgan M, Krauter J, Ganser A. Myeloid growth factors in acute myeloid leukemia: systematic review of randomized controlled trials. *Ann Hematol*. 2010;90(3):273–281.
14. Sasse EC, Sasse AD, Brandalise SR, Clark OAC, Richards S. Colony-stimulating factors for prevention of myelosuppressive therapy-induced febrile neutropenia in children with acute lymphoblastic leukaemia. In: The Cochrane Collaboration, Sasse EC, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005. Available at: http://doi.wiley.com/10.1002/14651858.CD004139.pub2. Accessed July 27, 2012.
15. Gurion R, Belnik-Plitman Y, Gafter-Gvili A, et al. Colony-stimulating factors for prevention and treatment of infectious complications in patients with acute myelogenous leukemia. In: The Cochrane Collaboration, Raanani P, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD008238.pub3. Accessed July 27, 2012.
16. Hutzschenreuter F, Skoetz N, Monsef I, Kreuzer K-A, Engert A, Bauer K. Granulocyte and granulocyte-macrophage colony stimulating factors for newly diagnosed patients with myelodysplastic syndromes. In: The Cochrane Collaboration, Bauer K, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. Available at: http://doi.wiley.com/10.1002/14651858.CD009310. Accessed July 27, 2012.

17. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47(1):8–32.
18. Anon. National Comprehensive Cancer Network NCCN Myeloid Growth Factors 1.2012 Update. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed July 23, 2012.
19. Anon. National Comprehensive Cancer Network NCCN Myeldysplastic Disorders Guidelines 1.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed July 27, 2012.
20. Anon. National Comprehensive Cancer Network NCCN Acute Myeloid Leukemia Guidelines 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed July 27, 2012.
21. Sebban C, Lefranc A, Perrier L, et al. A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). *Eur J Cancer*. 2012;48(5):713–720.
22. Beksac M, Ali R, Ozcelik T, et al. Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: Results of a randomized multicenter phase III trial. *Leukemia Research*. 2011;35(3):340–345.
23. Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologus peripheral blood stem cell transplantation. *Biol. Blood Marrow Transplant.* 2010;16(5):678–685.
24. Ladenstein R, Valteau-Couanet D, Brock P, et al. Randomized Trial of Prophylactic Granulocyte Colony-Stimulating Factor During Rapid COJEC Induction in Pediatric Patients With High-Risk Neuroblastoma: The European HR-NBL1/SIOPEN Study. *J Clin Oncol*. 2010;28(21):3516–3524.
25. Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim Appears Equivalent to Daily Dosing of Filgrastim to Treat Neutropenia After Autologous Peripheral Blood Stem Cell Transplantation in Patients With Non-Hodgkin Lymphoma. *Clin Lymph Mye Leuk*. 2010;10(3):186–191.
26. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol*. 2009;21(7):1482–1485.
27. Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. *Journal of Viral Hepatitis*. 2011;18(7):e381–e393.
28. Calvaruso V, Craxì A. 2011 European Association of the Study of the Liver hepatitis C virus clinical practice guidelines. *Liver International*. 2012;32:2–8.
29. Anonymous. Treatment of Anemia and Neutropenia in Patients with Chronic Hepatitis C Infection Treated with Peginterferon-Ribavirin Based Regimens With or Without Protease Inhibitors: A Review of the Clinical Evidence. *www.cadth.ca*. 2012. Available at: http://www.cadth.ca/media/pdf/htis/mar-2012/RC0327-002%20Anemia%20Final.pdf. Accessed August 2, 2012.
30. Yee HS, Chang MF, Pocha C, et al. Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *The American Journal of Gastroenterology*. 2012;107(5):669–689.
31. Talal AH, Liu R-C, Zeremski M, et al. Randomized trial comparing dose reduction and growth factor supplementation for management of hematological side effects in HIV/hepatitis C virus patients receiving pegylated-interferon and ribavirin. *J. Acquir. Immune Defic. Syndr.* 2011;58(3):261–268.
32. FDA. Safety Information: Neupogen (filgrastim). 2012. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219032.htm. Accessed July 27, 2012.

Appendix 1: Colony stimulating factor indications[6-8]

Filgrastim (G-CSF)	Febrile neutropenia, In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation; Prophylaxis Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis Febrile neutropenia, In patients with acute myeloid leukemia receiving chemotherapy; Prophylaxis Harvesting of peripheral blood stem cells Neutropenic disorder, chronic (Severe), Symptomatic
Pegfilgrastim (G-CSF)	Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis
Sargramostim (GM-CSF)	Allogeneic bone marrow transplantation, Myeloid reconstitution in HLA-matched related donors Autologous bone marrow transplant, Myeloid reconstitution following transplant in patients with non-Hodgkin's lymphoma, Hodgkin's disease, and acute lymphoblastic lymphoma Bone marrow transplant, Delay or failure of myeloid engraftment Febrile neutropenia, In acute myelogenous leukemia following induction chemotherapy; Prophylaxis Harvesting of peripheral blood stem cells Peripheral blood stem cell graft, Autologous, myeloid reconstitution following transplant in patients mobilized with granulocyte macrophage colony stimulating factor
CSF off-label indications	Crohn's disease Myelodysplastic syndrome AIDS induced neutropenia HCV treatment induced neutropenia Aplastic anemia Agranulocytosis

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Systematic Reviews

Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer*. 2011; 11(1):404.

Febrile neutropenia (FN) occurs following myelosuppressive chemotherapy and is associated with morbidity, mortality, costs, and chemotherapy reductions and delays. Granulocyte colony-stimulating factors (G-CSFs) stimulate neutrophil production and may reduce FN incidence when given prophylactically following chemotherapy. A systematic review and meta-analysis assessed the effectiveness of G-CSFs (pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. G-CSFs were compared with no primary G-CSFs prophylaxis and with one another. Nine databases were searched in December 2009. Meta-analysis used a random effects model due to heterogeneity. Twenty studies compared primary G-CSFs prophylaxis with no primary G-CSFs prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. All three G-CSFs significantly reduced FN incidence, with relative risks of 0.30 (95% CI: 0.14 to 0.65) for pegfilgrastim, 0.57

(95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN for any primary G-CSFs prophylaxis versus no primary G-CSFs prophylaxis was 0.51 (95% CI: 0.41 to 0.62). In terms of comparisons between different G-CSFs, five studies compared pegfilgrastim with filgrastim. FN incidence was significantly lower for pegfilgrastim than filgrastim, with a relative risk of 0.66 (95% CI: 0.44 to 0.98). Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim.

Kuderer NM. Meta-Analysis of Randomized Controlled Trials of Granulocyte Colony-Stimulating Factor Prophylaxis in Adult Cancer Patients Receiving Chemotherapy. In: Lyman GH, Dale DC, eds. *Hematopoietic Growth Factors in Oncology*.Vol 157. Boston, MA: Springer US; 2010:127–143.

Granulocyte colony-stimulating factor (G-CSFs) reduces the severity and duration of neutropenia associated with cancer chemotherapy [1–5]. In the pivotal phase III trial in patients with small cell lung cancer, patients were randomized to either G-CSFs or placebo following combination chemotherapy in a double-blind fashion [3]. A significant difference in the cumulative risk of febrile neutropenia (FN) between the control (77%) and the G-CSFs (40%) groups was observed despite the allowed use of secondary G-CSFs prophylaxis after an initial occurrence of FN in the control group ($P < 0.001$). Several additional clinical trials of prophylactic G-CSFs in patients with various malignancies receiving different treatment regimens have been reported [6–11].

Lyman GH, Dale DC, Wolff DA, et al. Acute Myeloid Leukemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy With Granulocyte Colony-Stimulating Factor: A Systematic Review. *J Clin Oncol*. 2010; 28(17):2914–2924.

To evaluate the risk of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and overall mortality in patients receiving chemotherapy with or without granulocyte colony-stimulating factor (G-CSFs), a systematic review of randomized controlled trials (RCTs) was conducted. Electronic databases searched through October 2008 identified 3,794 articles for initial screening. Eligibility included solid tumor or lymphoma patients randomly assigned to chemotherapy with or without G-CSFs support, ≥ 2 years of follow-up, and reporting AML/MDS or all second malignancies. Dual blinded data extraction was performed. Relative risk (RR) and absolute risk (AR) estimates ± 95% CIs were calculated by the Mantel-Haenszel method. In the 25 eligible RCTs, 6,058 and 6,746 patients were randomly assigned to receive chemotherapy with and without initial G-CSFs support, respectively. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSFs–treated patients, with an estimated RR of 1.92 (95% CI, 1.19 to 3.07; $P = .007$) and AR increase of 0.41% (95% CI, 0.10% to 0.72%; $P = .009$). Deaths were reported in 1,845 patients randomly assigned to G-CSFs and in 2,099 controls, for estimates of RR and AR decrease of 0.897 (95% CI, 0.857 to 0.938; $P < .001$) and 3.40% (95% CI, 2.01% to 4.80%; $P < .001$), respectively. Greater RR reduction for mortality was seen for both larger studies ($P = .05$) and greater chemotherapy dose-intensity ($P = .012$). Delivered chemotherapy dose-intensity and risk of AML/MDS are increased but all-cause mortality is decreased in patients receiving chemotherapy with G-CSFs support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.

Heuser M, Zapf A, Morgan M, Krauter J, Ganser A. Myeloid growth factors in acute myeloid leukemia: systematic review of randomized controlled trials. *Ann Hematol*. 2010; 90(3):273–281.

Randomized controlled trials (RCT) investigating administration of colony-stimulating factors (CSFs) during or after chemotherapy in acute myeloid leukemia (AML) patients have not been systematically reviewed. We performed a meta-analysis of all reported RCTs comparing prophylactic or concurrent use of CSFs in adult AML patients. Two reviewers extracted data independently. Summary estimates with 95% confidence intervals (CIs) were calculated using a fixed effects model. Fourteen RCTs (n = 4,069 patients) were identified investigating prophylactic CSFs administration. Time to neutrophil recovery (>500/μl) was significantly reduced in the CSFs group (−4.13 days; 95% CI, −4.23 to −4.04) as was the length of hospitalization (−2.06 days; 95% CI, −2.36 to −1.76). However, no significant reduction in infection-related mortality was observed in CSFs-treated compared with control patients (odds ratio (OR) 0.94; 95% CI, 0.8 to 1.1). Prophylactic CSFs administration did not impact complete remission (CR) rate or survival. Fourteen RCTs (n = 4,518 patients) were identified investigating administration of CSFs during chemotherapy. Summary estimates of CR, disease/event-free, or overall survival were not

significantly different for CSFs versus control patients. Prophylactic CSFs administration reduces the time to neutrophil recovery and length of hospitalization, but has no impact on documented infections or outcome. Economic analyses of prophylactic CSFs administration in AML patients are warranted.

Gurion R, Belnik-Plitman Y, Gafter-Gvili A, et al. Colony-stimulating factors for prevention and treatment of infectious complications in patients with acute myelogenous leukemia. In: The Cochrane Collaboration, Raanani P, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012.
Acute myelogenous leukemia (AML) is a fatal bone marrow cancer. Colony-stimulating factors (CSFs) are frequently administered during and after chemotherapy to reduce complications. However, their safety with regard to disease-related outcomes and survival in AML is unclear. Therefore, we performed a systematic review and meta-analysis to evaluate the impact of CSFs on patient outcomes, including survival. Objective: To assess the safety/efficacy of CSFs with regard to disease-related outcomes and survival in patients with AML. We conducted a comprehensive search strategy. We identified relevant randomized clinical trials by searching the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 7), MEDLINE (January 1966 to July 2010), LILACS (up to December 2009), databases of ongoing trials and relevant conference proceedings. Randomized controlled trials that compared the addition of CSFs during and following chemotherapy to chemotherapy alone in patients with AML. We excluded trials evaluating the role of CSFs administered for the purpose of stem cell collection and/or priming (e.g. before and/or only for the duration of chemotherapy). Two review authors appraised the quality of trials and extracted data. For each trial, we expressed results as relative risk (RR) with 95% confidence intervals (CI) for dichotomous data. We analyzed time-to-event outcomes as hazard ratios (HRs). The search yielded 19 trials including 5256 patients. The addition of CSFs to chemotherapy yielded no difference in all-cause mortality at 30 days and at the end of follow up (RR 0.97; 95% CI 0.80 to 1.18 and RR 1.01; 95% CI 0.98 to 1.05, respectively) or in overall survival (HR 1.00; 95% 0.93 to 1.08). There was no difference in complete remission rates (RR 1.03; 95% CI 0.99 to 1.07), relapse rates (RR 0.97; 95% CI 0.89 to 1.05) and disease-free survival (HR 1.00; 95% CI 0.90 to 1.13). CSFs did not decrease the occurrence of bacteremias (RR 0.96; 95% CI 0.82 to 1.12), nor the occurrence of invasive fungal infections (RR 1.40; 95% CI 0.90 to 2.19). CSFs marginally increased adverse events requiring discontinuation of CSFs as compared to the control arm (RR 1.33; 95% CI 1.00 to 1.56). In summary, colony-stimulating factors should not be given routinely to acute myelogenous leukemia patients post-chemotherapy since they do not affect overall survival or infectious parameters including the rate of bacteremias and invasive fungal infections.

Sasse EC, Sasse AD, Brandalise SR, Clark OAC, Richards S. Colony-stimulating factors for prevention of myelosuppressive therapy-induced febrile neutropenia in children with acute lymphoblastic leukaemia. In: The Cochrane Collaboration, Sasse EC, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.
Acute lymphoblastic leukaemia (ALL) is the most common cancer in childhood and febrile neutropenia is a potentially life-threatening side effect of its treatment. Current treatment consists of supportive care plus antibiotics. Clinical trials have attempted to evaluate the use of colony-stimulating factors (CSF) as additional therapy to prevent febrile neutropenia in children with ALL. Individual trials have not demonstrated significant benefit. Systematic reviews provide the most reliable assessment and the best recommendations for practice. Objectives: To evaluate the safety and effectiveness of the addition of granulocyte colony-stimulating factors (G-CSF) or granulocyte macrophage colony-stimulating factors (GM-CSF) to myelosuppressive chemotherapy in children with ALL in an effort to prevent the development of febrile neutropenia. Evaluation of number of febrile neutropenia episodes, length to neutrophil count recovery, incidence and length of hospitalisation, number of infectious disease episodes, incidence and length of treatment delays, side effects (flu-like syndrome, bone pain and allergic reaction), relapse and overall mortality (death). The search covered the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CANCERLIT, LILACS, and SciElo. We manually searched records of conference proceedings of ASCO and ASH from 1985 to 2003 and used the electronic databases of the ASCO and ASH web sites to search for abstracts from 2003 to September 2008, as well as databases of ongoing trials. We consulted experts and scanned references from the relevant articles. We looked for randomised controlled trials (RCTs) comparing CSF with placebo or no treatment as primary or secondary prophylaxis to prevent febrile neutropenia in children with ALL. Two authors independently selected and critically appraised studies and extracted relevant data. The end points of interest were: * Primary end points: number of febrile neutropenia episodes and overall mortality (death) * Secondary end points: time to neutrophil count recovery, incidence and length of hospitalisation, number of infectious diseases episodes, incidence and length of treatment delays, side effects (flu-like syndrome, bone pain and allergic reaction) and relapse. We conducted a meta-analysis of these end points and expressed the results as Peto odds ratios. For continuous outcomes we calculated a

weighted mean difference and a standardised mean difference. For count data, we conducted a meta-analysis of the logarithms of the rate ratios using generic inverse variance. We scanned more than 6800 citations and included six studies with a total of 333 participants in the analysis. There were insufficient data to assess the effect on survival. The use of CSF significantly reduced the number of episodes of febrile neutropenia episodes (Rate Ratio = 0.63; 95% confidence interval (CI) 0.46 to 0.85; P = 0.003, with substantial heterogeneity), the length of hospitalisation (weighted mean difference (WMD) = -1.58; 95% CI -3.00 to -0.15; P = 0.03), and number of infectious disease episodes (Rate Ratio = 0.56; 95% CI 0.39 to 0.80; P = 0.002). Despite these results, CSF did not influence the length of episodes of neutropenia (WMD = -1.11; 95% CI -3.55 to 1.32; P = 0.4) or delays in chemotherapy courses (Rate Ratio = 0.75; 95% CI 0.47 to 1.20; P = 0.23). Children with ALL treated with CSF benefit from shorter hospitalisation and fewer infections. However, there was no evidence of shortened duration of neutropenia nor fewer treatment delays. There was also no useful information about survival.

Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: systematic review and economic evaluation. *Journal of Viral Hepatitis*. 2011;18(7):e381–e393

Hepatitis C virus (HCV) treatment requires maximal adherence to pegylated interferon (Peg-IFN) and ribavirin to achieve a sustained virologic response (SVR). Neutropenia is the most common cause for Peg-IFN dose reduction. Our objectives were to evaluate the effectiveness, safety and cost-effectiveness of granulocyte colony-stimulating factor (G-CSF) versus Peg-IFN dose reduction for HCV therapy-associated neutropenia in treatment naïve adults. We conducted a systematic review to identify controlled trials and observational studies. Study selection, quality assessment and data extraction were completed independently by two investigators. Cost-effectiveness and cost-utility analyses compared G-CSF with dose reduction. Nineteen studies were included. In one trial, the SVR for those receiving G-CSF was 54.5% (95% CI: 34.7–73.1) compared with 26.3% (95% CI: 11.8–48.8) for dose reduction. The remaining studies were case series or retrospective cohorts and provided weak evidence for the relationship between SVR and G-CSF. The risk of adverse events, including infection, associated with G-CSF was low (13.1%; 95% CI: 8.0–20.8) and clinically insignificant. G-CSF had an incremental cost-effectiveness ratio of $41 701 per SVR achieved in genotype 1, and $16 115 per SVR achieved in genotype 2 or 3. Estimates were robust under a variety of resource and intervention scenarios. While administration of G-CSF may enable patients to remain on or resume optimal HCV therapy, there was weak evidence that this improves the likelihood of SVR compared with dose reduction. Adverse effects of G-CSF are mild. The economic evaluation was inconclusive.

Randomized Controlled Trials

Sebban C, Lefranc A, Perrier L, et al. A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). *Eur J Cancer*. 2012; 48(5):713–720.

To evaluate in a multicentre randomised study the effect on duration of febrile neutropenia (FN), the safety and cost-effectiveness of a single subcutaneous pegfilgrastim injection compared with daily injections of filgrastim after peripheral blood stem cell transplantation in patients receiving high dose chemotherapy for myeloma and lymphoma. Patients were randomly assigned to a single dose of pegfilgrastim at day 5 (D5) or daily filgrastim from D5 to the recovery of absolute neutrophil count (ANC) to 0.5 G/L. Duration of FN, of neutrophil and platelet recovery, transfusion and antibiotic requirements were the main end-points of the study. Costs were calculated from D0 until transplant unit discharge. The incremental cost-effectiveness ratio was expressed as the cost per day of FN prevented. Probabilistic sensitivity analysis was performed by non-parametric bootstrap methods. Between October 2008 and September 2009, 10 centres enrolled 151 patients: 80 patients with lymphoma and 71 patients with myeloma. The mean duration of FN was 3.07 days (standard deviation (SD) 1.96) in the pegfilgrastim arm and 3.29 (SD 2.54) in the filgrastim one. Mean total costs were 23,256 and 25,448 euros for pegfilgrastim and filgrastim patients, respectively. There was a 62% probability that pegfilgrastim strictly dominates filgrastim. Pegfilgrastim after PBSC transplantation in myeloma and lymphoma is safe, effective when compared with filgrastim and could represent a cost-effective alternative in this setting.

Beksac M, Ali R, Ozcelik T, et al. Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: Results of a randomized multicenter phase III trial. *Leukemia Research*. 2011; 35(3):340–345.
This prospective multicenter phase III clinical trial was designed to assess efficacy and safety of G-CSFs as an adjunct to *de novo* AML remission induction therapy (www.clinicaltrials.gov. NCT00820976). Patients' characteristics were similar in both arms. G-CSFs improved severity and duration of leukopenia. Three-year OS were similar (25.6 ± 5.1% vs. 31.8 ± 5.6%) in both arms except for patients with myeloblastic features. Significant factors for better survival were the use of G-CSFs ($p = 0.049$), female sex ($p = 0.05$) and single induction cycle ($p < 0.001$) in multivariate analysis. Female patients performed better than male patients. Better survival obtained among female AML patients needs to be validated within the context of cytogenetic analysis.

Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation. *Biol. Blood Marrow Transplant*. 2010; 16(5):678–685.
Nonrandomized trials suggest that pegfilgrastim, a pegylated granulocyte colony-stimulating factor, could be used in lieu of filgrastim after autologous peripheral blood stem cell transplantation. This phase III, randomized, double-blinded, placebo-controlled trial compared the efficacy, costs, and safety of single-dose pegfilgrastim (single 6 mg dose) versus daily filgrastim (5 microg/kg/day) for this indication. Seventy-eight patients, matched for age, sex, underlying disease, stage, and CD34/kg transplant dose were enrolled. Cytokines were started on day +1 posttransplant and continued to an absolute neutrophil count (ANC) of 5x10(9)/L for 3 days or 10x10(9)/L for 1 day. The median time to neutrophil engraftment (ANC >1.5x10(9)/L for 3 days or 5x10(9)/L for 1 day) was the same in both groups (12 days). No differences in platelet engraftment (11 versus 13 days), number of platelet transfusions (5 versus 4), percent with positive cultures for bacterial pathogens (23% versus 15%), days of fever (1 versus 2), deaths prior to engraftment (1 versus 1), or duration of hospital stay (19 versus 19 days) were seen between the pegfilgrastim and filgrastim groups, respectively. Using the average wholesale price for doses used in this trial, there was a per-patient savings of $961 for the pegfilgrastim group (P < .001). This phase III study failed to demonstrate a difference in time to neutrophil engraftment or any clinical sequelae between pegfilgrastim and filgrastim when given post-APBSCT, with pegfilgrastim achieving a cost savings over filgrastim.

Ladenstein R, Valteau-Couanet D, Brock P, et al. Randomized Trial of Prophylactic Granulocyte Colony-Stimulating Factor During Rapid COJEC Induction in Pediatric Patients With High-Risk Neuroblastoma: The European HR-NBL1/SIOPEN Study. *J Clin Oncol*. 2010; 28(21):3516–3524.
To reduce the incidence of febrile neutropenia during rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide given in a rapid delivery schedule) induction. In the High-Risk Neuroblastoma-1 (HR-NBL1) trial, the International Society of Paediatric Oncology European Neuroblastoma Group (SIOPEN) randomly assigned patients to primary prophylactic (PP) versus symptom-triggered granulocyte colony-stimulating factor (GCSFs; filgrastim). From May 2002 to November 2005, 239 patients in 16 countries were randomly assigned to receive or not receive PPGCSFs. There were 144 boys with a median age of 3.1 years (range, 1 to 17 years) of whom 217 had International Neuroblastoma Staging System (INSS) stage 4 and 22 had stage 2 or 3 *MYCN*-amplified disease. The prophylactic arm received a single daily dose of 5 µg/kg GCSFs, starting after each of the eight COJEC chemotherapy cycles and stopping 24 hours before the next cycle. Chemotherapy was administered every 10 days regardless of hematologic recovery, provided that infection was controlled. The PPGCSFs arm had significantly fewer febrile neutropenic episodes ($P = .002$), days with fever ($P = .004$), hospital days ($P = .017$), and antibiotic days ($P = .001$). Reported Common Toxicity Criteria (CTC) graded toxicity was also significantly reduced: infections per cycle ($P = .002$), fever ($P < .001$), severe leucopenia ($P < .001$), neutropenia ($P < .001$), mucositis ($P = .002$), nausea/vomiting ($P = .045$), and constipation ($P = .008$). Severe weight loss was reduced significantly by 50% ($P = .013$). Protocol compliance with the rapid induction schedule was also significantly better in the PPGCSFs arm shown by shorter time to completion ($P = .005$). PPGCSFs did not adversely affect response rates or success of peripheral-blood stem-cell harvest.

Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol*. 2009; 21(7):1482–1485.

American Society of Clinical Oncology guidelines recommend the use of growth factor after high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support. This randomized trial aims to demonstrate the noninferiority of pegfilgrastim (PEG) compared with filgrastim (FIL) after HDC. Eighty patients were assigned to FIL at a daily dose of 5 μg/kg or a single fixed dose of PEG (6 mg) 1 day after PBSC. The primary end point was the duration of neutropenia both in terms of absolute neutrophil count (ANC) $<0.5 \times 10^9$/l and of days to reach an ANC $>0.5 \times 10^9$/l. The mean duration of neutropenia was 6 and 6.2 days and the mean time to reach an ANC $>0.5 \times 10^9$/l was 11.5 and 10.8 in the FIL and PEG group, respectively. No differences were observed in the mean time to reach an ANC $>1.0 \times 10^9$/l (12.2 versus 12.0 days) in the incidence of fever (62% versus 56%) and of documented infections (31% versus 25%). The mean duration of antibiotic therapy was 5.7 and 4.0 days in FIL and PEG group, respectively. PEG is not inferior to FIL in hematological reconstitution and represents an effective alternative after HDC and PBSC

.

Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim Appears Equivalent to Daily Dosing of Filgrastim to Treat Neutropenia After Autologous Peripheral Blood Stem Cell Transplantation in Patients With Non-Hodgkin Lymphoma. *Clin Lymph Mye Leuk*. 2010; 10(3):186–191.

Filgrastim decreases the time to neutrophil recovery after autologous peripheral blood stem cell transplantation (PBSCT). We hypothesized that single-dose pegfilgrastim would mimic multiple daily doses of filgrastim, resulting in an equivalent shortening of post-PBSCT neutropenia. Patients who were eligible for PBSCT and aged ≥ 18 years were identified before high-dose chemotherapy, after the harvesting and cryopreservation of peripheral blood progenitor cells (ie, $> 2.5 \times 10^6$ CD34-positive cells/kg). Eligible patients received either standard carmustine/etoposide/cytarabine/melphalan (BEAM) or carmustine/etoposide/cytarabine/cyclophosphamide (BEAC) high-dose chemotherapy. Before high-dose chemotherapy, patients were randomly assigned to receive pegfilgrastim 6 mg on day 1 (arm A) or weight-based, dose-adjusted filgrastim beginning on day 1 (arm B) after transplantation until neutrophil engraftment. Results: One-hundred and one patients were enrolled between April 2003 and April 2007. Three patients were not treated. Demographics were well-balanced in terms of stage at diagnosis, Eastern Cooperative Oncology Group performance status, histology, and lines of previous therapy. Results (arm A/arm B) pertained to mean doses received (1.0/12.6), mean absolute neutrophil count recovery days (9.3/9.8), red blood cell transfusions (1.7/1.9), red blood cell transfusion units (3.1/3.8), platelet transfusions (3.1/2.8), positive blood culture rate (18%/29.2%), febrile neutropenia (FN; 18%/16.7%), and duration of FN (days; 7.1/6.9). Transplantation-related mortality and grade 3 or 4 adverse events were comparable between arms. Conclusion: Pegfilgrastim after PBSCT appears equivalent to multiple daily doses of filgrastim. This approach might be considered in lieu of filgrastim, thus obviating the need for multiple daily injections.

Talal AH, Liu R-C, Zeremski M, et al. Randomized trial comparing dose reduction and growth factor supplementation for management of hematological side effects in HIV/hepatitis C virus patients receiving pegylated-interferon and ribavirin. *J. Acquir. Immune Defic. Syndr.* 2011;58(3):261–26

Pegylated-interferon (PEG-IFN) and ribavirin (RBV), current standard treatment for hepatitis C virus (HCV) infection, are frequently associated with neutropenia and anemia, leading to high treatment discontinuation rates in HIV/HCV-coinfected patients. Our objective was to compare the effectiveness of intervening with hematologic growth factors versus dose reductions of standard HCV therapy for the management of treatment-induced hematologic disorders. Ninety-two HIV/HCV-coinfected, therapy-naive subjects received PEG-IFN alfa-2b 1.5 $\mu g \cdot kg^{-1} \cdot wk^{-1}$ and RBV 13 ± 2 $mg \cdot kg^{-1} \cdot d^{-1}$ for up to 48 weeks. Before treatment initiation, subjects were randomized to subsequently receive growth factors, recombinant human erythropoietin (rHuEPO) and/or granulocyte colony-stimulating factor, or dose reduction (RBV and/or PEG-IFN) for anemia and neutropenia management, respectively. We analyzed the ability of each management strategy to control anemia and neutropenia and the percentage of subjects who achieved a successful treatment outcome according to the different management strategies. During treatment, 43 subjects developed anemia (human erythropoietin, n = 24; dose reduction, n = 19), whereas 25 subjects developed neutropenia (granulocyte colony-stimulating factor, n = 10; dose reduction, n = 15). After the intervention, the increase in both hemoglobin and absolute neutrophil counts did not differ between the 2 side effect management strategies. Sustained response percentages were similar comparing anemic and neutropenic subjects regardless of management strategy (anemia: recombinant human erythropoietin, 29% versus dose reduction, 21%, P = 0.92; neutropenia: granulocyte colony-stimulating factor, 40% versus dose reduction, 20%, P = 0.46). Growth factor supplementation and dose reduction do not seem to differ as management strategies for anemia and neutropenia in HIV/HCV-coinfected individuals treated with PEG-IFN/RBV.

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 Class Review: Intravenous/Subcutaneous Pulmonary Arterial Hypertension Agents

Month/Year of Review: September 2012 **End of literature search:** July 2012

Drugs Included: Epoprostenol (Flolan® and Veletri®)
Treprostinil (Remodulin®)

Issues:

- Is there evidence of efficacy differences between intravenous (IV)/ subcutaneous (SQ) agents for pulmonary arterial hypertension (PAH)?
- Is there evidence of safety advantages between the available IV/SQ PAH agents?
- Are there unique patients or situations where one agent may be more effective or safer than other available agents?
- Is there evidence to suggest IV/SQ agents are superior or safer than oral or inhaled agents for PAH?

Conclusions:

- The efficacy and safety evidence for IV epoprostenol and IV/SQ treprostinil is very limited. There are no head to head trials comparing them for PAH.
- IV epoprostenol increases survival, exercise capacity, functional class and hemodynamic status in idiopathic PAH (IPAH) patients. Studies in patients with PAH associated with scleroderma spectrum of diseases (SSD) demonstrated improvements in exercise capacity and hemodynamics but no survival benefit.
- IV epoprostenol produces a substantial benefit in New York Heart Association (NYHA) functional class III and IV patients and is strongly recommended based on good evidence in the American College of Chest Physicians (ACCP) Guidelines.[1] IV epoprostenol is the treatment of choice in class IV patients in the ACCP Guidelines and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Consensus Document. [1,2]
- IV epoprostenol use requires a central venous catheter for continuous infusion and has a maximum of 24 hours stability at room temperature. Disruption in the infusion may cause rebound pulmonary hypertension and death due to short half-life (6 minutes).[3,4]
- IV/SQ treprostinil has been show to improve exercise capacity and hemodynamics.
- IV/SQ treprostinil is approved for use in patients with NYHA functional class II symptoms but ACCP Guidelines do not recommend it due to complex administration, side effects and cost (low level of evidence with small benefit).[1] IV/SQ treprostinil is associated with an intermediate benefit in functional class III and IV patients based on low to fair evidence in the ACCP Guidelines.[1]
- SQ treprostinil can be given without dilution and is stable at room temperature for up to 72 hours. IV treprostinil requires sterile dilution and is stable for up to 48 hours at room temperature. Due to the longer half-life of treprostinil, it is thought to be less likely to cause rebound pulmonary hypertension if discontinued. However, dose changes and discontinuations should not be done abruptly.[5]
- Blood stream infections, sepsis and death were associated with chronic use of a central venous catheter required for IV epoprostenol and IV treprostinil.[3.4.5]
- Oral and inhalation therapies are an appropriate option for class II-IV patients but do not negate the need for IV/SQ prostycyclins.[2]

- Due to limited evidence and substantial risk associated with administration, one IV/SQ product cannot be recommended over another.

Recommendations:

- Require prior authorization for both IV epoprostenol and IV/SQ treprostinil to insure appropriate use. Requirements should include: diagnosis of PAH with NYHA functional class III or IV and prescribed in consultation with a specialist (pulmonologist or cardiologist).

Reason for Review:

- PAH is progressive and associated with high mortality rates. There are four classes of therapies to treat PAH, which include oral, inhalation, and IV and SQ therapies. The role of IV/SQ therapies in PAH in relation to other agents will be reviewed.
- Epoprostenol is available in a generic formulation and can only be given IV. Treprostinil can be given SQ or IV and is available as the branded product, Remodulin. Data analysis of OHP patients revealed that Remodulin claims were in the top 40 drugs by cost. This review will evaluate available evidence to formulate recommendations to optimize the use of IV/SQ PAH agents.

Methods:

A Medline literature search ending July 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing epoprostenol and treprostinil to placebo and/or conventional therapy for PAH was conducted. 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.

Introduction/Background:

PAH is the result of constricted flow through the pulmonary vasculature resulting in increased pulmonary resistance. PAH is defined as a mean pulmonary artery pressure (mPAP) >25 mm Hg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units.[2] The cause of PAH is not fully understood but includes idiopathic, heritable (often from a mutation in the bone morphogenic protein receptor-2), drug and toxin induced or PAH caused by an underlying medical condition (e.g. connective tissue diseases and HIV infection).[6] Regardless of the etiology, PAH is usually progressive with the most common cause of death being right ventricular failure.[1]

Changes in vascular structure and function within the pulmonary arteries account for the common symptoms of PAH including dyspnea, syncope, fatigue, edema and others. Exercise tolerance, as measured by the 6 minute walk (6MW) distance, and hemodynamic improvements have been good prognostic indicators of survival. The 6MW is the most common outcome measured, which reflects the distance walked in meters. In patients with chronic obstructive pulmonary disease, a mean change of 54 m was associated with a noticeable clinical difference and another study in heart failure patients found a mean difference of 43 m

to be associated with a noticeable difference in their global rating of worsening symptoms.[6] Other outcomes measured in clinical trials are: functional class, dyspnea and/or quality of life and mortality.

The World Health Organization (WHO) classifies pulmonary hypertension (PH) into five groups based on etiology. WHO Group I includes PAH caused by idiopathic PAH (IPAH), heritable PAH, and PAH as a result of connective tissue diseases, HIV and portal hypertension. These same groups of PAH were formerly referred to as primary pulmonary hypertension (Table 1).[7] PH caused by secondary sources are included in Groups 2-5 and won't be the focus of this review. The WHO functional assessment classification system for PAH has been adapted from the New York Heart Association (NYHA) functional classification. Both systems are utilized in guidelines and studies to classify patients based on symptoms as well as for treatment guidance (Table 2).[8]

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)[7]

WHO Group I: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.4 Associated with
1.1 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Table 2. WHO Functional Assessment Classification[8]

Class	**Description**
I	Patients with PH with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; les than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

Significant advances in therapeutic options to treat PAH have evolved over the last 15 years including the use of combination therapy. Standard treatment options include calcium channel blockers (for those responsive to acute vasoreactivity testing), anticoagulants, diuretics, digoxin, oxygen, prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan) and phosphodiesterase-5 inhibitors (sildenafil) .[1] Patients with symptomatic PAH are provided treatment based on functional class. According to ACCP guidelines, general treatment measures include oral anticoagulants, diuretics and oxygen.[1] Patients whom respond well to acute vasodilator testing during cardiac catherization are good candidates for calcium channel blocker therapy. This usually applies to small subset of patients with IPAH with a sustained response to CCB therapy (functional class I or II with normal or near-normal hemodynamics after several months of treatment). Long-acting nifedipine or diltiazem or amlodipine are recommended. For functional class II patients sildenafil is strongly recommended and treprostinil (IV/SQ) is a less highly recommended option. Bosentan, sildenafil, epoprostenol, iloprost inhalation are strongly recommended for functional class III patients. In functional class IV patients epoprostenol is the treatment of choice.[1,2] There is fair evidence to support the use of bosentan and iloprost inhalation in functional class IV patients.[2]

Oral PAH agents have been reviewed previously, therefore, this review will focus on IV/SQ PAH agents, epoprostenol and treprostinil (Table 3). Epoprostenol and treprostinil are prostacyclins that cause vasodilation and inhibition of platelet aggregation. Deficiencies in prostacyclins are thought to be involved in the underlying pathology of PAH.

Issues with administration make both epoprostenol and treprostinil complex to use. Epoprostenol is limited in its use due to a short half-life (6 minutes or less) which requires continuous IV infusion via a central venous catheter. Interruption in the infusion may result in rebound pulmonary hypertension and death. Patients are asked to reconstitute epoprostenol using sterile technique and use reconstituted product within 24 hours if at room temperature.[3,4] Treprostinil may be given SQ or IV with the SQ route being preferred but associated with a high incidence of injection site pain. The half-life of treprostinil is longer (around 4 hours) making disruptions in infusion less prone to cause rebound hypertension.[5] SQ treprostinil does not have to be diluted and is stable at room temperature for 72 hours. IV treprostinil has to be diluted, using sterile technique, and is stable at room temperature for 48 hours.[5]

Table 3. IV/SQ Pulmonary Arterial Hypertension Agents

Drug Products	FDA approval	FDA approved indications	Usual Dose/Duration	Potential Off-label Uses	Other Considerations
Epoprostenol (Flolan®, Veletri®)[3,4]	Flolan 1995 Veletri 2008	Treatment of PAH (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective	Administer continuous chronic infusion of epoprostenol through central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Initiate chronic infusion of epoprostenol at 2 ng/kg/min and increase in increments of 2 ng/kg/min every 15 minutes or longer until dose-	PAH WHO Groups 2-5	Average doses in clinical trials range from 9-11 ng/kg/min at 12 weeks. Infusion disruption may cause rebound pulmonary hypertension and death. Most studies are open-label due to safety concerns with central venous catherization and obvious side effects of drug.

		tissue disorders.	limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted.		Due to the complex nature of administration and safety concerns it is recommended that epoprostenol only be administered by clinicians experienced in diagnosis and management of PAH.
Treprostinil (Remodulin®)[5]	2002 (SQ) 2004 (IV)	Treatment of PAH (WHO Group I) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies or idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases. Patients who require transition from epoprostenol to reduce the rate of clinical deterioration.	Initial dose to prostacyclin naive patients : 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated); dose increase based on clinical response (increments of 1.25 ng/kg/min per week). Limited experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided. * Continuous SQ infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if SQ infusion is not tolerated.	PAH WHO Groups 2-5	The average dose in clinical trials was 9 ng/kg/min after 12 weeks. It is recommended that treprostinil only be administered by clinicians experienced in diagnosis and management of PAH. Half-life of treprostinil is 4 hours and is stable at room temperature.

Guidelines:

2007 UPDATED ACCP EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES[1]

Prostacyclins are recommended by ACCP Guidelines for functional class II and higher. SQ and IV treprostinil were found to have a low level of evidence for benefit in functional class II patients with only a small benefit noted. Complex administration, adverse effects and cost make treprostinil a seldom used option for functional class II patients. In functional class III patients, IV epoprostenol is strongly recommended with a good level of evidence for substantial benefit. For this same class SQ treprostinil is found to have intermediate benefit with a fair level of evidence to support its use. IV treprostinil is considered to have low evidence for intermediate benefit in which the recommendation was considered weak for functional class III patients. In functional class IV, epoprostenol is considered the treatment of choice with good evidence of substantial benefit and strongly recommended. SQ treprostinil is considered to have a fair amount of evidence of intermediate benefit with a moderate recommendation. IV treprostinil was determined to have low level of evidence of intermediate benefit with a weak recommendation. The guidelines recognize that IV treprostinil may be a suitable alternative to epoprostenol in critically ill functional class IV patients. Due to the complexity of PAH it is recommended that patients be referred to a center that specializes in the treatment of PAH.

The ACCP guideline recommendations are based on quality of the evidence and the strength of the recommendation combined to produce the net benefit of the therapy to the patient (Table 4). Recommendations receive a quality of evidence rating of Expert opinion to Good and the strength of the recommendation ranges from "negative based on expert opinion only" to a "strong" recommendation.[1]

Table 4. Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits*[1]

	Net Benefit					
Quality of Evidence	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	D	I	D
Expert Opinion	E/A	E/B	E/C	I	I	E/D

** Strength of recommendation is based on a negative recommendation based on expert opinion only (E/D) to strong (A).*

ACCF/AHA 2009 EXPERT CONSENSUS DOCUMENT ON PULMONARY HYPERTENSION: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc. and the Pulmonary Hypertension Association.[2]

The ACCF/AHA Expert Consensus document regard prostacyclin agents as a mainstay of PAH treatment. The committee recommends treatment selection be considered based on severity of illness, route of administration, side effects, co-morbid illness, treatment goals, and clinician preference. The ACCF/AHA Consensus document recommends treatment with IV epoprostenol or IV treprostinil as first line in patients considered high-risk. SQ treprostinil is an alternative if the IV route cannot be utilized. Epoprostenol is the preferred treatment option for critically ill patients based on improvements in functional class, exercise tolerance, hemodynamics and survival in patients with IPAH. Oral therapy with an endothelin receptor antagonist or phosphodiesterase inhibitor is recommended first line for lower risk patients, not responsive to acute vasoreactivity testing.[2]

Data to support the ACCF/AHA recommendations for epoprostenol is based on two, open-label, randomized trials and observational studies showing changes in the 6MW of 47-94m. A survival benefit was demonstrated in the epoprostenol group of one study, however, a second study found no survival differences. Efficacy data to support the use of SQ treprostinil is based on one blinded, randomized controlled trial showing a median increase of16m in the 6MW. Data for IV treprostinil is from one open-label, uncontrolled trial demonstrating improvements of 82m in the 6MW.[2]

* This expert consensus document was peer reviewed and based on available limited evidence.[2]

Systematic Reviews:

PROSTACYCLIN FOR PULMONARY HYPERTENSION IN ADULTS COCHRANE REVIEW[9]

A 2009 Cochrane review included three studies of IV epoprostenol compared to usual care (diuretics, calcium channel blockers, oral anti-coagulants, cardiac glycosides, supplemental oxygen therapy and oral vasodilators) and two studies involving SQ treprostinil versus placebo. All studies were considered to be of adequate quality. The studies involving IV therapy were open-label due to the inherent risks of central line placement. Studies ranged from 8 -12 weeks. Studies with IV epoprostenol demonstrated improvements in exercise capacity (approximately 90 meters/98 yards), cardiopulmonary hemodynamics and NYHA functional class (Table 5). SQ treprostinil studies produced mixed results with one showing a significant improvement in exercise capacity, median improvement of 16 meters, as well as improved hemodynamics and symptom scores. However, a second study failed to show a difference between treprostinil and placebo (Table 5).[9]

Table 5. Cochrane Review Summary of Results[9]

Therapy	Outcome	Results	Comments
IV Epoprostenol vs. Usual Care * Pooled data on patients with IPAH and scleroderma unless otherwise indicated	Exercise Capacity (6MW)	SMD 0.69, 95% CI 0.40 to 0.97, p<0.00001	- Difference from pooled estimates translates into difference of 90 meters in 6MW.
	Improvement in at least one NYHA Functional Class	OR 37.99, 95% CI 8.43 to 171.22, p<0.00001	
	Mortality	OR 0.32, 95% CI 0.06 to 1.58 (all patients) OR 0.11, 95% CI 0.02 to 0.62 (exclusion of scleroderma patients)	- Survival benefit was demonstrated in IPAH patients - No survival benefit was demonstrated when data on scleroderma patients were included.
SQ Treprostinil * No studies on IV treprostinil available at time of review	Exercise Capacity (6MW)	Treprostinil: 10 meters Placebo: 0 meters p=0.006	- Second study found no significant difference between treprostinil and placebo. - Subgroup analysis showed greatest improvements in those with severe disease (NYHA class III)
	Improvement in at least one NYHA Functional Class	Not reported	
	Mortality	Treprostinil: 9 deaths Placebo: 10 deaths	No deaths reported in second study.

SMD- standard mean difference, WMD- weighted mean difference

Randomized Controlled Trials

There are no published head to head trials comparing epoprostenol to treprostinil. Previously discussed literature includes pivotal efficacy trials with the exception of one newly published study listed below.

TREPROSTINIL

A poor quality, randomized, multi-center (non-United States sites), placebo-controlled, double-blind study was done in 44 patients receiving IV treprostinil (n=30) or placebo (n=14).[10] Patients were treatment naïve to prostacyclin therapy and a majority (95%) were NYHA Class III with IPAH. Patients were also included if they were NYHA Class IV with PAH associated with HIV or collagen vascular disease. Inclusion criteria required a mean PA >35 mm, selecting out a severely ill population. The primary endpoint was change from baseline in the 6MW at 12 weeks. There is low strength of evidence that treprostinil is superior to placebo with a mean placebo-corrected difference of 93 meters in favor of treprostinil (p=0.022). Eleven patients in the treprostinil group experienced serious adverse events, 3 resulting in death, compared to 21 serious adverse events in the placebo group, 5 resulting in death. Adverse events that were more common in the treprostinil group include; headache, pain in extremity, diarrhea, and jaw pain. Details on randomization and blinding were not included, potentially increasing the risk of selection and performance bias. This factor as well as the high attrition rate (25% in the treprostinil group and 33% in the placebo group) and small number of patients contributed to the poor quality rating. Additionally, the use of sites outside of the United States and only in patients of Indian nationality limits the external validity of the results.[10]

Safety/tolerability:

EPOPROSTENOL

Clinical studies show epoprostenol use is associated with adverse effects, including: flushing, jaw pain, diarrhea, headaches, hypotension, anxiety, chest pain, dizziness and nausea and vomiting. More serious adverse effects include catheter-related sepsis, paradoxical embolism, sepsis, cellulitis, pneumothorax and hepatic failure.[3,4] In a study by Barst, attrition rates were around 4% due to adverse reactions with a similar rate noted in other studies.[11]

TREPROSTINIL

Pooled data from studies with treprostinil show that infusion site pain is more common with SQ treprostinil than with placebo (OR 17.32, 95% CI 10.96 to 27.39).[5] Studies have cited infusion site pain as reason for study withdrawal in the treprostinil group and pooled data shows withdrawal due to drug-related adverse events is more common with treprostinil (OR 13.47, 95% CI 2.57 to 70.48).[9] Treprostinil use is also associated with diarrhea, jaw pain, vasodilation, and nausea. More serious adverse effects associated with IV treprostinil are sepsis, arm swelling, paresthesias, hematoma, and pain.[5]

References:

1) Badesch D, Abman S, Simonneau G, et al. Medical Therapy for Pulmonary Arterial Hypertension: Updated ACCP Evidence-Based Clinical Practice Guidelines. Chest 2007; 131: 1917-1928.
2) McLaughlin V, Archer S, Badesch D, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in Collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 2009; 119:2250-2294.
3) Flolan Prescribing Information. GlaxoSmithKline. 3/2011.
4) Veletri Prescribing Information. Actelion Pharmaceuticals US, Inc.3/2011.
5) Remodulin Prescribing Information. United Therapeutics Corp. 5/2002.
6) American Thoracic Society. Guidelines for the Six-Minute Walk Test. Am J Crit Care Med 2002; 166 (1):111-117.
7) Simonneau I, Robbins I, Beghetti M, et al. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol 2009; 54:S43-S54.
8) Rubin L. Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004; 126:7S-10S.
9) Paramothayan N, Lasserson T, Walters E. Prostacyclin for Pulmonary Hypertension in Adults (Review). Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No: CD002994. DOI: 10.1002/14651858. CD002994.pub2.
10) Hiremath J, Thanikachalam S, Parikh K, et al. Exercise Improvement and Plasma Biomarker Changes with Intravenous Treprostinil Therapy for Pulmonary Arterial Hypertension: A Placebo-controlled Trial. J Heart Lung Transplant 2010: 29:137-49.
11) Barst RJ, Rubin LJ, Long WA, et al. A Comparison of Continuous Intravenous Epoprostenol (prostacyclin) with Conventional Treatment for Primary Pulmonary Hypertension: The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996; 334:296-302.

Appendix 1: Drug Information

Pharmacology:

Epoprostenol[3,4]	**Treprostinil**[5]
Epoprostenol causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.	Treprostinil causes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Pharmacokinetics:

Table 1. Pharmacokinetic comparison

Parameters	Epoprostenol[3,4]	Treprostinil[5]
Half-life (h)	~ 6 minutes	4 hours
Metabolism	Spontaneous degradation and enzymatic	CYP2C8
Elimination	82% renal, 4% feces	79% renal, 13% feces
Renal Dose Adjustment	None	Not studied
Hepatic Dose Adjustment	None	In mild to moderate hepatic insufficiency decrease dose to 0.625 ng/kg/min ideal body weight. Not studied in severe hepatic insufficiency
Food effect on pharmacokinetics	None	None

Contraindications/Warnings

Epoprostenol[3,4]

- **Contraindication:** Congestive heart failure due to severe left ventricular systolic dysfunction, pulmonary edema, and hypersensitivity to epoprostenol.
- **Warnings:**
  - **General:** Epoprostenol should only be administered by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. Do not abruptly lower the dose or withdraw dosing. All dosing initiation and changes should be closely monitored.

Treprostinil[5]

- **Contraindication:** None

- **Warnings:** Administration of treprostinil via an indwelling central venous catheter has been associated with blood stream infections and sepsis, which may be fatal. Treprostinil should only be used by clinicians experienced in the diagnosis and treatment of PAH. Dosage adjustments should be based on clinical response and doses should not be abruptly lowered or discontinued.

Appendix 2 : New Authorization Criteria

IV/SQ Pulmonary Arterial Hypertension Agents

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which agents for pulmonary arterial hypertension (PAH) has been shown to be effective and safe.

Length of Authorization: 12 months

Requires PA:

- Epoprostenol (Flolan®, Veletri ®)
- Treprostinil (Remodulin®)

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of pulmonary arterial hypertension (PAH) classified as World Health Organization (WHO) Group 1 (see table 1 below)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Does the client have WHO or New York Heart Association (NYHA) Functional Class III-IV symptoms (see table 2 below)?	**Yes:** Go to #4	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the drug being prescribed by a PAH specialist (pulmonologist or cardiologist)?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny (medical appropriateness)

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

WHO Group I: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.5 Associated with
1.2 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease
	1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn
	1'. Pulmonary veno-occulsive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

** Simonneau, G, et al. Updated Clinical Classification of Pulmonary Hypertension. J AM Coll Cardiol 2009; 54:S43-S54.*

Table 2. World Health Organization (WHO) Functional Classification of Pulmonary Hypertension

Class	**Description**
I	Patients with pulmonary hypertension (PH) with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; les than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

** Rubin, Lewis. Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidende-Based Clinical Practice Guidelines. CHEST 2004; 126:7S-10S)*

.

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: September 2012
Date of Last Review: April 2010
PDL Classes: Growth Hormone (GH)
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: SOMATROPIN (GENOTROPIN®, NUTROPIN®, SAIZEN®)
- Non-preferred Agents: SOMATROPIN (HUMATROPE®, NORDITROPIN®, NUTROPIN AQ®, OMNITROPE®, TEV-TROPIN®, ZORBTIVE®, SEROSTIM®)

Previous Recommendations:

1. There is no evidence to support a difference in efficacy or effectiveness.
2. Evidence does not support a difference in adverse events or harm.
3. There is insufficient evidence to show a clinically significant benefit in HIV patients with respect to wasting.
4. Evidence is insufficient to identify a clinically meaningful benefit in adults.
5. It is recommended that at least one product be included with pediatric indications. There is insufficient evidence to determine a recommendation for coverage for adult patients.

PA Criteria/QL:

All medications require a prior authorization (PA) for OHP coverage (Appendix 1). GH for adults is not covered by OHP. Approval for new therapy in patients <18 years old requires the prescriber be a pediatric endocrinologist or pediatric nephrologist, have one approvable diagnosis including: Turner's syndrome (TS), Noonan syndrome, pre-transplant chronic renal insufficiency, Prader-Willi syndrome (PWS), neonatal hypoglycemia associated with growth hormone deficiency, x-linked hypophosphotemia, pituitary dwarfism, and short stature homeobox (SHOX), and bone age is <16 years in males and <14 years in females. Criteria for renewal requires a growth velocity greater than 2.5 cm per year and it is continued only until adult height as determine by bone age is achieved.

Methods:

A MEDLINE OVID search was conducted using all included drugs in children with either growth hormone deficiency (GHD), turner syndrome, chronic renal insufficiency (CRI), PWS, SHOX, Noonan syndrome, neonatal hypoglycemia, pituitary dwarfism, or x-linked hypophosphotemia and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. 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. A search for any new evidence demonstrating a benefit in adult indications was also done. 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.

Indications of Included Agents:

	Genotropin®	Humatrope®	Norditropin®	Nutropin®	Omnitrope®	Saizen®	Serostim®	Tev-Tropin®
Pediatric Indications								
Growth failure associated with chronic renal insufficiency before renal transplant				X				
Growth failure associated with Noonan syndrome			X					
Growth failure associated with Prader-Willi syndrome	X				X			
Growth failure associated with short-stature homeobox-containing gene deficiency		X						
Growth failure associated with Turner syndrome	X	X	X	X	X			
Growth failure in children born small for gestational age	X	X	X		X			
Growth hormone deficiency	X	X	X	X	X	X		X
Idiopathic short stature	X	X		X	X			
Adult Indications								
Growth hormone deficiency	X	X	X	X	X	X		
Human immunodeficiency virus-associated wasting or cachexia							X	

New Systematic Reviews:

Cochrane Collaboration

1) A recent review was conducted to determine whether the use of recombinant growth hormone (rhGH) therapy in children with x-linked hypophosphatemia (XLH) is associated with outcomes associated with changes in longitudinal growth.[1] A literature search through May 2011 resulted in only one small study that met inclusion criteria. This was a randomized, double-blind cross-over study over 24-months in five children with XLH.[1] RhGH only or combined with conventional treatment (calcitriol and oral phosphate) was compared with either placebo or conventional treatment alone. The primary outcome was longitudinal growth measured by growth velocity z score and height z score. Growth hormone therapy improved the height standard deviation score from a mean baseline of -2.66 to -2.02 and to -1.46 after 3 and 12 months. After 12 months of placebo administration, the height z score changed from -2.27 to -2.22. The growth velocity standard deviation score was -1.90 during the 12 months of placebo administration and 4.04 during the 12 months of growth hormone therapy. No significant side effects were observed during the study. Due to the limited data and that the study only included five children; the results reported should be interpreted with caution. Although allocation concealment and the method of blinding were adequate, generation of

randomization sequence was not described.[1] Authors concluded that the data are too few and of insufficient quality to provide recommendations for practice

2) Another systematic review from the Cochrane Collaboration was performed to look at the long term benefits and harms of rhGH use in children ≤18 years old with chronic kidney disease (CKD).[2] A literature search through December 2011 identified sixteen studies (809 children) with mostly poor study quality or poorly reported. The primary outcome was the end of treatment height standard deviation score (HSDS) and the end of treatment height velocity. The effect of growth hormone compared to placebo on HSDS was reported in eight studies (331 participants). There was moderate quality evidence that over a one year period, children treated with growth hormone showed an increase in HSDS of 0.82 compared to placebo (95%CI 0.56 to 1.07). This translates to approximately 5 cm of growth in one year. There were nine studies that compared growth hormone with placebo and presented data on height velocity. Two studies showed an increase in height velocity of 2.85 cm (95%CI 2.22 to 3.48) over six months (low quality evidence) and seven studies showed an increase in height velocity of 3.88cm/year (95%CI3.32 to 4.44) over 1 year (moderate quality evidence) with growth hormone therapy. Seven studies presented data on bone age in growth hormone versus placebo and found no significant difference between the two groups. [2] Data also suggested that children should be treated with 28 IU/m2/week of rhGH due to significant increases in height compared to 14 IU/m2/week but no differences compared to 56 IU/m2/week. Included data was based on relatively short duration, with maximum being two years. The most important height outcome is adult height. No RCT's have been published reporting final adult height as an outcome.

3) An additional systematic review was done to evaluate the efficacy of growth hormone with or without glutamine supplementation for adult patients with short bowel syndrome.[3] A literature search identified five trials that met inclusion criteria to evaluate the primary outcome of change in body weight. Data pooled from three of the studies demonstrated a statistically significant increase in body weight with rhGH compared to placebo (MD 1.66 kg, 95% CI 0.69 to 2.63, p=0.0008). [3] An increase in lean body mass and absorptive capacities was also seen, although these effects only lasted with treatment and the benefit disappeared after therapy was stopped. Authors concluded that the evidence demonstrated a possible short term benefit in weight gain and fat absorption, but the small number of patients, unsustainable benefits seen, and unknown long term safety demand these results be interpreted with caution. [3] Therefore, the available literature does not support the routine use of rhGH in short bowel syndrome in adults.

<u>Agency for Healthcare Research and Quality (AHRQ)</u>

1) A comparative effectiveness review was prepared to analyze the benefits and harms associated with rhGH in patients with cystic fibrosis (CF) to include a literature search through April 2010 which resulted in ten unique randomized controlled trials (nine fair quality and one good quality).[4] Although not indicated for use in CF, because of decreased growth measures associated with poorer outcomes in CF, rhGH has been investigated for this use. There was insufficient evidence to determine the effects of rhGH on most final health outcomes, including frequency of required intravenous antibiotic treatments, quality of life, bone fracture, or mortality. [4] There was moderate evidence to suggest that rhGH reduces the rate of hospitalizations (1.6 fewer hospitalizations per year; 95% CI 1.26 to 1.98)). Treatment with rhGH did improve certain intermediate outcomes including pulmonary function measures (significantly greater improvement in FVC, WMD 0.67L; 95% CI 0.24 to 1.09L; three trials, I^2=55%, moderate strength of evidence), change in height (WMD 3.13 cm; 95% CI 0.88 to 5.38 cm; three trials, I^2=77.3%, low strength of evidence), and change in weight (WMD 1.48kg, 95% CI 0.62 to 2.33 kg; five trials, I^2=49%, moderate strength of evidence). There were no significant effects on predicted FEV1 (moderate strength of evidence) and FEV1 Z score (insufficient evidence) from pooled results of trials from 6-12 months duration. [4] Authors noted that since predicted values of FEV1 are dependent upon a patient's height, simultaneous clinical improvements in both absolute FEV1 and height may attenuate or invalidate improved in predicted FEV1.
This review also looked at the strength of the evidence that links the intermediate outcomes affected by rhGH to final health outcomes including quality of life, bone consequences, and mortality. [4] The relationship between

absolute change in FVC and percent predicted FVC to mortality was weak. The evidence to support a relationship between percent predicted FEV1 and mortality was stronger with many trials finding an association with higher percent predicted FEV1 and improved survival. However, data pooled in the review did not demonstrate that rhGH significantly increased percent predicted FEV1. There was also no strong link seen between measures of height or weight and mortality. [4]

Guidelines:

National Institute for Health and Clinical Excellence

Nice guidelines on the use of somatropin for the treatment of growth failure in children was updated in May 2010.[5] Somatropin is recommended as treatment option for children with growth failure associated with GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, and those born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency. [5] The NICE guidelines continue to recommend that somatropin be initiated and monitored by a pediatrician and that the choice of brand name product should be made on an individual basis after consideration of likelihood of adherence to treatment and cost. The treatment of somatropin should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues, or if final height is attained. [5] Clinical guidelines do not prefer one growth hormone product over another.

Endocrine Society

Guidelines for the evaluation and treatment of adult growth hormone deficiency were updated in 2011, guided by systematic reviews of evidence and consensus discussions.[6] The Grading for Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to describe the strength of the recommendations and quality of evidence. The following recommendations were included in the updated guidelines[6] :

- A strong recommendation based on moderate quality evidence that therapy GH therapy offers significant clinical benefits in body composition and exercise capacity.
- A weak recommendation based on low quality evidence that GH therapy offers significant clinical benefits in skeletal integrity.
- A weak recommendation based on low quality evidence that GH therapy improves several cardiovascular surrogate outcomes, but increases insulin resistance.
- A weak recommendation based on very low quality evidence that GH therapy has not been shown to improve mortality and low quality evidence that GH therapy does improve the quality of life of most patients.
- A strong recommendation based on low quality evidence that after documentation of persistent GHD that GH therapy be continued after reaching adult height to obtain full skeletal and muscle maturation during the transition period (new recommendation in update) [6]

New Trials:

A total of 12 citations resulted from the initial MEDLINE search and after review for inclusion, 3 potentially relevant clinical trials were identified. The other clinical trials were excluded due to lack of relevant outcomes. These trials are briefly described in Table 1.

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Davenport, et al.[7] Prospective, randomized, controlled, open-label clinical trial	GH (50ug/kg/day) vs. placebo	Girls aged 9 months to 4 years with TS	Occurrence rates of otitis media (OM), middle ear (ME) dysfunction	Annual occurrence of OM episodes GH: 1.5±1.6 Placebo: 1.9±1.4 p=0.17 Occurrence of ME dysfunction GH: 39±8%

			and hearing loss.	Placebo: 34±5% NS Prevalence of hearing loss from baseline to endpoint GH: 35% to 17% Placebo: 15% o 21% NS
Pfutzner, et al.[8] Noninterventional, randomized, open-label, crossover study	FlexPro containing 10 mg GH in 1.5 mL vs. Genotropin pen containing 12mg in 1.0 mL vs. easypod device containing 8.8 mg in 1.5 mL (in the intuitiveness group vs. instruction group)	Patients age >10 to <18 years who were diagnosed with growth hormone deficiency (GHD) or Turner syndrome or who were born small for gestational age	Mean injection time in patients provided with no instruction in the use of the device (intuitiveness group) and in patients instructed (instruction group)	Mean time to administer GH injection Intuitiveness group / Instruction group *FlexPro* 47 seconds / 30.7 seconds *Genotropin* 95.1 seconds / 40.7 seconds *Easypod* 219.2 seconds / 59.6 seconds *P-value* <0.01 / <0.001
Tanaka, et al.[9] 156-week extension study of an initial 104-week multicenter, randomized, double-blind, parallel-group trial	GH 33ug/kg/day vs. 67ug/kg/day vs. untreated (for 52 weeks) then treated with either 33ug or 67ug/kg/day GH	Japanese children born small for gestation age (age 3 to <8 years)	To evaluate long-term efficacy of two doses of GH by change in height velocity standard deviation scores (SDS) from baseline	Change in Height Velocity SDS from baseline at 4 years Untreated (then GH 33ug): 0.54 Untreated (then GH 57ug): 2.19 p<0.042 Change in Height Velocity SDS from baseline 4 years / 5 years 33ug/kg/day 0.40 / 0.46 67ug/kg/day 1.47 / 0.80 p<0.0001

New drugs:
None

New Formulations/Indications:
Flexpro® (somatropin recombinant 5mg/1.5mL; 10mg/1.5mL; 15mg/1.5mL) was approved by the US Food and Drug Administration (FDA) in March 2010 and is the most recent pen device developed to deliver Norditropin®. Norditropin Flexpro® is a multidose, disposable pen device designed to replace Norditropin Nordiflex pens, which are no longer manufactured. [10] One study by Pfutzner et al compared injection time, ease of use, usability, overall preference, and dose accuracy of the Norditropin® Flexpro® with two other injection devices in 56 pediatric patients. No efficacy or safety outcomes were evaluated.[8] Results showed that Flexpro® was associated with shorter injection times and greater intuitiveness than the other devices.

New Indications:
Omnitrope® – Treatment of children with growth failure due to Turner Syndrome (7/2011) and treatment of children with growth failure due to Idiopathic Short Stature (8/2010) were added to indications.

New FDA safety alerts:
In December 2010, the FDA issued a MedWatch to inform the public that results from a study conducted in France; the Sante Adulte GH Engant (SAGhE) study, found that persons with certain kinds of short stature (idiopathic growth

hormone deficiency and idiopathic or gestational short stature) treated with rhGH during childhood and who were followed over a long period of time, were at a small increased risk of death when compared to individuals in the general population of France.[11] In August 2011, the FDA determined that the evidence found in the SAGhE study is inconclusive due to a number of study design weaknesses that limit the interpretability of the study results. The FDA states that healthcare professionals and patients should continue to prescribe and use recombinant human growth according to the labeled recommendations.[11]

Recommendations:

1. No further research or review needed at this time.
2. Further evaluate comparative costs due to no difference in efficacy or safety between agents and include at least one agent with pediatric indications as preferred.

References:

1. Yang HM, Mao M, Yang F, Wan C. Recombinant growth hormone therapy for X-linked hypophosphatemia in children. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2011. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004447.pub2/abstract. Accessed August 1, 2012.

2. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003264.pub3/abstract. Accessed August 1, 2012.

3. Wales PW, Nasr A, de Silva N, Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. *Cochrane Database Syst Rev*. 2010;(6):CD006321.

4. Phung OJOJ, Coleman CICI, Baker ELEL, et al. Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21938797. Accessed August 6, 2012.

5. NICE. Human growth hormone (somatropin) for the treatment of growth failure in children: guidance. 2010. Available at: http://publications.nice.org.uk/human-growth-hormone-somatropin-for-the-treatment-of-growth-failure-in-children-ta188. Accessed July 31, 2012.

6. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011;96(6):1587–1609.

7. Davenport ML, Roush J, Liu C, et al. Growth Hormone Treatment Does Not Affect Incidences of Middle Ear Disease or Hearing Loss in Infants and Toddlers with Turner Syndrome. *Hormone Research in Paediatrics*. 2010;74(1):23–32.

8. Pfutzner A, Hartmann K, Winter F, et al. Intuitiveness, ease of use, and preference of a prefilled growth hormone injection pen: a noninterventional, randomized, open-label, crossover, comparative usability study of three delivery devices in growth hormone-treated pediatric patients. *Clinical Therapeutics*. 2010;32(11):1918–34.

9. Tanaka T, Yokoya S, Seino Y, et al. Long-Term Efficacy and Safety of Two Doses of Growth Hormone in Short Japanese Children Born Small for Gestational Age. *Hormone Research in Paediatrics*. 2011;76(6):411–418.

10. Yuen KCJ, Amin R. Developments in administration of growth hormone treatment: focus on Norditropin® Flexpro®. *Patient Prefer Adherence*. 2011;5:117–124.

11. Commissioner O of the. Safety Alerts for Human Medical Products - Recombinant Human Growth Hormone (somatropin): Ongoing Safety Review - Possible Increased Risk of Death. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm237969.htm. Accessed July 31, 2012.

Hormones – Growth Hormone

(Somatropin)

Goal(s):

- *Cover drugs only for covered diagnoses and those where there is medical evidence of effectiveness and safety.*

NOTE: Growth Hormone treatment is no longer covered by OHP for adult diagnoses, including isolated deficiency of human growth hormone, AIDS wasting in adults or other conditions in adults.

Length of Authorization: 1 year

Preferred Alternatives: All medications require a PA for OHP Coverage. GH for adults is not covered by OHP. For preferred products for children see: http://cms.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx

Note: Criteria is divided by: **Pediatric (<18 years old)**

- New therapy
- Renewal therapy

Requires PA: All drugs in HIC3 = P1A

Pediatric Approval Criteria (<18 years old) – New Therapy		
1. Is the patient an adult (> 18 years old)?	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP).	**No:** Go to #2.
2. Is this a request for initiation of growth hormone	Yes: Go to question #3	**No:** Go to renewal therapy
3. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #4	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the diagnosis promotion of growth delay in a child with 3rd degree burns (ICD-9 codes 941.3-949.3)?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #5
5. Is the diagnosis one of the following? • Turner's Syndrome (758.6) • Noonan Syndrome (759.89) • Pre-transplant chronic renal insufficiency (CRI) (593.9) • Prader - Willi Syndrome(PWS) (759.81) • Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6) • X-linked Hypophosphotemia • Pituitary Dwarfism (253.3)	**Yes:** Document and go to #6	**No:** Pass to RPH; Deny (Not covered by the OHP)

• SHOX (Short stature homeobox gene)(783.43)		
6. If male, is bone age < 16 years? If female, is bone age < 14 years?	**Yes:** Go to #7	**No:** Pass to RPH; Deny (medical appropriateness)
7. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #8	**No:** Pass to RPH; Deny (medical appropriateness)
8. Is the product requested preferred?	**Yes:** Approve for 1 year	**No:** Go to #9
9. Will the prescriber consider a change to a preferred product? **Message:** • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. Reports are available at: http://pharmacy.oregonstate.edu/drug_policy/reviews	**Yes**: Inform provider of covered alternatives in class. http://cms.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx Approve for 1 year.	**No**: Approve for 1 year.
Pediatric Approval Criteria (<18 years old) – Renewal Therapy		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	**Yes:** go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is male bone age < 16 years and Is female bone age < 14 years?	**Yes:** Approve for 1 year	**No:** Pass to RPH; Deny (medical appropriateness)

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: September 2012 **Date of Last Review:** September 2010
PDL Class: Aminosalicylates (Drugs for Ulcerative Colitis) **Source Document:** Provider Synergies

Current Status of PDL Class:

- Preferred Agents: MESALAMINE CAPSULES ER 24H (APRISO®), MESALAMINE TABLET DR (ASACOL®), MESALAMINE ENEMA, MESALAMINE WITH CLEANSING WIPES KIT, OLSALAZINE SODIUM CAPSULE (DIPENTUM®), SULFASALAZINE TABLET DR, SULFASALAZINE TABLET
- Non-preferred Agents: BALSALAZIDE, MESALAMINE TABLETS DR HIGH DOSE (ASACOL HD®), MESALAMINE TABLETS MMX (LIALDA®), MESALAMINE CAPSULES (PENTASA®), MESALAMINE ENEMAS SULFITE-FREE (SFROWASA®), MESALAMINE SUPPOSITORIES (CANASA®)

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness between the aminosalicylates.
2. Evidence does not support a difference in harms/adverse events between the aminosalicylates.
3. Olsalazine can cause secretory diarrhea and is only indicated for maintenance therapy.
4. Mesalamine MMX (Lialda®) and Mesalamine extended release capsules (Apriso™) have no long term studies.
5. Mesalamine MMX (Lialda®) and Mesalamine capsules (Pentasa®) are only indicated for mild to moderate ulcerative colitis.

PA Criteria/QL: The generic non-preferred drugs in PDL classes Prior Authorization is in place to support preferred PDL ulcerative colitis agents and to cover for OHP above the line diagnoses only.

Methods: A Medline literature search ending August 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing aminosalicylates in patients with ulcerative colitis (UC) 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 September 2010 to current and limits placed were humans, English, and all clinical trials.

New Trials: A literature search for RCTs using the above criteria and limits resulted in 28 citations. After reviewing the inclusion criteria, 6 potentially clinically relevant trials resulted (Appendix 1). Trials were excluded mainly because of irrelevant comparisons, duplicate trials, and lack of UC indication. The following table describes these trials; a quality assessment was not performed.

Table 1: Potentially relevant clinical trials

Study	Comparison	Population	Primary Outcome	Results
Ito H, et al. MC, RCT, DB, PC [1]	Asacol 2.4g/day, Asacol 3.6 g/day vs. Pentasa 2.25 g/day vs.	Japanese nationality with mild-moderate UC N=229	A decrease in the UC disease activity index (UC-DAI)	UC-DAI Score Decrease patients enrolled and followed-up in 21 month period (improvement defined as patients with decrease by 2 points or more)

	Placebo			ASA-2.4 g: 1.5 ASA-3.6 g: 2.9 PEN-2.25 g: 1.3 Placebo: 0.3 ASA 3.6g vs PEN 2.25g: difference of 1.6 (95% CI: 0.6, 2.6); p=0.003 ASA2.4 g vs PEN2.25g: 0.2 (95% CI:-0.8, 1.2; no p-value reported
Ito H, et al. MC, RCT, DB, DC[2]	Mesalamine Asacol -2.4g/day vs. Pentasa - 2.25g/day	Japanese nationality with mild-moderate UC N=131	Proportion of patients without bloody stools	Proportion of patients without bloody stools at the end of 12 months ASA2.4g: 76.9% PEN2.25g: 69.2% Difference: 7.7% (95% CI:-7.4, 22.8)
Sandborn W, et al. MC, RCT, DB, DC[3]	Mesalamine 1.6-2.4g/day QD vs. BID	Patients with mild-moderate UC currently in clinical remission N=1023	Maintenance of clinical remission at month 6	Clinical remission maintenance at month 6 QD: 90.5% remission BID: 91.8% remission Difference of 1.3;BID-QD 95% CI: -2.3, 4.9 p-value=0.50
Lichtenstein G, et al. RCT, DB, PC[4]	Mesalamine Granules (MG) Apriso 1.5 gram vs. placebo QD	Patients with UC in remission N=305	Percentage of patients who remained relapse-free at month 6/end of treatment	Percentage of patients who remained relapse-free at month 6/end of treatment MG: 78.9% P: 58.3% P<0.001
Kruis W, et al. MC, RCT, DB, DD, DC[5]	Mesalamine oral granules3.0g QD, 1.5g QD, 0.5g TID	Endoscopically and histologically confirmed ulcerative colitis in remission N=648	Proportion of patients still in clinical remission at the final visit	Proportion of patients still in clinical remission at 52 weeks (ITT population) 3.0g: 75% 1.5g: 61% 0.5g: 69% For all three doses, =0.024; 95% CI: -0.026, 0.143 3.0g vs.1.5g p<0.001; 95% CI: 0.050, 0.225

RCT = randomized controlled trial, PC = placebo controlled, DB = double blind; DD= double-dummy MC=multicenter; DC=direct comparison; SB=single blind

New drugs:
None

New Formulations/Dosage Forms:
None

New FDA Indications:

- Mesalamine MMX Tablets (Lialda®) was updated to include induction and maintenance of remission of ulcerative colitis-July 2011[6]
    - The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g or 4.8 g. The recommended dosage for the maintenance of remission is two 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g. [6]
- Mesalamine Capsules (Pentasa) was updated to include maintenance of remission of ulcerative colitis

New FDA safety alerts:[7]
No unlabeled or unexpected serious adverse events were identified for Asacol HD (mesalamine) after a postmarketing drug safety evaluation was completed from January 2011 through June 2011.

New Systematic Reviews:
Three systematic reviews and meta-analyses from the American Journal of Gastroenterology were identified (Appendix 2). [8],[9],[10] These reviews met the PRISMA criteria for good quality reviews, but lacked individual RCT risk of bias assessment; and therefore data should be interpreted with caution. One evaluated the general efficacy of 5-aminosalicylates (5-ASA) in UC; another looked at the efficacy of oral vs. topical 5-ASA or combined therapy in UC; and the third compared once daily dosing versus conventional therapy of mesalamine in UC. These reviews concluded that combined therapy of topical and oral 5-ASA was superior to oral therapy for induction of remission in mild to moderate UC (RR of no remission = 0.65; 95 % CI = 0.47 – 0.91; number needed-to-treat (NNT) = 5), and doses greater than 2.0 grams/day of 5-ASA therapy were more effective for inducing remission and preventing relapse (RR = 0.91; 95 % CI 0.85 – 0.98). In addition, once daily dosing of mesalamine was as effective as conventional scheduled dosing for prevention of relapse of quiescent UC (RR of relapse = 0.94; 95 % CI: 0.82 – 1.08), but data on compliance with once daily dosing is lacking.

In the Efficacy of 5-ASA in UC systematic review (SR) [8], there were 37 trials in total, (19 reviewing 5-ASA therapy in active UC and 18 reviewing 5-ASA therapy in quiescent UC). Many of the individual trials in this study lacked randomization and details on allocation concealment, but only a couple were unclear about the blinding process. Of these trials, 11 (n=2086; two considered low risk of bias) looked at 5-ASA versus placebo in inducing remission in active UC, finding there was no statistical significance between the 5-ASA agents, but the data favored 5-ASA over placebo (NNT=6). Ten trials (n=2414) compared high dose mesalamine therapy versus standard dosing in inducing remission in active UC, with the data favoring the higher doses (>2 grams/day). There were no differences in adverse events between the high dose verses the standard dose. Eight trials (n=1015; one trial with low risk of bias) favored the high or standard dose of 5-ASA versus low dose in inducing remission in active UC. Eleven trials (n=1502; two with low risk of bias) favored 5-ASA therapy versus placebo in relapsing quiescent UC (NNT=4). Seven trials (n=1534) favored 5-ASA high dose or standard dose therapy over low dose in preventing relapsing quiescent UC.

In the Once Daily Dosing vs. Conventional Dosing SR[9], seven trials in total (n=2745) compared once-daily dosing (n=1349) of mesalamine with a conventional dosing schedule (n=1396) to an identical total daily dose of mesalamine. Many of these trials were unclear about the randomization and concealment procedure, and the majority of the studies were single-blinded. Two of the trials were at a low risk for bias, and the majority of the trials evaluated mesalamine use in preventing relapse in quiescent UC. Five trials compared once-daily therapy to twice daily and two trials compared it to three times daily. In total 423 (31.4%) of the patients taking once daily mesalamine relapsed compared to 461 (33.0%) using conventional therapy (RR 0.94; 95% CI: 0.82-1.08), demonstrating no statistically significant difference between them. Five studies provided extractable adverse event data, but no statistically significant differences were noted between the once-daily dosing and conventional therapy.

Twelve trials met inclusion criteria in the Efficacy of Oral vs. Topical, or Combined Oral and Topical 5-Aminosalicylates in UC review[10], comparing a mix of topical versus oral mesalamine and sulfasalazine therapy versus combined topical and oral therapy. The majority of the RCTs lacked randomization and concealment data and a few were single blinded and unblended. Four trials (n=214) compared topical versus oral therapy in inducing remission in active UC. Overall, there was no statistically significant difference in failure to achieve remission with topical 5-ASA compared to oral therapy, with 52 (49.5%) of 105 patients receiving topical 5-ASA therapy failing to achieve remission, compared to 64 (58.7%) of 109 patients receiving oral therapy (RR 0.82; 95% CI: 0.52-1.28). Four trials (n=322) compared combined topical and oral therapy with oral therapy in inducing remission in active UC with one trial at low risk of bias. The NNT with combined 5-ASA therapy in one patient failing to achieve remission was 5, with the results favoring the combined therapy (95% CI: 3-13). Topical 5-ASA therapy versus oral in preventing relapse in quiescent UC was compared in three trials (n=129), with the data favoring intermittent topical therapy over oral therapy (NNT=4). Combined oral and topical therapy versus oral 5-ASA therapy in preventing relapse in quiescent UC (n=96) resulted in a RR of relapse of 0.48 (95% CI: 0.17-1.38). One of these trials was unblinded and stopped early due to concern of relapse rates being higher in the oral therapy group.

Guidelines:
Guidelines from the American College of Gastroenterology in 2010 recommend the following:
-Induction of remission-mild to moderate distal colitis:

- Either oral aminosalicylates or topical mesalamine
- Topical mesalamine agents are considered superior to oral aminosalicylates
- The combination of oral and topical aminosalicylates is more effective than either alone
- In patients refractory to oral aminosalicylates, mesalamine enemas or suppositories may still be effective

-Induction of remission-mild to moderate extensive colitis:

- Begin therapy with oral sulfasalazine in daily doses titrated up to 4 – 6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicylate acid (5-ASA) moiety

-Maintenance of remission in distal colitis:

- Mesalamine suppositories are effective in patients with proctitis
- Mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night
- Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission
- The combination of oral and topical mesalamine is more effective than either one alone for remission maintenance

-Maintenance of remission in extensive colitis:

- Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses

Recommendations:

- Accept scan as is; no further research or review needed at this time. Evaluate comparative costs of agents in executive session.
- Continue to include at least one drug in each formulation as preferred on the PDL.

References:

1. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1567–74.

2. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1575–82.

3. Sandborn W, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology*. 2010;138(4):1286–96.

4. Lichtenstein G, Gordon G, Zakko S, et al. Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis - a 6-month placebo-controlled trial. *Alimentary Pharmacology & Therapeutics*. 2010;32(8):990–9.

5. Kruis W, Jonaitis L, Pokrotnieks J, et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2011;33(3):313–22.

6. Anonymous. Drugs@FDA. *Label and Approval History: Lialda*. 2011.

7. Research C for DE and. Surveillance - Postmarketing Drug Safety Evaluation Summaries Completed from January 2011 through June 2011.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm296188.htm

8. Ford A, Achkar J, Khan K, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(4):601–16.

9. Ford A, Khan K, Sandborn W, Kane S, Moayyedi P. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(12):2070–7.

10. Ford A, Khan K, Achkar J, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2012;107(2):167–76.

Appendix 1: Abstracts of new randomized controlled trials.

1. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1567–74.

BACKGROUND: Mesalamine is the first-line drug for the treatment of ulcerative colitis (UC). We directly compared the efficacy and safety of two mesalamine formulations for the induction of remission in patients with UC.
METHODS: In a multicenter, double-blind, randomized study, 229 patients with mild-to-moderate active UC were assigned to 4 groups: 66 and 65 received a pH-dependent release formulation of 2.4 g/day (pH-2.4 g) or 3.6 g/day (pH-3.6 g), respectively; 65 received a time-dependent release formulation of 2.25 g/day (Time-2.25 g), and 33 received placebo (Placebo). The drugs were administered three times daily for eight weeks. The primary endpoint was a decrease in the UC disease activity index (UC-DAI).
RESULTS: In the full analysis set (n = 225) the decrease in UC-DAI in each group was 1.5 in pH-2.4 g, 2.9 in pH-3.6 g, 1.3 in Time-2.25 g and 0.3 in Placebo, respectively. These results demonstrate the superiority of pH-3.6 g over Time-2.25 g (P = 0.003) and the noninferiority of pH-2.4 g to Time-2.25 g. Among the patients with proctitis-type UC, a significant decrease in UC-DAI was observed in pH-2.4 g and pH-3.6 g as compared to Placebo, but not in Time-2.25 g. No differences were observed in the safety profiles.
CONCLUSIONS: Higher dose of the pH-dependent release formulation was more effective for induction of remission in patients with mild-to-moderate active UC. Additionally, the pH-dependent release formulation was preferable to the time-dependent release formulation for patients with proctitis-type UC

2. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1575–82.

BACKGROUND: Mesalamine has been used as the first-line medication for the treatment of ulcerative colitis (UC). We directly compared the efficacy and safety of two different mesalamine formulations in the maintenance of remission in patients with UC.
METHODS: In a multicenter, double-blind, randomized study, 131 patients with quiescent UC were assigned to two groups: 65 to receive a pH-dependent release formulation of mesalamine at 2.4 g/day (pH-2.4 g) and 66 to receive a time-dependent release formulation of mesalamine at 2.25 g/day (Time-2.25 g). Both formulations were administered three times daily for 48 weeks. The primary endpoint was the proportion of patients without bloody stools.
RESULTS: In the full analysis set (n = 130), the proportion of patients without bloody stools was 76.9% in the pH-2.4 g and 69.2% in the Time-2.25 g, demonstrating the noninferiority of pH-2.4 g to Time-2.25 g. No statistically significant difference in time to bloody stools was found between the two formulations (P = 0.27, log-rank test), but the time to bloody stools tended to be longer in pH-2.4 g compared to Time-2.25 g, and a similar trend was observed with regard to the time to relapse. No differences were observed between the safety profiles of the two formulations.
CONCLUSIONS: The pH- and time-dependent releases of mesalamine formulations were similarly safe and effective. Interestingly, the remission phase tended to be longer in the group that received the pH-dependent formulation compared to the group that received the time-dependent formulation.

3. Sandborn W, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology*. 2010;138(4):1286–96.

BACKGROUND & AIMS: The practice of dosing mesalamines in divided doses for the treatment of ulcerative colitis (UC) began with sulfasalazine and was driven by sulfapyridine toxicity. This convention and the assumption that dosing multiple times a day is necessary to treat UC had not been challenged until recently. This study was conducted to determine the efficacy and safety of once-daily dosing of delayed-release mesalamine (Asacol 400-mg tablets) compared

with twice-daily dosing for maintaining remission in UC patients.
METHODS: A multicenter, randomized, investigator-blinded, 12-month, active-control trial was conducted to assess the noninferiority of delayed-release mesalamine 1.6-2.4 g/day administered once daily compared with twice daily in patients with mild-to-moderate UC currently in clinical remission. The primary end point was maintenance of clinical remission at month 6.
RESULTS: A total of 1023 patients were randomized and dosed. The primary objective of noninferiority was met. At month 6, 90.5% of patients receiving once-daily dosing had maintained clinical remission, compared with 91.8% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -2.3 to 4.9). At month 12, 85.4% of patients receiving once-daily dosing had maintained clinical remission, compared with 85.4% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -4.6 to 4.7). Both regimens had low rates of withdrawals as a result of adverse events and serious adverse events.
CONCLUSIONS: Once-daily dosing of delayed-release mesalamine at doses of 1.6-2.4 g/day was shown to be as effective as twice-daily dosing for maintenance of clinical remission in patients with UC.

4. Lichtenstein G, Gordon G, Zakko S, et al. Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis - a 6-month placebo-controlled trial. *Alimentary Pharmacology & Therapeutics*. 2010;32(8):990–9.

BACKGROUND: Ulcerative colitis (UC) is a chronic relapsing and remitting idiopathic inflammatory bowel disorder.
AIM: To evaluate once-daily mesalamine (mesalazine) granules (MG) for maintenance of remission of UC.
METHODS: Randomized, double-blind, placebo-controlled trial of patients (n=209 MG, n=96 placebo) with UC in remission [revised Sutherland Disease Activity Index (SDAI) rectal bleeding=0, mucosal appearance <2] who took MG 1.5 g or placebo once-daily for up to 6 months. Primary efficacy endpoint: the percentage of patients who remained relapse-free at month 6/end of treatment. Relapse was defined as SDAI rectal bleeding score >=1 and a mucosal appearance score >=2, a UC flare, or initiation of medication to treat a UC flare.
RESULTS: The percentage of relapse-free patients at month 6/end of treatment was higher with MG than placebo (78.9% vs. 58.3%, P < 0.001) in the intent-to-treat analysis. Significant differences (P <= 0.025) favouring MG were observed for most secondary endpoints including improvement in rectal bleeding, physician's disease activity rating, stool frequency, the SDAI at month 6/end of treatment, patients classified as a treatment success and relapse-free duration. The incidence of adverse events was similar between groups.
CONCLUSIONS: Once-daily mesalamine (mesalazine) was effective in maintaining remission of UC for 6 months.

5. Kruis W, Jonaitis L, Pokrotnieks J, et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2011;33(3):313–22.

BACKGROUND: Comparative data regarding different regimens of oral mesalazine (mesalamine) for maintaining remission in ulcerative colitis are limited.
AIM: To evaluate whether 3.0 g mesalazine once-daily (OD) is superior to the standard treatment of 0.5 g mesalazine three times daily (t.d.s.) and to prove the therapeutic equivalence of OD vs. t.d.s. dosing of total 1.5 g mesalazine for remission maintenance in patients with ulcerative colitis.
METHODS: A 1-year, multicentre, double-blind, double-dummy study was undertaken in patients with endoscopically and histologically confirmed ulcerative colitis in remission. Patients were randomised to oral mesalazine 3.0 g OD, 1.5 g OD or 0.5 g t.d.s. The primary efficacy endpoint was the proportion of patients still in clinical remission at the final visit, with clinical relapse being defined as CAI score >4 and an increase of >=3 from baseline.
RESULTS: The primary efficacy endpoint occurred in 162/217 3.0 g OD patients (75%), 129/212 1.5 g OD patients (61%) and 150/218 0.5 g t.d.s. patients (69%) in the intention-to-treat population, and in 152/177 (86%), 121/182 (67%) and 144/185 (78%) in the per protocol population respectively; 3.0 g OD was superior to both low-dose regimens for the primary endpoint (i.e. P < 0.001, 3.0 g OD vs. 1.5 g OD; P = 0.024, 3.0 g OD vs. 0.5 g t.d.s.; superiority test, per protocol population). Safety analysis, including comprehensive renal monitoring, revealed no concern in any treatment group.

CONCLUSION: Mesalazine 3.0 g once daily was the most effective dose for maintenance of remission in ulcerative colitis of the three regimens assessed, with no penalty in terms of safety.

Appendix 2: Abstracts of Systematic Reviews

8. Ford A, Achkar J, Khan K, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(4):601–16.

OBJECTIVES: The efficacy of 5-aminosalicylic acids (5-ASAs) in ulcerative colitis (UC) has been studied previously in meta-analyses. However, several randomized controlled trials (RCTs) have been published recently, and no previous meta-analysis has studied the effect of 5-ASA dosage used.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through

December 2010). Eligible trials recruited adults with active or quiescent UC, comparing different doses of 5-ASAs with themselves or placebo. Dichotomous data were pooled to obtain relative risk (RR) of failure to achieve remission in active UC, and RR of relapse of disease activity in quiescent UC, with a 95 % confidence interval (CI). The number needed to treat (NNT) was calculated from the reciprocal of the risk difference.

RESULTS: The search identified 3,061 citations, and 37 RCTs were eligible. Of these, 11 compared 5-ASA with placebo in active UC remission, with the RR of no remission with 5-ASAs of 0.79 (95 % CI 0.73 –

0.85; NNT = 6). Doses of ≥ 2.0 g / day were more effective than < 2.0 g / day for remission (RR = 0.91; 95 % CI 0.85 – 0.98). There were 11 RCTs comparing 5-ASAs with placebo in preventing relapse of quiescent UC, with the RR of relapse of 0.65 (95 % CI 0.55 – 0.76; NNT = 4). Doses of ≥ 2.0 g / day appeared more effective than < 2.0 g / day for preventing relapse (RR = 0.79; 95 % CI 0.64 – 0.97).

CONCLUSIONS: 5-ASAs are highly effective for inducing remission and preventing relapse in UC. Evidence suggests that doses of ≥ 2.0 g / day have greater efficacy, although doses > 2.5 g / day do not appear to lead to higher remission rates.

9. Ford A, Khan K, Sandborn W, Kane S, Moayyedi P. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(12):2070–7.

OBJECTIVES: Maintenance therapy with 5-aminosalicylates (5-ASAs) is recommended in patients with quiescent ulcerative colitis (UC), but compliance rates are low. Once-daily dosing may improve adherence, but impact on the relapse of disease activity is unclear as no previous meta-analysis has studied this issue.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through

April 2011). Eligible randomized controlled trials (RCTs) recruited adults with quiescent UC, and compared once-daily dosing of 5-ASAs with a more frequent dosing schedule of an identical total daily dose of the same 5-ASA drug. Minimum treatment duration was 6 months. Trials reported a dichotomous assessment of relapse of disease activity at last point of follow-up. Data concerning noncompliance and adverse events were extracted, where reported. Effect of once-daily vs. more frequent dosing schedule was reported as relative risk (RR) of relapse with a 95 % confidence interval (CI).

RESULTS: The search identified 3,061 citations, and seven RCTs containing 2,745 patients were eligible.

All RCTs used mesalamine. Relapse rates were not significantly different between once-daily and conventional dosing schedules for mesalamine (RR of relapse = 0.94; 95 % CI: 0.82 – 1.08). Noncompliance

(RR = 0.87; 95 % CI: 0.46 – 1.66) and adverse events were no more likely with once-daily dosing (RR = 1.08; 95 % CI: 0.97 – 1.20).

CONCLUSIONS: Once-daily dosing with mesalamine is as effective as conventional dosing schedules for the prevention of relapse of quiescent UC, although there is no definitive evidence that compliance with once daily dosing is better. Adverse events occur at a similar frequency.

10. Ford A, Khan K, Achkar J, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2012;107(2):167–76.

OBJECTIVES: Efficacy of 5-aminosalicylic acids (5-ASAs) in ulcerative colitis (UC) has been studied previously in meta-analyses. However, no recent meta-analysis has studied the relative efficacies of differing routes of administration.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through May 2011). Eligible trials recruited adults with mildly to moderately active UC, or quiescent UC, and compared oral 5-ASAs with either topical 5-ASAs or a combination of oral and topical 5-ASAs. Dichotomous data were pooled to obtain relative risk (RR) of failure to achieve remission in active UC, and RR of relapse of disease activity in quiescent UC, with a 95 % confidence interval (CI).The number needed to treat (NNT) was calculated from the reciprocal of the risk difference.

RESULTS: The search identified 3,061 citations, and 12 randomized controlled trials (RCTs) were eligible. Four compared topical with oral 5-ASAs in active UC remission, with an RR of no remission with topical 5-ASAs of 0.82 (95 % CI = 0.52 – 1.28). Four trials compared combined with oral 5-ASAs in active UC (RR of no remission = 0.65; 95 % CI = 0.47 – 0.91; NNT = 5). Three RCTs compared intermittent topical with oral 5-ASAs in preventing relapse of quiescent UC (RR = 0.64; 95 % CI = 0.43 – 0.95; NNT = 4), and two compared combined with oral 5-ASAs (RR of relapse = 0.48; 95 % CI = 0.17 – 1.38).

CONCLUSIONS: Combined 5-ASA therapy appeared superior to oral 5-ASAs for induction of remission of mildly to moderately active UC. Intermittent topical 5-ASAs appeared superior to oral 5-ASAs for preventing relapse of quiescent UC.

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: September 2012
PDL Class: Opthalmic Antibiotics
Literature Search End Date: June week 1, 2012

Date of Last Review: December 2009
Source Document: Provider Synergies (PS)

Current Status of PDL Class:

Preferred Agents	Non-Preferred Agents
Aminoglycosides	
Gentamicin drops and ointment	
Tobramycin drops and Tobramycin (Tobrex®) ointment	
Fluoroquinolones	
Ciprofloxacin drops	Besifloxacin (Besivance®) drops
Gatifloxacin (Zymar®) 0.3% drops	Ciprofloxacin (Ciloxan®) ointment
Levofloxacin 0.5% drops	Gatifloxacin (Zymaxid®) 0.5% drops
Moxifloxacin (Vigamox®) drops	Levofloxacin (Iquix®) 1.5% drops
Ofloxacin drops	
Macrolides	
Erythromycin base ointment	Azithromycin (AzaSite®)
Others	
Bacitracin/polymyxin B ointment	Bacitracin ointment
Natamycin (Natacyn®) drops	Neomycin/polymyxin B/bacitracin ointment
Neomycin/polymyxn B/gramicidin drops	Sulfaetamide ointment
PolymiyxinB/TMP drops	
Sulfacetamide drops	

Previous Recommendations:

1. There is high-quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
2. Consider at least one medication from each class (aminoglycosides, macrolides, fluoroquinolones and others).
3. Include natamycin as it is the only medication that carries FDA approval for fungal infections.

4. Consider having drops and ointments available.
5. Consider step therapy for 4th and 5th generation fluoroquinolones.
6. Surgical consideration regarding 4th and 5th generation fluoroquinolones which are commonly used pre- and post-op.

Background:
Acute conjunctivitis is usually a benign, self-limited condition or is easily treated. Acute conjunctivitis can be classified as infectious (bacterial or viral) and noninfectious (allergic or nonallergic). Bacterial conjunctivitis is more common in children than in adults.[1] Bacterial conjunctivitis is commonly caused by Staphylococcus aureus, Streptococcus pneuminiae, Haemophilus influenza, and Moraxella catarrhalis. S. aureus infection is common in adults; the other pathogens are common in children.[2] While acute bacterial conjunctivitis is often self-limiting, empiric therapy with opthalmic antibiotics is a common practice.

Methods:
A MEDLINE OVID search was conducted using all ophthalmic antibiotics 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. 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.

New Trials:
A total of 18 citations resulted and after review for inclusions, two potentially relevant clinical trials were identified (Appendix 1). A multicenter, randomized, investigator-masked and active-controlled, 15-day study evaluated 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. 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. The authors concluded 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.[3]

Another trial was a multicenter, prospective, randomized, double-masked, vehicle-controlled, parallel-group study evaluated the efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days compared with vehicle (formulation without besifloxacin) in the treatment of adults and children with bacterial conjunctivitis. Of 202 patients randomized to treatment (mean [SD] age, 25.2 [24.3] years; 56.9% female; 76.7% white), 109 had culture-confirmed bacterial conjunctivitis (53 besifloxacin ophthalmic suspension, 56 vehicle). At visit 2, the besifloxacin ophthalmic suspension group had significantly greater rates of clinical resolution compared with the vehicle group (37/53 [69.8%] vs 21/56 [37.5%], respectively; $P < 0.001$), as well as significantly greater rates of bacterial eradication (46/53 [86.8%] vs 32/56 [57.1%]; $P < 0.001$). At visit 3, rates of bacterial eradication were also significantly greater in the besifloxacin ophthalmic suspension group compared with the vehicle group (46/53 [86.8%] vs 39/56 [69.6%]; $P = 0.038$). The incidence of ocular AEs did not differ significantly between treatment groups (4/94 [4.3%] vs 8/98 [8.2%]).[4]

New drugs:
None

New FDA Indications:
None

New FDA safety alerts:
None

New Systematic Reviews:
None identified

Guidelines:
None identified.

Recommendations:

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

References:

1. Anon. Conjunctivitis. Available at: http://www-uptodate-com.liboff.ohsu.edu/contents/conjunctivitis?source=search_result&search=acute+conjunctivitis&selectedTitle=1%7E150#H20. Accessed June 6, 2012.

2. Friedlaender MH. A review of the causes and treatment of bacterial and allergic conjunctivitis. *Clinical Therapeutics*. 1995;17(5):800–810.

3. 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. *Current Medical Research and Opinion*. 2011;27(1):171–178.

4. Silverstein BE, Allaire C, Bateman KM, et al. Efficacy and Tolerability of Besifloxacin Ophthalmic Suspension 0.6% Administered Twice Daily for 3 Days in the Treatment of Bacterial Conjunctivitis: A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study in Adults and Children. *Clinical Therapeutics*. 2011;33(1):13–26.

Appendix 1

1. Torkildsen GL, Cockrum P, Meier E, Hammonds WM, Silverstein B, Silverstein S. 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 Jan;27(1):171-8. Epub 2010 Dec 7

   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).
   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.

2. Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. *Clin Ther.* 2011 Jan;33(1):13-26.

   Background: Besifloxacin is a topical fluoroquinolone with potent in vitro activity against a broad spectrum of ocular pathogens, including drug-resistant strains. Besifloxacin ophthalmic suspension 0.6% given 3 times daily for 5 days has been reported to be more effective than its vehicle in the treatment of bacterial conjunctivitis. Pharmacokinetic/pharmacodynamic modeling suggests that besifloxacin might also be effective given twice daily.
   Objective: This study evaluated the efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days compared with vehicle (formulation without besifloxacin) in the treatment of adults and children with bacterial conjunctivitis.
   Method: This was a multicenter, prospective, randomized, double-masked, vehicle-controlled, parallel-group study. Patients aged ≥1 year with bacterial conjunctivitis were randomized to receive besifloxacin ophthalmic suspension or vehicle administered twice daily for 3 days. There were 3 study visits: the baseline visit, visit 2 (day 4 or 5), and visit 3 (day 7±1). Participants recorded the times of medication instillation in a patient diary. The primary end points were clinical resolution and bacterial eradication of the baseline bacterial infection at visit 2 in patients with culture-confirmed bacterial conjunctivitis. Secondary end points were clinical resolution and bacterial eradication of the baseline bacterial infection at visit 3, individual clinical outcomes (ocular conjunctival discharge and bulbar conjunctival injection) at the follow-up visits, and microbial and clinical outcomes for overall bacterial species and individual gram-positive and gram-negative bacterial species. Tolerability assessments included ocular adverse events (AEs), changes in visual acuity, biomicroscopy and ophthalmoscopy findings, and nonocular AEs.

Results: Of 202 patients randomized to treatment (mean [SD] age, 25.2 [24.3] years; 56.9% female; 76.7% white), 109 had culture-confirmed bacterial conjunctivitis (53 besifloxacin ophthalmic suspension, 56 vehicle). At visit 2, the besifloxacin ophthalmic suspension group had significantly greater rates of clinical resolution compared with the vehicle group (37/53 [69.8%] vs 21/56 [37.5%], respectively; P < 0.001), as well as significantly greater rates of bacterial eradication (46/53 [86.8%] vs 32/56 [57.1%]; P < 0.001). At visit 3, rates of bacterial eradication were also significantly greater in the besifloxacin ophthalmic suspension group compared with the vehicle group (46/53 [86.8%] vs 39/56 [69.6%]; P = 0.038). Results for the individual clinical outcomes and microbial and clinical outcomes by gram-positive and gram-negative species were consistent with the primary efficacy outcomes. The incidence of ocular AEs did not differ significantly between treatment groups (4/94 [4.3%] vs 8/98 [8.2%]). Ocular AEs in all treated eyes in the respective groups included bacterial conjunctivitis (3/157 [1.9%] and 5/154 [3.2%]), conjunctivitis (3/157 [1.9%] and 4/154 [2.6%]), and allergic conjunctivitis (2/157 [1.3%] and 1/154 [0.6%]). These events were of mild or moderate severity. Changes in visual acuity and biomicroscopy and ophthalmoscopy findings were comparable between groups. There were few nonocular AEs (2/94 [2.1%] vs 3/98 [3.1%]; P = NS), none of them considered treatment related.
Conclusion: In these adults and children with bacterial conjunctivitis, treatment with besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days was effective and well tolerated.

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: September 2012 **Date of Last Review:** September 2010
PDL Classes: Phosphate Binders **Source Document:** Provider Synergies

Current Status of PDL Class:

- Preferred Agents: CALCIUM ACETATE
- Non-preferred Agents: SEVELAMER (RENAGEL®), SEVELAMER CARBONATE (RENVELA®), LANTHANUM CARBONATE (FOSRENOL®), CALCIUM CARBONATE/ MAG CARB (MAGNEBIND®)

Previous Conclusions & Recommendations:

1. Pediatric safety and efficacy not yet determined.
2. Calcium based binders (based on evidence) especially in infants and younger children may be OK.
3. Sevelamer and calcium based (opinion based) may be ok in older children and adolescents.
4. Lanthanum long term effects on bone is unclear.
5. Consider step therapy with calcium acetate first then resin based agents.

PA Criteria/QL: Default prior authorization required for non-preferred drugs to ensure that non-preferred drugs are used for an above-the-line condition.

Methods:
A MEDLINE OVID search was conducted using all included drugs and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. 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. A search for any new evidence demonstrating a benefit in adult indications was also done. 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.

New Systematic Reviews:
Cochrane Collaboration
A systematic review from the Cochrane Collaboration assessed the benefits and harms of phosphate binders in adults with chronic kidney disease (CKD).[1] From a literature search through March 2010, 60 studies (7631 participants) were identified, comparing phosphate binders to placebo or other phosphate binders. There were two independent reviewers who assessed the risk of bias for the included studies, and concluded overall that the study quality varied among the included studies. The following contributed to the overall quality variance: allocation concealment was adequate in approximately 18% of the studies and unclear in others; participants and investigators were blinded in approximately 17% of the studies and outcome assessors were blinded in none of the studies; 22% were analyzed on an intention-to-treat basis; and lost-to-follow-up ranged from 0-31%, but did not differ between the treatment and control groups of the studies. [1] Overall, there was no significant reduction in all-cause mortality (10 studies, 3079 participants: RR 0.73, 95% CI 0.46 to 1.16) or serum calcium-phosphorus (Ca x P) product with sevelamer hydrochloride compared to calcium-based agents.[1] The Ca x P product has been shown with limited evidence to increase the risk for development of calcification and possibly increase the risk for lower patient survival

in CKD if it is >55 mg^2/dL^2.[2] There was a significant reduction in serum phosphorous (16 studies, 3126 participants: MD 0.23 mg/dL, 95% CI 0.04 to 0.42) and parathyroid hormone (PTH) (12 studies, 2551 participants; MD 56 pg/mL, 95% CI 26 to 84), but a significant increase in the risk of hypercalcemia (12 studies, 1144 participants: RR 0.45, 95% CI 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride.[1] There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride in comparison to calcium salts (5 studies, 498 participants: RR 1.58, 95% CI 1.11 to 2.25). Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants: MD -0.30 mg/dL, 95% CI -0.64 to -0.25) and the Ca x P product, but not serum phosphorus levels. There was no significant difference in phosphorus levels with calcium acetate in comparison to calcium carbonate (5 studies, 143 participants, MD -0.19 mg/dL, 95% CI -0.61 to 0.24).[1] Authors concluded that all phosphate binders reduce serum phosphorous when compared to placebo, and there is insufficient data to conclude the comparative superiority of novel non-calcium agents over calcium-containing binders for patient centered outcomes of all-cause mortality and cardiovascular end-points in CKD.[1] The primary advantage of more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) was found to be a reduction in hypercalcemia.

Another Cochrane review from 2010 investigated the benefits and harms of interventions for the prevention and treatment of bone disease in children with CKD.[3] A total of 15 randomized controlled trials (369 children) were identified, but only four studies included phosphate binders as the intervention. Overall, the quality of the evidence was very low for both the comparison of calcium carbonate versus sevelamer and calcium carbonate versus aluminum hydroxide in all measured outcomes because of small patient numbers, large loss to follow-up and risk of bias in study design.[3] The authors concluded that phosphate binders (aluminum hydroxide, calcium carbonate or acetate and sevelamer) had indistinguishable effects in lowering serum phosphate, reducing PTH and on mean height standard deviation score (SDS) but that hypercalcemia was more common with calcium-containing binders.[3]

Meta-Analyses

A meta-analysis reviewing the effects of calcium-based versus non-calcium based phosphate binders on mortality included a total of eight trials (2873 patients), with 1434 receiving sevelamer (the only non-calcium-based phosphate binder noted in the trials) and 1439 receiving calcium-based phosphate binders.[4] Trials ranged in size from 42 to 2103 subjects with a duration of follow-up between five and 44 months. Three of the studies were rated as high risk of bias, due to inadequate sequence generation, allocation concealment and/or blinding. Two studies were rated as unclear risk of bias because of failure to indicate sequence generation, allocation concealment and/or blinding, and three studies were at low risk of bias. The authors concluded that there was a non-significant reduction in all-cause mortality of 32% (RR 0.68; 95% CI of 0.41-1.11) in favor of non-calcium-based phosphate binders. Only two trials reported information on cardiovascular events, favoring sevelamer (RR 0.85 95% CI 0.35-2.03); although not statistically significant. Authors concluded that they did not find a statistically significant difference in cardiovascular mortality in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. This meta-analysis was considered good quality according to the AMSTAR tool.[5]

Another good quality meta-analysis compared sevelamer and calcium-based phosphate binders (CBPB) on cardiovascular calcification in hemodialysis (HD) patients.[6] It included 14 trials with a total of 3,271 patients.[6] The duration of the trials ranged from 8 weeks to 45 months. The Jadad score was used to assess the quality of the trials, and six out of 14 trials ended up scoring three or more on the score, which is considered a high quality trial.[7] All 14 trials included statements regarding randomization and five of the trials described the detailed methods used for randomization. Four trials reported changes in the coronary artery calcium (CAC) score from baseline, but taken together, there was no significant difference between the sevelamer group and the CBPB group (weighted mean difference -74.87; 95% CI -159.96 to 10.22). The levels of intact parathyroid hormone were significantly higher in the sevelamer groups than in the CBPB group (weighted mean difference 55.85; 95% CI 14.47-97.24). Overall, the authors concluded that the meta-analysis found no significant differences in cardiovascular calcification between sevelamer and CBPB. Sevelamer-treated patients had higher intact parathyroid hormone levels, lower phosphorus levels, lower calcium-phosphorus product, and fewer episodes of hypercalcemia without altering serum calcium.[6]

Guidelines:

Kidney Disease International: Global Outcomes Clinical Practice Guidelines (KDIGO)[8]

The KIDGO Clinical Practice Guidelines from 2009 discuss the use of phosphate binders in CKD. The AGREE II guideline appraisal tool was used to assess the overall quality of the KDIGO guidelines.[9] The overall quality of the guidelines was considered six out of seven for highest possible quality, and would be recommended for use. Areas for improvement include the search method utilized (only the Medline search database was used) and the evidence and recommendation connection (some of the recommendations were opinions only due to lack of randomized controlled trials).

The KDIGO guidelines graded the strength of their recommendations by providing levels (level 1=strong evidence; level 2=weak evidence) and grades (A=high quality; B=moderate; C=low; D=very low) for the quality of evidence used to back up their recommendations. The following are the major recommendations:

- For patients with CKD stages 3-5, maintaining serum phosphorous in the normal range is suggested (2.5-4.5 mg/dL) (level of evidence 2C).
- In patients with CKD stage 5D, lowering elevated phosphorus levels toward the normal range is suggested (2C).
- In patients with CKD stages 3-5 (2D) and 5D (2B), using phosphate-binding agents in the treatment of hyperphosphatemia is suggested. The choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).
- In patients with CKD stages 3-5D and hyperphosphatemia, it is recommended to restrict the dose of calcium-based phosphate binders in the presence of persistent or recurrent hypercalcemia (1B).
- In patients with CKD stages 3-5D and hyperphosphatemia, restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low is suggested (2C).
- In patients with CKD stages 3-5D, avoiding long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication is recommended (1C).
- In patients with CKD stages 3-5D, limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments is suggested (2D).
- In patients with CKD stages 5D, increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia is recommended (2C).

New Trials (Abstracts in Appendix 1):

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
Qunibi et al.[10] RCT, DB, PC	Calcium acetate vs. placebo	Nondialyzed patients with GFR<30ml/min/1.73m2 and phosphorous >4.5mg/dl (n=110)	Serum phosphorous at 12 weeks	Serum phosphorous at 12 weeks: Ca: 4.4 ± 1.2 mg/dL Pa: 5.1 ± 1.4 mg/dL P = 0.04 % with target serum phosphorous: Ca: 59.5% Pl: 36.6% P = 0.04 Intact parathyroid hormone levels: Ca: 150 ± 157 pg/ml Pa: 351 ± 292 pg/ml P <0.001 Albumin-adjusted serum calcium: Ca: 9.5 ± 0.8 Pa: 8.8 ± 0.8; P <0.001
Gulati, et al.[11] Open-label RCT	Sevelamer vs. calcium acetate	Patients aged 2-18, with CKD stages 3 to 4 (n=22)	Decrease in serum phosphorous after 12 weeks of treatment.	-Patients receiving calcium acetate had a reduction in mean phosphate from 6.6 mg/dl to 5.8 mg/dl at 12 weeks (P = 0.7). -The mean levels of phosphate declined from6.2 mg/dl to 6.0 mg/dl in the sevelamer group (P = 0.2). -There were no significant differences in blood levels of phosphate at 12 weeks between the two groups.

Definitions used: RCT=randomized controlled trial, DB=double blind, PC=placebo-controlled, GFR=glomerular filtration rate.

Recommendations:

1) No further research needed at this time.
2) Evaluate comparative costs for further class decisions.

Appendix 1: Abstracts of clinical trials.

Qunibi W, Winkelmayer WC, Solomon R, Moustafa M, Kessler P, Ho CH, Greenberg J, Diaz-Buxo JA. A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease.

BACKGROUND: Hyperphosphatemia in patients with chronic kidney disease (CKD) contributes to secondary hyperparathyroidism, soft tissue calcification, and increased mortality risk. This trial was conducted to examine the efficacy and safety of calcium acetate in controlling serum phosphorus in pre-dialysis patients with CKD.

METHODS: In this randomized, double-blind, placebo-controlled trial, 110 nondialyzed patients from 34 sites with estimated GFR < 30 mL/min/1.73 m^2 and serum phosphorus > 4.5 mg/dL were randomized to calcium acetate or placebo for 12 weeks. The dose of study drugs was titrated to achieve target serum phosphorus of 2.7-4.5 mg/dL. Serum phosphorus, calcium, iPTH, bicarbonate and serum albumin were measured at baseline and every 2 weeks for the 12 week study period. The primary efficacy endpoint was serum phosphorus at 12 weeks. Secondary endpoints were to measure serum calcium and intact parathyroid hormone (iPTH) levels.

RESULTS: At 12 weeks, serum phosphorus concentration was significantly lower in the calcium acetate group compared to the placebo group (4.4 ± 1.2 mg/dL vs. 5.1 ± 1.4 mg/dL; p = 0.04). The albumin-adjusted serum calcium concentration was significantly higher (9.5 ± 0.8 vs. 8.8 ± 0.8; p < 0.001) and iPTH was significantly lower in the calcium acetate group compared to placebo (150 ± 157 vs. 351 ± 292 pg/mL respectively; p < 0.001). At 12 weeks, the proportions of subjects who had hypocalcemia were 5.4% and 19.5% for the calcium acetate and the placebo groups, respectively, while the proportions of those with hypercalcemia were 13.5% and 0%, respectively. Adverse events did not differ between the treatment groups.

CONCLUSIONS: In CKD patients not yet on dialysis, calcium acetate was effective in reducing serum phosphorus and iPTH over a 12 week period.

Gulati A, Sridhar V, Bose T, Hari P, Bagga A. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. Int Urol Nephrol. 2010 Dec;42(4):1055-62. Epub 2009 Dec 18.

BACKGROUND: The relative effectiveness and safety of sevelamer, a mineral-free phosphate binder, for treatment of hyperphosphatemia in children with chronic kidney disease is uncertain.

AIM: This study was designed to compare the efficacy and acceptability of sevelamer hydrochloride to calcium acetate as a phosphate binder in pediatric patients with chronic kidney disease.

METHODS: A 12-week open-label trial of sevelamer hydrochloride vs calcium acetate was initiated in 22 patients, aged 2-18, with CKD stages 3 and 4. After a 2-week washout of phosphate binders and vitamin D, patients were randomized to receive sevelamer hydrochloride or calcium acetate. The effect of therapy was adjusted for baseline blood levels of calcium, phosphorus, calcium-phosphate product, alkaline phosphatase, PTH and GFR using ANOVA. The primary end point was the decrease in serum phosphorus levels after 12 weeks of treatment.

RESULTS: Of the 22 patients enrolled, data of 19 patients were used for analysis. The adjusted mean serum phosphate levels at 12 weeks did not differ significantly between calcium acetate- (5.3 mg/dl) and sevelamer-treated subjects (6.1 mg/dl) (P adjusted means = 0.6). The adjusted blood level of calcium at 12 weeks was significantly lower in the sevelamer-treated patients (8.2 mg/dl) compared to those treated with calcium acetate (9.1 mg/dl) (P adjusted means = 0.01). In the sevelamer group, there was a non-significant decrease in serum bicarbonate, whereas the total and LDL cholesterol significantly decreased at 12 weeks (P = 0.04). Sevelamer hydrochloride was well tolerated and without adverse effects related to the drug.

CONCLUSIONS: Compared to calcium acetate, use of sevelamer in children with chronic kidney disease is associated with similar reduction in serum phosphate levels, lower risk of hypercalcemia, and marked decrease in serum lipid levels.

References:

1. Navaneethan SD, Palmer SC, Vecchio M, et al. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. *Cochrane Database Syst Rev*. 2011;(2):CD006023.

2. KDOQI Clinical Practice Guidelines. Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_bone/guide6.htm. Accessed August 27, 2012.

3. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev*. 2010;(1):CD008327.

4. Jamal SA, Fitchett D, Lok CE, Mendelssohn DC, Tsuyuki RT. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis. *Nephrol. Dial. Transplant.* 2009;24(10):3168–3174.

5. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10.

6. Zhang Q, Li M, Lu Y, et al. Meta-analysis comparing sevelamer and calcium-based phosphate binders on cardiovascular calcification in hemodialysis patients. *Nephron Clin Pract*. 2010;115(4):c259–267.

7. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12.

8. KDIGO Work Group Members. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int. Suppl.* 2009;(113):S1–130.

9. Brouwers M. Introduction to AGREE II. *AGREE Enterprise website*. Available at: http://www.agreetrust.org/index.aspx?o=1193. Accessed August 27, 2012.

10. Qunibi W, Winkelmayer W, Solomon R, et al. A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease. *BMC Nephrol*. 2011;12(9). Available at: http://www-ncbi-nlm-nih-gov.liboff.ohsu.edu/pubmed?term=A%20randomized%2C%20double-blind%2C%20placebo-controlled%20trial%20of%20calcium%20acetate%20on%20serum%20phosphorus%20concentrations%20in%20patients%20with%20advanced%20non-dialysis-dependent%20chronic%20kidney%20disease. Accessed August 28, 2012.

11. Gulati A, Sridhar V, Bose T, Hari P, Bagga A. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. *International Urology & Nephrology*. 2010;42:1055–1062.