Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, June 28, 2012 1:00-4:00 PM
Hewlett-Packard Building
4070 27th Ct SE
Salem, OR 97302
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 and Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. OLD BUSINESS
- a. Dificid® (fidaxomicin)* — M. Herink (OSU)
  1. Infectious Disease Consult
  2. Public Comment
- b. New Drug Evaluation* — K. Sentena (OSU)
  1. Kalydeco® (ivacaftor)
  2. Public comment

III. NEW BUSINESS

- a. ESA Class Update and New Drug Review* — K. Ketchum (OSU)
  1. Omontys® (peginesatide)
  2. Public comment
- b. Nitrates Abbreviated Class review and New Drug Evaluation* — B. Liang (OSU)
  1. Rectiv® (nitroglycerin ointment 0.4%)
  2. Public Comment
- c. Targeted Immune Modulators Drug Class Review* — M. Herink (OSU)
  1. TIMS Executive Summary
  2. DERP P&T Committee Brief
  3. Public Comment
- d. New Drug Review* — S. Willard (OSU)
  1. Ferriprox® (Deferiprone)
  2. Public Comment

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. 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)*

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 31, 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; Phillip Levine, PhD; Meena Mital, MD; William Origer, MD; David Pass, MD; Stacy Ramirez, PharmD; James Slater, PharmD; Cathy Zehrung, RPh;
Staff Present: Bing-Bing Liang, PharmD; Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA: HA; Ted Williams, PharmD; Valerie Smith, Richard Holsapple, RPh; Ralph Magrish, MPA
Staff Present by Phone: Kathy Sentena, PharmD
Audience: Barry Benson (Merck); Nathan Wood, MD (Merck); Shane Hall (Purdue); Venus Holder (Eli Lilly); John Brokers (Eli Lilly); Deron Grothe (Teva); Greg Marchak (GSK); Joanna Turbeville (GSK); Bruce Smith (GSK); Rob Pearson; Chris Adams (Lundbeck); Reenie Traether (Lundbeck); Cheryl Fletcher (Abbott); Deborah Griffs (Abbott); Jeana Colabianchi (Sunovion); David Barba (Forest); Kathy Kirk (OPMC); Richard Kosesan; Tzeli Triantafillou; Anne Marie Licos (MedImmune); Barbara Felt; Mike Willett (Pfizer); Dr. Robert Mendelson (FAAP); Dr. William Lavia (FAAP)

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I. CALL TO ORDER

a. The meeting was called to order at approximately 1pm.
b. Conflict of interest declarations were reviewed and no new conflicts were reported.
c. The April 26, 2012 meeting minutes were reviewed.

ACTION: Approved as is.

II. DUR ACTIVITIES

a. Mr. Magrish reported that DMAP will post an Invitation to Bid (ITB) for a generic preferred drug list will be posted soon as a result of a budget note from the special 2012 Legislative Session.
b. Mr. Holsapple presented the ProDUR report.
c. Dr. Williams presented the RetroDUR report and recommended doing some housekeeping to the report and cleaning up some outdated pieces.

***ACTION:** Recommendations approved.

d. Mr. Citron presented the Quarterly Utilization Reports.
e. Ms. Ketchum presented the ICS/LABA Policy Evaluation recommending continuing PA requirements for ICS/LABA combinations, consider loosening electronic criteria to require only a diagnosis of COPD or prior anti-cholinergic inhaler use, implement RetroDUR education lettering on LABA monotherapy in the absence of COPD indicators, further study to evaluate patient outcomes after encountering a PA for ICS/LABA, and further study of patients without a diagnosis.

***ACTION:** Recommendations approved

f. Dr. Sentena presented the Oregon State Drug Review on the current findings in the off-label use of Atypical Antipsychotics.

III. HOUSEKEEPING

a. Mr. Citron recommended removing the Ondansetron quantity limit.

***ACTION:** The Committee approved recommendation after executive session.

IV. OLD BUSINESS

a. Dr. Sentena presented Synagis Drug Use Evaluation recommending requiring prior authorization for use of palivizumab in compliance with AAP recommendations and limiting payment to pharmacy providers to eliminate the possibility of duplicate payment between pharmacy and medical providers. Dr. Mendleson presented public comment. Bill Lavia from MedImmune presented public comment.

***ACTION:** All in favor with additional recommendation of requiring at least 10 tests in a week to determine season onset/offset.

V. NEW BUSINESS

a. Dr. Sentena presented Asthma Controller Class Update recommending removing Aerobid due to no rebateable product availability, verify SRA on Pulmicort,remove if not contracted and grandfather current clients, and update PA criteria. Barbara Felt with GlaxoSmithKline presented public comment.

***ACTION:** The Committee approved recommendation after executive session.

b. Dr. Herink presented Seizure Medication Class Update and New Drug Reviews recommending adding clobazam to the oral anticonvulsant class on the PDL with PA for diagnosis verification, make ezogabine second line non-preferred oral anticonvulsant to ensure appropriate use and continue to prefer generic alternatives when appropriate. Barbara Felt with GlaxoSmithKline presented public comment.

***ACTION:** The Committee approved recommendation after executive session.

c. Ms. Ketchum presented Topical Antiparasite Class Update and New Drug Reviews recommending spinosad 0.9% topical suspension and ivermectin 0.5% lotion non-preferred due to insufficient evidence of effectiveness or safety relative to permethrin.

***ACTION:** The Committee approved recommendation after executive session.

d. Dr. Liang presented Other Lipid Lowering Agents Abbreviated Class Review recommending adding Other Lipid Lowering Agents to the PDL and include cholestyramine as the preferred bile acid sequestrant, include gemfibrozil, fenofibrate tablets, fenofibric acid tablets and Triplix pending supplemental rebate contract negotiations, make Niaspan and Niacor preferred, make ezetimibe and Lovaza non-preferred. Rob Pearson with GlaxoSmithKline presented public comment. Deborah Griffis with Abbott presented public comment. Robert Shipiro with OHSU submitted written public comment. Nancy Curosh, MD submitted written public comment.

***ACTION:** All in favor with deferment of fish oil action pending review of evidence for other indications.

VI. HERC COVERAGE GUIDANCE

a. Dr. Livingston and Dr. Alison Little presented guidelines on Low Back Pain. John Brokars with Eli Lilly presented public comment. The Committee recommended specifying acute versus chronic back pain, a requirement of documentation of improved functionality for coverage, requirement of initial risk assessment and that a caveat be included for the herbal recommendations that they are not regulated by the FDA.

VII. The meeting adjourned at approximately 4:50 pm.

May 18th, 2012

Megan Herink, OSU College of Pharmacy
Oregon Health Authority
Pharmacy and Therapeutics Committee

Ms. Herink,

Thank you for the opportunity to comment on proposed coverage policies for drugs for *Clostridium difficile* infection (CDI) for the Oregon Health Plan.

First-line treatment of CDI with metronidazole is a reasonable recommendation. Metronidazole is efficacious, and an appropriate recommendation for anyone whose disease is not severe enough to require hospital admission. Although no universally-accepted standard exists to define severity of disease, I consider the necessity of a hospital admission to define a severe case of CDI. In severe cases, vancomycin is preferred as first-line treatment, due to its favorable colonic intraluminal pharmacokinetic properties compared with metronidazole.

In the outpatient setting, metronidazole is a cost-effective treatment option, as vancomycin oral capsules are quite expensive despite the recent availability of a generic alternative, and the IV solution can be hard to locate from outpatient pharmacies. I routinely use oral metronidazole as first-line therapy for all non-severe patients and utilize it again for the first relapse. In regards to the committee's concern on the risk of metronidazole resistance of *C. difficile*, I do not feel that the rare anecdotal reports are sufficient to deter its routine clinical use.

Likewise, I am not convinced that the emergence of vancomycin-resistant bacteria, whether vancomycin-resistant *E. faecium* or vancomycin-intermediate *S. aureus*, has been shown to present a large-enough risk to preclude routine use of vancomycin treatment of CDI in hospitalized patients, except perhaps in repeated or prolonged use in certain situations (eg liver transplant). Moreover, oral vancomycin is generally not absorbed systematically, so systemic toxicity risk is vanishingly small. Relapse, not resistant bacteria, is the main concern when treating CDI. It is not uncommon for practitioners to confuse relapse or recurrence of disease with antimicrobial resistance.

The evidence does not support a clinical advantage of fidaxomicin over currently approved agents, and it is significantly more expensive. Although studies demonstrated a lower rate of recurrence with use compared to vancomycin, when looking specifically at the cohort of patients on concomitant antibiotics, rates were not as substantial. Many patients in clinical practice are commonly on other antibiotics. In clinical practice, step-wise therapy for non-severe disease commonly starts with metronidazole for initial treatment and first relapse, then vancomycin, then a taper or addition of rifampin before fidaxomicin is considered.

Sincerely,

James E. Leggett, MD

Assistant Director, Medical Education (Infectious Disease), Providence Portland Medical Center

Associate Professor, Internal Medicine, Oregon Health and Sciences University

Fidaxomicin (Dificid)

Goal(s):

- To optimize appropriate treatment of *Clostridium difficile* associated diarrhea

Length of Authorization: 10 days

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
Requires PA: fidaxomicin (Dificid®).

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of *Clostridium Difficile* Associated Diarrhea (CDAD)? (ICD-9 008.45)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a preferred antibiotic? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go to #4
4. Does the patient have a documented trial of appropriate therapy with vancomycin or metronidazole for a first recurrence or contraindication to therapy?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Does the patient have severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Approve for up to 10 days

P&T Board Action: 4-25-2012
Revision(s):
Initiated:

Oregon State University
College of Pharmacy

Month/Year of Review: June 2012
Generic Name: Ivacaftor
Comparator Therapies: None

End date of literature search: April 2012
Brand Name (Manufacturer): Kalydeco (Vertex Pharmaceuticals)
Dossier received: Yes

FDA Approved Indications: Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator used for the treatment of cystic fibrosis (CF) in patients 6 years and older who have the G551D mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.[1] Ivacaftor is given twice daily as a 150 mg capsule with fatty food to increase absorption.

Key Questions:

1. Is ivacaftor more effective than currently available preferred agents for the treatment of CF?
2. Is ivacaftor better tolerated than currently available preferred agents?
3. Are there specific populations which ivacaftor would be better tolerated or more effective?

Conclusions: There is moderate level of evidence to suggest that ivacaftor is superior to placebo in patients (≥12 years old) with the G551D mutation, as illustrated by an increase in FEV_1. There is also moderate evidence that ivacaftor is well tolerated with adverse effects resulting in discontinuations rates less than placebo. There are no head-to-head trials comparing ivacaftor to other CF treatments. Changes in FEV_1 with ivacaftor were similar to therapies used in the chronic management of CF. There is insufficient evidence to grade ivacaftor treatment in children under 12. Limited unpublished data suggests similar efficacy and safety as in patients over 12 years of age. Due to the robust nature of the results and benefits that outweigh the risks, use in this population is also recommended.

The efficacy and safety evaluation of ivacaftor is limited by small study populations, study durations of only one year and unpublished data. Ivacaftor has been shown to be effective only in the CF population with the G551D mutation, making ivacaftor a treatment option in only a small percentage of patients with CF. The effects of ivacaftor on long term disease progression are unknown.

Recommendations:

It is recommended to use clinical prior authorization criteria (Appendix) to limit the use of ivacaftor to patients that are six years and older, diagnosed with CF, have the G551D mutation in the CFTR gene, is prescribed by or in consultation with a pulmonologist, has a baseline FEV1% predicted between 40-90%, and has had an adequate trial of standard medication therapy. Renewal criteria will be implemented to monitor for a clinical response and adherence.

Summary:

CF is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality. The effects on the lungs are characterized by dehydration of the airway surface liquid and impaired mucociliary clearance which leads to chronic pulmonary infection.[2] Current available treatments for CF focus on symptom management. Guidelines for chronic treatment of CF suggest that there is good evidence that inhaled tobramycin and dornase alfa provide substantial benefit to patients with moderate to severe lung disease. Studies have shown improvement in FEV_1 ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa. There is also fair evidence to suggest that macrolide antibiotics provide substantial benefit for all levels of disease with improvements in FEV_1 from 3.6%-6.2%.[2] Hypertonic saline, oral nonsteroidal anti-inflammatory drugs (NSAIDS) and inhaled $beta_2$ agonists also play a role in the chronic management of CF.[2]

Efficacy:

The primary morbidity associated with CF is loss of pulmonary function. An important outcome in monitoring pulmonary function is the absolute change in forced expiratory volume in one second (FEV_1). FEV_1 is the standard for measuring lung function in CF patients, which is associated with pulmonary outcomes and general morbidity and mortality.[3] Pulmonary exacerbations are also considered to be associated with reduced lung function and mortality and therefore can be an important indirect measurement of pulmonary function.[4] The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on respiratory health perception, quality of life, and clinically relevant respiratory symptoms.[3] A minimally clinically important difference of 4 points was established for this domain.[5] Weight is an important secondary outcome as studies have shown that lower than average birth weights and poor growth are correlated with lower lung function, increased morbidity and mortality in children with CF.[3]

Approval of ivacaftor was based on two phase III, randomized, double-blind, placebo controlled studies; STRIVE (published) and ENVISION (unpublished).[6,7] Studies included patients with CF and the G551D mutation on at least one CFTR allele. The main difference between the studies was STRIVE included patients 12 years and older with an average age of 26 and ENVISION enrolled patients 6 to 11 years with an average age of 9. STRIVE was a good quality study that showed that there was moderate strength of evidence that ivacaftor was more effective than placebo (mean absolute treatment difference in percent predicted FEV_1 was 10.6%, 95% CI 8.6 to 12.6, $p<0.001$).[6] ENVISION was not published and therefore did not meet our study inclusion criteria of being peer reviewed. However, results from ENVISION were similar to STRIVE suggesting a similar level of efficacy in patients 6 to 11 years (mean absolute treatment difference in percent predicted FEV_1 was 12.5%, $p<0.0001$).[7]

Safety: Ivacaftor was well tolerated with lower rates of discontinuation compared to placebo, 1% and 5%, respectively.[6] Increased hepatic enzymes were the cause of drug discontinuation and the manufacturer recommends that they be monitored throughout treatment. The most common adverse events experience with ivacaftor include; headache (24%), oropharyngeal pain (22%), upper respiratory tract infection (22%), nasal congestion (20%), abdominal pain (16%), nasopharyngitis (15%) and diarrhea (13%).[1] Severe adverse events occurring more often with ivacaftor were abdominal pain, increased hepatic enzymes and hypoglycemia.[1] Ivacaftor is metabolized by CYP3A enzymes and should not be given with strong CYPf3A inducers due to reductions in ivacaftor exposure which may reduce effectiveness.[1]

BACKGROUND/CURRENT LANDSCAPE

CF is a genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality. The effects on the lungs are characterized by dehydration of the airway surface liquid and impaired mucociliary clearance which leads to chronic pulmonary infection.[2] Available treatments for CF include aerosolized antibiotics, dornase alfa, hypertonic saline, oral corticosteroids, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, macrolide antibiotics, inhaled bronchodilators (β-agonists and anticholinergic medications) and oral antistaphylococcal antibiotics.[2] Recommendations for treatment are often based on the severity of lung disease, defined by forced expiratory volume (FEV_1) percentage of predicted (Table 1).

Table 1. Categorization of lung function based on FEV_1 percentage of predicted[2]

Category	Percentage of Predicted
Normal	>90% predicted
Mildly impaired	70-80% predicted
Moderately impaired	40-69% predicted
Severely impaired	<40% predicted

The 2007 Cystic Fibrosis Foundation Pulmonary Guidelines outlines 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 (Table 2). In CF patients with moderate to severe lung disease, inhaled tobramycin, dornase alfa and macrolide antibiotics (for all levels of disease) have been shown to provide substantial benefit in improvement in lung function.[2]

Several Cochrane reviews evaluated treatments options for patients with CF. Their findings suggests improved lung function as a result of inhaled tobramycin, hypertonic saline, dornase alfa, macrolide antibiotics and inhaled $beta_2$ agonists.[8-12] They found no benefit with inhaled corticosteroids and insufficient evidence to support oral nonsteroidal use.[13,14] Oral steroids did provide some benefit but were associated with high rates of adverse events.[15]

Table 2. Cystic Fibrosis Pulmonary Guidelines for Chronic CF Treatment[2]

Treatment	Estimated Benefit	Mean Changes in FEV1*	Strength of Recommendation
Inhaled tobramycin (moderate-severe lung disease)	Substantial	7.8% - 12.0%	Good
Dornase alfa (moderate-severe lung disease)	Substantial	5.8% - 7.3%	Good
Inhaled tobramycin (asymptomatic-mild disease)	Moderate	No change	Fair
Dornase alfa (asymptomatic-mild disease)	Moderate	3.2%	Fair
Hypertonic saline	Moderate	3% - 7.7%	Fair
Oral NSAIDS	Moderate	Slowed rate of decline	Fair
Macrolide antibiotics	Substantial	3.65 – 6.2%	Fair
Inhaled Beta2 agonists	Moderate	-	Good

* Not head-to-head trials comparisons.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:
- Change in forced expiratory volume (FEV_1)
- Pulmonary exacerbations (days in hospital/ days on antibiotics)
- Cystic Fibrosis Questionnaire-revised Score
- Weight Change
- All-cause Mortality

Study Endpoints:

STRIVE:
- Change in forced expiratory volume (FEV_1)
- Pulmonary exacerbations
- Cystic Fibrosis Questionnaire-revised score
- Sweat chloride concentrations
- Weight Change

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
STRIVE[6]									
Ramsey, et al Design: International, DB, PC,RCT, phase III	1. Ivacaftor 150 mg every 12 hours 2. Placebo	Average Age: 26 years <18 years: 22% ≥ 18 years: 78% Male: 48% Baseline FEV_1: 63.6% <70% FEV_1 predicted: 58% ≥ 70% FEV_1 predicted: 42% Sweat chloride: 100.2 mmol/L <u>Inclusion:</u> Patients ≥12 year old with CF, G551D mutation on at least one CFTR allele and FEV1 of 40 to 90% of predicted value. <u>Exclusion:</u> Ongoing illness, pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks of start; abnormal liver or renal function,	1. 84 2. 83	48 weeks (evaluated at 24 and 48 weeks)	**Primary:** <u>FEV_1% predicted absolute change from baseline (mean) at week 24:</u> Ivacaftor (83): 10.4 Placebo (78): -0.2 Tx effect: 10.6% 95% CI 8.6 to 12.6, p < 0.0001 **Secondary:** <u>FEV_1% predicted absolute change from baseline (mean) at week 48:</u> Ivacaftor (83): 10.1 Placebo (78): -0.4 Tx effect: 10.5% 95% CI 8.5 to 12.5, p<0.0001 <u>Pulmonary exacerbation at 48 weeks:</u> Ivacaftor (28): 33.7% Placebo (44): 56.4% RR: 0.43 p= 0.0003 95% CI 0.27 to 0.68 <u>Mean absolute change from baseline in CFQ-R at week 48</u>: Ivacaftor (74): 5.9	ARR= 22.7% NNT= 4.41	<u>Discontinuation due to AE</u>: Ivacaftor: 1 (1%) Placebo: 4 (5%) ARR: 0.04 95% CI -0.02 to 0.11 <u>Severe AE:</u> Ivacaftor: 20 (24%) Placebo: 33 (42%) ARR: 0.18 95% CI 0.04 to 0.32	NA NA	• Good Quality • Internal Validity Review of Bias:: <u>Selection:</u> low bias; clear randomization and allocation concealment <u>Performance</u>: low bias.; blinding of patients and care givers. <u>Detection</u>: low bias.; study monitors blinded. <u>Attrition</u>: low attrition; ITT analysis. • Subgroup analysis performed for baseline FEV1, geographic region, sex, and age which revealed similar significant treatment results. • Changes in sweat chloride concentrations have not been correlated to clinically meaningful outcomes and therefore not reported. • Patients allowed to continue pre-study medications.

		history of prolonged QT/QTc interval, transplantation history, colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *B. cenocepacia, B. dolosa,* and *M. abcessus*), concomitant use of inhibitors/inducers of CYP3A4 or use of inhaled hypertonic saline treatment (required to stop inhaled 4 weeks prior to first dose of study drug).			Placebo (62): -2.7 Treatment effect: 8.6 P<0.001 <u>Mean change from baseline in weight (kg) at 48 weeks:</u> Ivacaftor (77): 3.1 Placebo (68): 0.4 Treatment effect: 2.7kg P<0.001				

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, FAS = full analysis set data, LOCF= last observation carried forward.
[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)
Clinical Abbreviations: CFQ-R=Cystic Fibrosis Questionnaire-revised

CLINICAL EFFICACY-

Ivacaftor was approved by the FDA in January of 2012 on the basis of two phase III studies, STRIVE (published) and ENVISION (unpublished).[1,5] Both studies were randomized, double-blind, placebo controlled trials comparing ivacaftor 150mg twice daily to placebo with evaluations at 24 and 48 weeks. Inclusion criteria for both studies was a diagnosis of CF, G551D mutation on at least one CFTR allele and a FEV_1 of 40-90% (STRIVE) and 40-105% (ENVISION) of the predicted value for persons of their age, sex and height. STRIVE enrolled patients 12 years of age and older where ENVISION included patients 6 to 11 years. In both studies patients were allowed to continue on pre-study medications with the exception of hypertonic saline treatments. The primary outcome in both trials was the FEV_1% predicted absolute change from baseline at week 24.[6,7]

STRIVE was a good quality study enrolling 167 patients with an average age of 25 years and baseline FEV_1 of 64%.[6] There was moderate strength of evidence that ivacaftor was superior to placebo in improving FEV_1 at 24 weeks (mean treatment effect 10.6%, 95% CI 8.6 to 12.6, $p<0.001$). This effect was sustained at 48 weeks with similar statistically significant results. The percentage of patients experiencing a pulmonary exacerbation at 48 weeks was higher for placebo than ivacaftor; with an ARR of 22.7% and NNT of 4.41. Ivacaftor was also shown to be statistically superior to placebo in the outcomes of weight gain and improvements on the respiratory symptom scale (Cystic Fibrosis Questionnaire). Benefits of ivacaftor were also shown in analyses of subpopulations regardless of age, gender, disease severity or geographic region. There was moderate strength of evidence that ivacaftor was well tolerated with discontinuation rates less than placebo, 1% and 5%, respectively.

ENVISION was not graded because it was not published and therefore did not meet our inclusion criteria for being peer reviewed. Results are presented for information purposes, as this study is the only study in patients under 12. Ivacaftor (n=26) was found to be superior to placebo (n=26) for mean absolute change in percent predicted FEV_1 through 24 weeks, difference of 12.5% ($p<0.0001$).[7]

Limitations associated with STRIVE and ENVISION include small sample sizes and study durations lasting 48 weeks. Only patients with the G551D mutation have been shown to benefit with ivacaftor treatment. A study by Flume et al, was done in patients with the F508del-CFTR mutation which showed no benefit in lung function or patient-reported outcomes.[16] The FDA summary review of ivacaftor found efficacy results to be "robust". Additional data on long term efficacy is being obtained in an ongoing open-label extension study (PERSIST).[17]

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APPENDIX 1: SPECIFIC DRUG INFORMATION

CLINICAL PHARMACOLOGY[1]

Ivacaftor works by potentiating the G55ID-CFTR protein, which facilitates increased chloride transport by increasing the time that activated CFTR channels at the surface of the cell are open. This effect translates into assistance in regulating salt and water absorption and secretion throughout the body. The CFTR protein can be found on the epithelial cells in multiple organs including the lungs, pancreas, sweat glands and gastrointestinal tract.

PHARMACOKINETICS[1]

Parameter	Result
Absorption	increased 2- to 4-fold when given with food containing fat
Protein Binding	approximately 99% bound to plasma proteins
Elimination	87.8% in feces
Half-Life	12 hours
Metabolism	hepatic via CYP3A to M1 and M6*

* M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 isn't pharmacologically active.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): None known.

Cautions: Ivacaftor has been shown to cause elevated transaminases. Liver function tests should be done at baseline and every three months for the first year of therapy and annually for following years. Concomitant use with CYP3A inducers may reduce ivacaftor concentrations and reduce effectiveness and therefore this combination is not recommended.

Adverse Effects: Adverse effects occurring in more than 8% of study patients were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea and dizziness (Table 4). Severe adverse events occurring more often with ivacaftor were abdominal pain, increased hepatic enzymes and hypoglycemia.[1]

Table 4. Incidence of Adverse Drug Reactions in ≥8% of KALYDECO-Treated Patients with a *G551D* Mutation in the *CFTR* Gene and Greater than Placebo in 2 Placebo-Controlled Phase 3 Clinical Trials of 48 Weeks Duration [1]

Adverse Reaction (Preferred Term)	Incidence: Pooled 48-week Trials	
	KALYDE	Placebo N=104 n (%)

	CO N=109 n (%)	
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

Tolerability (Drop-out rates, management strategies): Ivacaftor was well tolerated with discontinuation rates less than placebo, 1% and 5%, respectively.[6]

Pregnancy/Lactation rating: Pregnancy category B, use only if clearly indicated. Ivacaftor excretion into milk is probable.

Unanswered safety questions: The safety and efficacy of ivacaftor beyond one year is unknown. Elevated transaminase levels experienced in small study populations may become more problematic when used in a large number of patients. The safety and efficacy in children under 6 and in individuals with other CF mutations has not been studied at this point.

Lab Tests: Elevated transaminases have been reported with ivacaftor treatment and monitoring of ALT and AST is recommended prior to therapy initiation and every 3 months during the first year and then annually. It is recommended that ivacaftor is discontinued if ALT or AST is 5 times the upper limit of normal. In studies two patients in the ivacaftor group experienced a serious adverse reaction of elevated liver transaminases compared to none in the placebo group.

Dose Index (efficacy/toxic): No overdoses have been reported. Doses up to 800mg were studied without any adverse events.

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

NME Drug Name	Lexi-Comp	ISMP	Clinical Judgment

LA/SA for invacaftor (generic)	None	None	Indinivir Invirase
LA/SA for Kalydeco (brand)	None	None	Kalbitor Kaletra

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Ivacaftor 150mg	Tablet	Oral	150 mg every 12 hours	Not studied. No dose adjustments are recommended for patients with mild to moderate renal impairment. Caution is advised when ivacaftor is used in patients with severe renal impairment (CrCl ≤30 mL/min) or end stage renal disease.	No dose adjustment for mild hepatic disease. 150mg once daily is recommended for patients with moderate (Child-Pugh Class B) hepatic impairment. Caution is advised when used in patients with severe hepatic impairment (Child-Pugh class C) and a dose of 150mg daily or less is recommended.	150 mg every 12 hours	Not studied	Must be taken with fat-containing food .

ALLERGIES/INTERACTIONS[1]

Drug-Drug: Ivacaftor is metabolized via CYP3A and therefore co-administration with other strong CYP3A inhibitors increases ivacaftor concentrations. It is recommended that ivacaftor dose be reduced to 150mg twice weekly if combined with a strong CYP3A inhibitor, for example ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin. For moderate CYP3A inhibitors (fluconazole and erythromycin) it is recommended that the dose be decreased to 150mg of ivacaftor once daily. Strong CYP3A inducers (rifampin, rifabutin,

phenobarbital, carbamazepine, phyenytoin and St.John's Wort) may decrease ivacaftor concentrations and therefore it is not recommended. ivacaftor and its metabolite may inhibit CYP3A and P-gp, causing increases in exposure to drugs that are substrates of CYP3A and/or P-gp. Use ivacaftor cautiously in patients on CYP3A and/or P-gp subtrates such as digoxin, cyclosporine and tacrolimus. When ivacaftor is used with CYP2C9 substrates monitoring is recommended (i.e. warfarin).

Food-Drug: Ivacaftor should not be taken with grapefruit or Seville oranges due to possible increased exposure to ivacaftor.

Allergy/Cross Reactive Substances: None known.

APPENDIX 2: Suggested PA Criteria

Ivacaftor (Kalydeco)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization: One year.

Approval Criteria

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the client have a diagnosis of cystic fibrosis and is 6 years of age or older?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented G551D mutation in the CFTR gene? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation.	Yes: Go to #4.	No: Pass to RPH; Deny (medical appropriateness)
4. Is the request from or in consultation with a pulmonologist?	Yes: Go to #5	No: Pass to RPH; Deny (medical appropriateness)
5. Does the patient have a baseline FEV_1% predicted between 40-90%?	Yes: Go to #6	No: Pass to RPH; Deny (medical appropriateness)
6. Is the patient on ALL or has had an adequate trial of the following medications below: - Dornase alfa (Pulmozyme®) AND - Hypertonic saline (Hyper-Sal®) AND - Inhaled or oral antibiotics (if appropriate)	Yes: Go to #7	No: Pass to RPH; Deny (medical appropriateness)
7. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	Yes: Approve for 3 months	No: Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	Yes: Go to #2	No: Go to #3
2. Does the patient have documented response to therapy, as indicated by an increase in FEV_1 by ≥5% after 3 months of therapy?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness)
3. Has the patient been compliant with therapy, as determined by refill claims history?	Yes: Go to #4	No: Pass to RPH; Deny
4. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	Yes: Approve for 3 months	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.
• Ivacaftor has not been studied in other populations of patients with Cystic Fibrosis.

P&T Action: 4/26/12 (MH/KS)
Revision(s):
Initiated:

Appendix 3: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.

5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf

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Abbreviated Update
Erythropoeiesis Stimulating Agents

Month/Year of Review: June 2012 **Literature Search End Date:** April Week 3 201
New drugs: peginesatide (Omontys®) **Manufacturer:** Affymax & Takeda Pharmaceuticals America (dossier received)

Current Status of PDL Class:

- Preferred Agents: DARBEPOETIN ALFA, EPOETIN ALFA (EPOGEN® - BRAND ONLY)
- Non Preferred: EPOETIN ALFA (PROCRIT®), PEGINESATIDE (pending review)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of ESAs?
- Is peginesatide more effective or safer for the treatment of anemia due to chronic kidney disease (CKD) than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

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Conclusions:

- For ESA treatment of CKD anemia, there is no target Hb level that is considered at less risk for death, serious cardiovascular events or stroke. Recommendations are to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.
- For treatment of chemotherapy induced anemia there is evidence of higher mortality, tumor progression and higher thromboembolic events associated ESA therapy. The majority of these trials targeted Hb targets > 12 g/dl. Both American and European updated treatment guidelines caution that ESA initiation should incorporate patient preferences for risk and benefit. The lowest ESA dose to prevent transfusion should be used. Non-responders should discontinue ESA after 6-8 weeks and there are no differences in efficacy or safety between the epoetin and darbepoetin.
- There is insufficient evidence to assess efficacy and safety of peginesatide relative to epoetin or darbepoetin.

Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.
- Recommend modifying the initial PA approval lengths for anemia associated with CKD and chemotherapy induced anemia to 8 weeks to assess adequate response.
- Recommend listing peginesatide as non-preferred until more safety and efficacy data are available.
- Recommend HERC update OHP guideline note 7 with current FDA labeling.

Reason for Review:
In June 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the erythropoeiesis stimulating agents (ESAs). A March 2010 Provider Synergies Review was used as the evidence source.[1] Since this review, peginesatide (Omontys®) has been approved by the Food and Drug Administration (FDA) for the treatment of the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.[2] In addition, The FDA published new safety warning for the ESAs and several new systematic reviews and clinical practice guideline updates have been published.

Previous HRC Conclusions (June 2010):

- Evidence does not support a difference in efficacy/effectiveness between darbepoetin and epoetin
- Evidence does not support a difference in harms/adverse events between darbepoetin and epoetin
- Recommend inclusion of both chemical entities.
- The committee expressed concern about initiation of therapy that would increase Hb above 12.
    - PA indicated to insure oncology patients initiate with Hb < 10
    - PA indicated to insure CKD patients maintain Hb < 11 with individual patient consideration for therapy Hb > 11

Background: ESAs reduce the need for and risks of repeated transfusions. ESAs are FDA approved for reducing the need for transfusion in patients with anemia associated with chronic renal failure (both requiring dialysis and not requiring dialysis with hemoglobin < 10 g/dL) and anemia in non-myeloid cancer patients on chemotherapy. Epoetin has additional indications for anemia in zidovudine-treated HIV-infected patients and anemic patients (hemoglobin 10-13 g/dL) having elective non-cardiac, nonvascular surgery.[4] ESAs are also used off-label for ribavirin induced anemia, anemia associated with chronic heart failure and potentially other anemias. All ESAs must be used under a Risk Evaluation and Mitigation Strategy program because the use of ESA to achieve hemoglobin ≥ 11 g/dL is associated with increased risk for serious adverse events including death. There are also case reports of pure red cell aplasia which may be caused by neutralizing anti-erythropoietin antibodies.[4] Epoetin is typically dosed three times a week whereas darbepoetin is longer acting and dosed weekly. The Effective Health Care Program[3] published a comparison of epoetin and darbepoetin for managing chemotherapy induced anemia and concluded the evidence did not show a clinically significant difference in hemoglobin response, transfusion reduction and thromboembolic event. The Canadian Agency for Drugs and Technologies in Health (CADTH)[5] published a review of ESAs for CKD and found that based upon the pooled results of three moderate quality trials of 1 year comparing epoetin to darbepoetin (n=775) there were no significant differences in all cause mortality (n=670) or risk of cardiovascular death (n=160).

Methods:
A Medline literature search ending April Week 3 2012 for meta-analyses or randomized active-controlled trials (RCT's) comparing peginesatide or hermatide or erythropoietin or epoetin or darbepoetin for treatment of anemia. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic

reviews and RCTs. The FDA website was searched for background information from advisory committees, new 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. After review of the citations from Medline and the manual searches, one FDA safety warning for ESAs was identified[6]; one general ESA review[4], one new systematic reviews[7] and one clinical guideline update[8] regarding use in CKD were identified; three systematic reviews [9 10 11] and two updated clinical guidelines[12 13 14] regarding use in oncology were identified; one systematic review[15] regarding use in HIV, and two systematic reviews[16 17] regarding use in heart failure were evaluated. No relevant published RCTs evaluating peginestatide were identified and the pivotal trial details were not located on the FDA website. ClinicalTrials.gov indicates 18 trials registered with 13 completed, 3 terminated and 2 still recruiting but no publications were provided. The dossier provided did not identify any fully published trials.

Systematic Reviews and Guidelines

CKD:

Dynamed[4] reported new Level 2 (mid-level) evidence of higher hemoglobin targets associated with increased risk of stroke, hypertension and vascular access thrombosis compared to lower targets in patients with chronic kidney disease from a systematic review[18] of 27 trials with methodological limitations and involving 10,452 CKD patients treated with ESAs. Higher hemoglobin targets were associated with an increased risk of stroke (RR 1.51, 95% CI 1.03-2.21) in analysis of 6 trials with 7,054 patients, increased risk of vascular access thrombosis (RR 1.33, 95% CI 1.16-1.53) in analysis of 8 trials with 6,844 patients and trends toward increased risk of mortality (RR 1.09, 95% CI 0.99-1.2) in analysis of 18 trials with 9,951 patients, serious cardiovascular events (RR 1.15, 95% CI 0.98-1.33) in analysis of 7 trials with 6,880 patients, and end-stage kidney disease requiring renal replacement therapy (RR 1.08, 95% CI 0.97-1.2) in analysis of 10 trials with 7,318 patients.[4]

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The October 2010 Clinical Evidence[7] review of chronic renal failure treatments reported that moderate quality evidence suggests in people with anemia and chronic renal failure, ESAs do not lower cardiovascular events or mortality, or prevent or slow the progression to end-stage renal disease. However, ESAs reduce the risk of blood transfusions but increase the risk of stroke. This finding was based upon the same review noted by Dynamed.[18]

NICE updated the ESA monitoring recommendations in the guideline for "Anaemia management in people with chronic kidney disease".[8] The guide now recommends to keep the Hb level between 10-12 g/dl for adults, young people and children aged 2 years and older, and between 9.5 and 11.5 g/dl for children younger than 2 years of age but not to wait until Hb levels are outside the range before adjusting treatment (for example, take action when Hb levels are within 0.5 g/dl of the range's limits).[8] It is also recommended to consider accepting Hb levels below the agreed range if: high doses of ESAs are required to achieve the response or the response is not achieved despite escalating ESA doses.[8] People with anemia of CKD should be considered resistant to ESAs when: the desired Hb is not achieved despite treatment with $\geq$300 IU/kg/week of subcutaneous epoetin or $\geq$ 450 IU/kg/week of intravenous epoetin or 1.5 micrograms/kg/week of darbepoetin, or there is a continued need for the

administration of high doses of ESAs to maintain the desired Hb.[8] Previous recommendations indicate there is no evidence of a clinical difference between epoetin and darbepoetin.[8]

Oncology:

A meta-analysis[9] of survival and other safety outcomes of ESA use in oncology related anemia found no effect on mortality (60 studies: OR 1.06; 95% CI: 0.97–1.15) or disease progression (26 studies: OR 1.01; 95% CI: 0.90–1.14). There was in increased risk of venous-thromboembolic events (44 studies: OR 1.48; 95% CI: 1.28–1.72). The effect on transfusion requirements and quality of life was not investigated. This review was systematic in approach and modeled a previous Cochrane review[19] methods but failed to explicitly quality assess the studies.

The Cochrane review was updated in 2009[10] and the authors concluding that ESA treatment in cancer patients increased mortality and worsened overall survival. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded. A total of 13,933 cancer patients from 53 trials were analyzed. ESAs were associated with mortality (HR1.17; 95% CI 1.06-1.30) and worsened overall survival (HR 1.06; 95% CI 1.00-1.12), with little heterogeneity between trials.

A CADTH[11] review confirmed the Cochrane finding but also reported treatment with ESAs prevented transfusions, compared with treatment with no ESA (RR: 0.64 [95% CI 0.56 to 0.73]), but led to an increased risk of thrombotic events (RR 1.69 [95% CI 1.27 to 2.24]) and serious adverse events (RR: 1.16 [95% CI 1.08 to 1.25]).

The AHRQ has published a protocol in June 2010[20] to address the conflicting results from the most recent meta-analyses cited above as well as two previous published in 2009.[21] [22] No estimated completion date is provided.

The American Society of Clinical Oncology and the American Society of Hematology have jointly published updated guidelines on the use of ESAs in adult cancer patients.[12] [13] New recommendations include:

- Clinicians should discuss potential harms (e.g. thromboembolism, shorter survival) and benefits (e.g., decreased transfusions) of ESAs and compare these with potential harms (e.g. serious infections, immune-mediated adverse reactions) and benefits (e.g. rapid Hb improvement) of RBC transfusions for patients undergoing myelosuppressive chemotherapy who have hemoglobin < 10 g/dL.
- If used, ESAs should be administered at the lowest dose possible and should increase Hb to the lowest concentration possible to avoid transfusions. Available evidence does not identify Hb 10 g/dL either as a threshold for initiating treatment or as a target for ESA therapy.
- ESAs should be discontinued after 6 to 8 weeks in nonresponders.
- ESAs should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk for myelodysplastic syndromes.
- Caution should be exercised when using ESAs with chemotherapeutic agents in diseases associated with increased risk of thromboembolic complications.

The European Society for Medical Oncology published clinical practice guidelines for ESAs in the treatment of anemia in cancer patients.[14] Levels of Evidence [I–IV] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology. Relevant recommendations are:

- There is no difference between different ESAs in relation to effectiveness and safety [Evidence Level I].
- Indicated for chemotherapy-induced anemia in adults with non-myeloid malignancies to prevent transfusions and improve health related quality of life. Patients not treated with chemotherapy there is no indication for the use of ESAs and there might be an increased risk of death when targeting Hb of 12-14 g/dl (Evidence Level I, A)
- The influence of ESAs on tumor response and overall survival in anemic cancer patients remains unclear. Several randomized trials have demonstrated decreased survival times and poorer regional control or progression-free survival but the design of these studies was aimed at Hb levels of >12 g/dl and included patients with a baseline Hb level of >11 g/dl [Level II].
- Consider ESA at a Hb of $\leq$ 10 g/dl to increase to < 2 g/dl or to prevent further decline (Evidence Level II,A)
- In patients with low-risk myelodysplastic syndromes based on bone marrow blast percentage, number of cytopenias and cytogenetic analysis, ESAs [+/- granulocyte-colony stimulating factor (G-CSF)] can be used to improve anemia (Evidence Level II).
- The relative risk of thromboembolic events is increased by 67% in patients treated with ESAs compared with placebo (RR 1.67; 95% CI 1.35–2.06) [Evidence Level I]. The use of ESAs should be carefully reconsidered in patients with a high risk of thromboembolic events.

HIV:

A Cochrane review[15] found evidence that epoetin compared with placebo does not reduce mortality, does not reduce transfusion requirements, did not increase hemoglobin levels, and did not improve quality of life in HIV-infected patients with anemia. The results were based on six RCTs with high risk of bias and the evidence was graded "very low". Despite this, the authors recommend epoetin for treating anemia in patients with AIDS is not justified. HIV anemia treatment guidelines are dated and still recommend epoetin.[23]

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Heart Failure:

Two meta-analyses of 9 of the same RCTs and evaluating the use of ESAs for anemia associated with chronic heart failure were identified.[16] [17] This indication is an off-label use. The Cochrane review[17] was based upon 11 small RCTs and concluded ESA treatment may improve exercise tolerance, reduce symptoms, and have benefits on clinical outcomes in anemic patients with heart failure. The other review[16] concluded ESAs are associated with a decrease in CHF-related hospitalizations and improved quality of life and exercise tolerance. Neither review was able to evaluate mortality.

FDA warnings:

On June 24, 2011 the FDA modified recommendations for more conservative dosing of ESAs for patients with CKD and the manufacturers have revised the Black Box Warning.[6] In controlled trials, CKD patients experienced greater risk of death, serious cardiovascular adverse events and stroke when targeting a hemoglobin level of > 11 g/dl.[6] Labels now do not recommend a target level because no trial has demonstrated an optimal

hemoglobin level. Previously the label recommended a target hemoglobin range of 10-12 g/dl.[6] The label now recommends to individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.[6]

New Drug Evaluation- Peginesatide:

FDA approved indications: It is indicated for the treatment of anemia due to CKD in adult patients on dialysis.[2]

Potential Off-label Use: It is not for use in CKD patients not on dialysis, in patients with cancer, or as a substitute for RBC* transfusions in patients who require immediate correction of anemia.[2] A phase I[24] and phase II[25] were identified as well as very small (n=14) open-label trial evaluating use in patients with pure red-cell aplasia.[26]

Clinical Efficacy & Safety Data:

No published RCTs were identified evaluating the peginesatide. The dossier references the FDA materials, posters, abstracts and file data. The FDA approved this drug based upon two randomized, active-controlled, open-label, multi-center trials in 1,608 patients with CKD on dialysis.[27]

The FDA reviewer presentation describes four active control trials. [28] Studies AFX01-12 and AFX01-14 were conducted in 1,608 patients on dialysis and previously received epoetin. Hemoglobin levels at study entry and target levels were generally higher than what is currently recommended in the ESA labeling. In terms of change in hemoglobin at week 29-36, the primary endpoint, peginesatide was found to be non-inferior to epoetin. The safety outcomes were similar for both products but the FDA reviewer noted that patients were initially stabilized on epoetin before the study. [28] Studies AFX01-11 and AFX01-13 were in CKD patients who were not on dialysis or ESA therapy the previous three months and were iron replete. Patients were randomized 1:1:1 on peginesatide 0.025mg/kg or 0.04mg/kg every four weeks, or darbepoetin 0.75mcg/kg every two weeks. Peginesatide was found to be non-inferior to darbepoetin. However, in these studies, there was a higher rate of the adverse event composite endpoint for peginesatide (22%) vs. darbepoetin (17%) (HR 1.32 90% CI 1.02 -1.72). The primary components driving this were major adverse cardiac events. [28]

It carries the same black box warning as the other ESAs.

References:

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY: Peginesatide is a synthetic pegylated dimeric erythropoietin receptor activating peptide that is chemically unlike erythropoietin.[28] *In vitro*, it binds to and activates the human erythropoietin resceptor and stimulates erythropoiesis in human red cell precursors.[2]

PHARMACOKINETICS[2]

Parameter	Result
SQ Bioavailability	46%, Cmax at ~48 hours
Protein Binding	Not reported
Elimination	Urinary excretion predoinates
Half-Life	IV: 25 ± 7.6 hours SQ: 53 ± 17.7 hours
Metabolism	Not metabolized

DOSE & AVAILABILITY[2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Single use PF vials: 2mg/0.5ml 3mg/0.5ml 4mg/0.5ml 5mg/0.5ml 6mg/0.5ml Single use PF syringes: 1mg/0.5ml 2mg/0.5ml 3mg/0.5ml	IV or SQ	Every 4 weeks	Initial: 0.04mg/kg See labeling for conversion from epoetin or darbepoetin	None	None	Not studied	No Adjustment	Must be refrigerated and protected from light. Must be discarded after 30 days if stored between 47 and 77 degrees. Multiple use vials should be discarded after 28 days after first use.

4mg/0.5ml 5mg/0.5ml 6mg/0.5ml Multiple use vials: 10mg/ml 20mg/2ml								

PF=preservative free

DRUG SAFETY[2]

Serious (REMS, Black Box Warnings, Contraindications): Carries ESA Black Box Warning ESAs regarding the increased risk of death, myocardial infarction , stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. It is contraindicated in patients with uncontrolled hypertension.

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

Drug Name	Lexi-Comp	ISMP	Clinical Judgment
peginesatide	pegaptanib, pegaspargase, pegfilgrastim, peginterferon, pegvisomant	None	
Omontys®	None	None	Omnipen, Omnihib, Omniprope

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Special populations:

It has not been studied in nursing mothers, pregnant women or children. It is in FDA Pregnancy Category C.

Tolerability:[2]

Table 3 Adverse Reactions Occurring in ≥10% of Dialysis Patients treated with OMONTYS

Adverse Reactions	Dialysis Patients Treated with OMONTYS (N = 1066)	Dialysis Patients Treated with Epoetin (N = 542)
Gastrointestinal Disorders		
Diarrhea	18.4%	15.9%
Nausea	17.4%	19.6%
Vomiting	15.3%	13.3%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18.4%	19.4%
Cough	15.9%	16.6%
Injury, Poisoning and Procedural Complications		
Arteriovenous Fistula Site Complication	16.1%	16.6%
Procedural Hypotension	10.9%	12.5%
Nervous System Disorders		
Headache	15.4%	15.9%
Musculoskeletal and Connective Tissue Disorders		
Muscle Spasms	15.3%	17.2%
Pain in Extremity	10.9%	12.7%
Back Pain	10.9%	11.3%
Arthralgia	10.7%	9.8%
Vascular Disorders		
Hypotension	14.2%	14.6%
Hypertension	13.2%	11.4%
General Disorders and Administration Site Conditions		
Pyrexia	12.2%	14.0%
Metabolism and Nutrition Disorders		
Hyperkalemia	11.4%	11.8%
Infections and Infestations		
Upper Respiratory Tract Infection	11.0%	12.4%

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Appendix 4: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.

• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf

Erythropoiesis Stimulating Agents (ESAs)

Goals:
Cover ESAs according to OHP guidelines and current medical literature.
Cover preferred products when feasible
Initiative: ESA
Requires PA: All ESAs require PA for clinical appropriateness
Length of Authorization : 8 weeks initially; then up to 1 year with 34 day limit per Rx

Approval Criteria		
1. What diagnosis is being treated?	recode ICD9 code:	
2. Is the diagnosis covered by OHP?	Yes: Go to #3	No: Pass to RPh; Deny (Not covered by the OHP)
3. Is this continuation therapy?	Yes: Go to #12	No: Go to #4
4. Is product requested preferred?	Yes: Go to #6	No: Go to #5
5. Will provider change to a preferred product?	Yes: Inform provider of preferred products and go to #6	No: Go to #6
6. Is the diagnosis anemia due to chronic renal failure or chemotherapy?	Yes: Go to #7	No: Go to #8
7. Is Hb < 10g/dl or Hct < 30% AND Transferrin saturation >20% and/or ferritin >100ng/ml?	Yes: Approve for 8 weeks with additional approval based upon adequate response.	No: Pass to RPh; Deny (Not Medically Appropriate)
8. Is the diagnosis anemia due to HIV?	Yes: Go to #9	No: Go to #10
9. Is the Hb < 10g/dL or Hct < 30% AND Transferrin saturation ≥ 20% AND Endogenous erythropoietin ≤ 500 iu/L AND If on Zidovudine is dose ≤ 4200mg/week?	Yes: Approve for length of Rx or 1 year, whichever is less.	No: Pass to RPh; Deny (Not Medically Appropriate)

P&T/DUR Action: 6/28/2012(KK); 9/16/2010 (DO)
Revision:
Initiated: 1/1/11

10. Is the diagnosis anemia due to ribavirin treatment?	Yes: Go to #11	No: Pass to RPh; Deny (Not Medically Appropriate)
11. Is the Hb < 10g/dL or Hct < 30% AND Is the transferrin saturation >20% and/or ferritin >100ng/ml AND Has the dose of ribavirin been reduced by 200mg/day and anemia persisted ≥ 2 weeks?	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh; Deny (Not Medically Appropriate)
#12. Has patient responded to initial therapy?	Yes, approve for length of prescription or 1 year, whichever is less.	No: Pass to RPh; Deny (Not Medically Appropriate)

Nitrates Review

Month/Year of Review: June 2012 **Date of Last Review:** NA
Classes Included: Nitrates

Reason for Review:
Nitrates including nitroglycerin, isosorbide dinitrate and isosorbide mononitrate have been used for many years, however they are currently not on Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Issues:
- Is there any reliable evidence showing nitrates' role in management of angina or other conditions?
- Is there evidence showing nitrates differ in benefits and harms within subgroups of patients?
- Is there any difference in effectiveness or harms among different formulations of nitrates?

Conclusions:
- Most studies of short acting nitrate treatment in unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI) have been small and uncontrolled. The rationale for NTG in UA/NSTEMI is extrapolated from pathophysiological principles and extensive, although uncontrolled, clinical observations. Recommendations from American College of Cardiology Foundation/American Heart Association (ACCF/AHA) in this setting have Class I recommendation as first line treatment, yet they only have evidence level C grading.
- The role for long acting nitrates is for patients with stable angina who cannot tolerate or are contraindicated to a beta-blocker or calcium channel blocker.
- The efficacy of isosorbide dinitrate and hydralazine is further recognized in clinical practice guidelines for the management of congestive heart failure.
- Available formulations differ in both onset and duration of action. There is insufficient evidence demonstrating differences in formulations.
- Headache, dizziness and hypotension are common side effects associated with nitrate use. Nitrate tolerance is a limitation of long term use and is dose and duration dependant.

Recommendations:
- Add nitrates to PDL
- Include a short acting nitrate for angina prevention and treatment. There is no clinical advantage of nitroglycerin spray over NTG sublingual.
- Include a long-acting nitrate for angina prophylaxis and treatment of angina and include isosorbide dinitrate ER for the management of heart failure.
- Further evaluate costs of various formulations for preference.

Background:

Coronary artery disease (CAD) is the most common type of heart disease. In 2008, 405,309 people died from CAD.[1] Every year approximately 785,000 Americans have a first coronary attack, and another 470,000 Americans have recurrent attack.[2] In 2010, coronary heart disease alone was projected to cost the United States $108.9 billion, which includes the cost of health care services, medications, and lost productivity.[3] Angina is a symptom of CAD, commonly known as chest pain. It is discomfort that occurs when the heart muscle is not getting enough blood. There are two forms of angina – stable or unstable. Stable angina happens during physical activity or under mental or emotional stress. Unstable angina (UA) is chest pain that occurs even at rest, without apparent reason. This type of angina is a medical emergency.[4] UA and closely related conditions of non-ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of CAD. These conditions are characterized by an imbalance between myocardial oxygen supply and demand.

Nitrates are vasodilators that are used to prevent and relieve chest pain due to CAD. The most common types of nitrates are nitroglycerin (NTG), isosorbide dinitrate, and isosorbide mononitrate. NTG was the first introduced in 1879 for treatment of angina. NTG in its immediate release form remains as first line therapy for acute anginal symptoms. In patients with exertional stable angina, chronic nitrate therapy in oral or transdermal preparations, improves exercise tolerance, time to onset of angina, and ST-segment depression during exercise testing. In addition, isosorbide dinitrate in combination with hydralazine serves a role in the management of heart failure as an adjunct to standard treatment. Nitrates reduce myocardial demand while enhancing myocardial oxygen delivery. These effects are achieved at both cellular and cardiovascular level. At a cellular level, nitrates, upon interacting with reduced sulfhydryl groups (probably supplied by cysteine and a necessary co-factor) located within or near organic nitrate receptors located on smooth muscle cells of blood vessels, are converted to nitric oxide and, in turn, are able to activate guanylate cyclase, increase intracellular cyclic guanosine monophosphate (cGMP) concentrations, and, as a result, cause vasodilation of venous and arterial blood vessels. Depletion of sulfhydryl groups during this metabolic process may be a major factor in development of nitrate tolerance, along with compensatory physiologic mechanisms. Data also exists suggesting that organic nitrates increase intraplatelet cGMP concentrations thereby impeding platelet activity. These pharmacologic actions of nitrates appear to preferentially occur within portions of blood vessels containing damaged endothelium, thus making them extremely useful in the pharmacotherapy of acute ischemic events. In addition, the sulfhydryl group plays a role in the vasodilation effect of nitroglycerin. Addition of N-acetylcysteine (NAC), a sulfhydryl donor, to intracoronary administration of nitroglycerin increased the proximal and distal coronary artery diameters by additional 11% and 8%, respectively. The potentiative effects of NAC in patients with coronary artery disease were much smaller. At cardiovascular level, When administered to ischemic patients, nitrates cause both peripheral and coronary venous and arterial vasodilation resulting in decreased preload and afterload and increased coronary blood flow, thus increasing myocardial oxygen supply and decreasing myocardial oxygen demand. Clinical investigation has also suggested that organic nitrates interrupt platelet hyperactivity. These effects improve congestive symptoms in heart failure and improve the myocardial perfusion gradient in patients with CAD. Normal coronary artery cross-sectional area can be increased by 20% with either sublingual nitroglycerin or isosorbide. Both pre- and poststenotic vessels can be dilated by 30% to 40%, as well as eccentric lesions which retain some dynamic component. As a result of both lowered cardiac demand and increased regional flow from either direct venodilation of stenosis or improved collateral flow, nitrates can "homogenize" myocardial blood flow.[5]

Methods:
A MEDLINE Ovid search was conducted using all nitrates including: cardiovascular disease, angina, nitrates, NTG, isosorbide dinitrate and isosorbide mononitrate. The search was limited to meta-analysis, English language, and to studies conducted in humans from 2002 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Drugs Included in This Review

Drug	Dosage Form	Generic Availability
NTG	Sublingual tablet	Y
	Sublingual spray	N
	Transdermal patch	Y
	Transdermal ointment	N
Isosorbide mononitrate	Oral immediate or extended release tablets	Y
Isosorbide dinitrate	Oral immediate or extended release tablets	Y
	Oral extended release capsules	N

Guidelines
The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) updated treatment guidelines on UA and NSTEMI in (May 2011.)[6] The task force committee members reviewed and compiled published reports through a series of computerized literature searches of the English-language literature since 2002 and a final manual search of selected articles. The recommendations made were based primarily on these published data. The weight of the evidence was ranked highest (A) to lowest (C). The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with UA/NSTEMI summarize both clinical evidence and expert opinion. The key recommendations on role of nitrates therapy in UA/NSTEMI are as follow:

- Health care providers should instruct patients with suspected acute coronary syndrome (ACS) for whom nitroglycerin [NTG] has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely. *(Class I; Level of Evidence: C)*

- It is reasonable for health care providers and 9-1-1 dispatchers to advise patients who tolerate NTG to repeat NTG every 5 min for a maximum of 3 doses while awaiting ambulance arrival. *(Class IIa; Level of Evidence: C)*
- Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. *(Class I; Level of Evidence: C)*
- Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or ACE inhibitors. *(Class I; Level of Evidence: B)*
- Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 beats per minute), tachycardia (more than 100 beats per minute) in the absence of symptomatic HF, or right ventricular infarction. *(Class III; Level of Evidence: C)*
- Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. *(Class III; Level of Evidence: C)*
- All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. *(Class I; Level of Evidence: C)*
- Medical therapy with nitrates, beta blockers, and calcium channel blockers, alone or in combination, is recommended in patients with cardiovascular syndrome X. *(Class I; Level of Evidence: B)*

NICE Treatment Guideline on Stable Angina (July 2011):[7]

<u>Recommendations on preventing and Treating Episodes of Angina</u>

Offer a short-acting nitrate for preventing and treating episodes of angina. Advise people with stable angina:

- How to administer the short-acting nitrate
- To use it immediately before any planned exercise or exertion
- That side effects such as flushing, headache and lightheadedness may occur
- To sit down or find something to hold on to if feeling light-headed

When a short-acting nitrate is being used to treat episodes of angina, advise people:

- To repeat the dose after 5 minutes if the pain has not gone
- To call an emergency ambulance if the pain has not gone 5 minutes after taking a second dose

<u>Recommendations on Drugs for Treating Stable Angina</u>

- Offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina. Decide which drug to use based on comorbidities, contraindications and the person's preference.
- If the person cannot tolerate the beta blocker or a calcium channel blocker, consider switching to the other option (calcium channel blocker or beta blocker).
- If the person's symptoms are not satisfactorily controlled on a beta blocker or a calcium channel blocker, consider either switching to the other option or using a combination of the two. When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, slow release nifedipine, amlodipine or felodipine.
- Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.
- If the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:
  - A long-acting nitrate or
  - Ivabradine (not available in the US) or
  - Nicorandil (not available in the US) or
  - Ranolazine

- Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.
- For people on beta blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:
  - A long-acting nitrate or
  - Ivabradine (not available in the US) or
  - Nicorandil (not available in the US) or
  - Ranolazine

Institute for Clinical Systems Improvement (ICSI) treatment guidelines on management of stable coronary artery disease:[8]

- In patients with mild, stable coronary artery disease, drug therapy may be limited to short-acting sublingual nitrates on an as-needed basis. Use of lower dose (e.g., 0.3 mg or one-half of a 0.4-mg tablet) may reduce the incidence of side effects such as headache or hypotension in susceptible patients;
- If beta-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy, low cost, and relatively few side effects. Tolerance to long-acting nitrates is an important clinical issue in some patients and can be avoided by appropriate daily nitrate-free intervals.

American College of Cardiology/American Heart Association: Guideline Update for the Diagnosis and Management of Chronic Heart Failure (2009)[9]:

For the treatment of heart failure, these guidelines recommend the combination of a fixed dose of isosorbide dinitrate and hydralizine to a standard medical regimen to improve outcomes for African Americans, with an NYHA functional class III or IV (Level of Evidence: A).[9]

New Systematic Reviews

There are very limited systematic reviews available that were published in the last decade. The only systematic review found within timeframe defined for this review was a meta-analysis of randomized clinical trials on nitrates use in stable angina by Wei J et al published in 2011.[10] The results based on 51 trials with 3,595 patients showed both intermittent and continuous regimens of nitrates lengthened exercise duration significantly by 31 seconds (95% CI 11.28 to 51.47, p=0.002) and 53 seconds (95%CI 15.86 to 89.27, p=0.005) respectively. The number of angina attacks was significantly reduced by 2.89 episodes weekly for continuous administration (95%CI 0.58 to 5.19, p=0.01) and 1.5 episodes (95%CI 0.92 to 2.08, p<0.00001) weekly for intermittent administration. With intermittent administration, increased dose provided with 21 seconds more length of exercise duration. With continuous administration, exercise duration was pronged more in low-dose group. Quality of life was not improved by continuous application of NTG patches and was similar between continuous and intermittent groups. In addition, 51.6% patients receiving nitrates complained of headache. The authors concluded long-term administration of nitrates was beneficial for angina prophylaxis and improved exercise performance but might be ineffective for improving quality of life. With continuous regimen, low-dose nitrates were more effective than high-dose ones for improving exercise performance. By contrast, with intermittent regimen, high-dose nitrates were more effective. In addition, intermittent administration could bring zero-hour effect. The heterogeneity test was performed to evaluate these trials, however the review did not conduct quality assessment due to lack of information on allocation concealment and randomization procedure in most trials.

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New Dosage Formulation

Month/Year of Review: June 2012
Generic Name: Nitroglycerin ointment 0.4%
PDL Class: N/A

End date of literature search: May 2012
Brand Name (Manufacturer): Rectiv®
Dossier Received: No (Requested)

FDA Approved Indications: Nitroglycerin ointment 0.4% (Rectiv) is a nitrate vasodilator indicated for the treatment of moderate to severe pain associated with chronic anal fissure.[1]

Research Questions:

- Does commercially available nitroglycerin ointment 0.4% (Rectiv®) fundamentally change the treatment of and progression of chronic anal fissures?
- Is commercially available nitroglycerin ointment 0.4% (Rectiv®) more effective and safer for the treatment of any covered Oregon Health Plan indication than currently available agents?

Conclusions:

- There is low quality evidence that topical nitroglycerin (NTG) ranging from 0.2% to 0.4% is marginally but significantly better in healing anal fissures compared to placebo.
- There is no evidence demonstrating a difference in efficacy of NTG compared to topical calcium channel blockers or botulinum toxin.
- There is no evidence demonstrating a difference in efficacy between different doses of topical NTG.
- Nitroglycerin ointment 0.4% (Rectiv®) is the first commercially available and FDA approved product for chronic anal fissures and there is insufficient evidence to compare the efficacy to currently available products. Limited, unpublished data demonstrated a significant difference in a patient rated pain score compared to placebo.
- There is no evidence that commercially available nitroglycerin ointment 0.4% is more effective or safer for the treatment of any covered Oregon Health Plan indication.

Recommendations:

- Make nitroglycerin ointment 0.4% non-preferred.
- Require prior authorization for approved OHP diagnoses only (Appendix 1).

Background: Recommendations for initial therapy of anal fissures include conservative measures such as sitz baths, psyllium fiber, bulking agents, and topical anesthetics or anti-inflammatory ointments.[2] Additional medications are recommended for refractory or chronic anal fissures, including topical nitroglycerin (NTG). Nitroglycerin ointment (Rectiv) is the only FDA-approved prescription product in the United States and has previously been available in Europe and other countries. Currently, locally compounded formulations of topical NTG are used and are generally applied as a 0.2% to 0.4% ointment for anal fissure.[3] Rectiv is the first commercially available nitroglycerin ointment that does not have to be compounded. When applied topically to the anus, it increases local blood flow, relaxes anal sphincter tone, and reduces anal pressure.[3] After treatment with topical NGT, recurrence of anal fissures occurs in about one-third of the patients over 18 months.[3] Other pharmacologic treatments used include calcium channel blockers (CCBs), such as diltiazem and nifedipine, and botulinium toxin (Botox) injected into the anal sphincter.[4] Topical CCBs also have to be compounded by pharmacies as they are not available in topical form.

A recent 2012 Cochrane assessed the efficacy of medical therapies for anal fissure in an updated systematic review including a total of 5031 participants.[5] This review demonstrated that in terms of healing anal fissure, there is low quality evidence that topical NTG is marginally but significantly superior to placebo (48.9% vs. 35.5%, $p<0.0009$; OR 0.35; 95% CI 0.19 to 0.65) and topical NTG causes headache significantly more than those on placebo (OR 4.54; 95% CI 3.01 to 6.85).[5] All of these studies were in chronic anal fissures only and were of short duration. This review also demonstrated no statistically significant difference in cure rate between NTG and CCBs (OR 0.88; 95% CI 0.54 to 1.42), between topical NTG and the NTG patch (OR 1.07; 95% CI 0.50 to 2.27), or between NTG and botox (OR 0.56; 95% CI 0.20 to 1.57) but in all comparisons, NTG was associated with more adverse events, specifically headache. The risk of headache in the studies combined was 30%.[5] Three studies evaluated different doses of topical NTG (0.05% to 0.4%) and found that there was no dose response in cure rate (OR 0.91; 95% CI 0.57 to 1.45).

Clinical Efficacy: Nitroglycerin ointment 0.4% was approved based on the reanalysis of the data from a previous Phase 3 clinical unpublished trial that had been unsuccessful in demonstrating effectiveness.[6] The first analysis of the data used an imputation strategy of baseline-observation-carried-forward (BOCF) and showed no statistically significant difference in pain intensity from baseline between nitroglycerin and placebo ($p=0.118$). It was positioned that the BOCF method was potentially overly conservative in this situation. Two additional methods to impute missing

data were then utilized; the Retrieved Drop-out method and the last-observation-carried-forward (LOCF)/BOCF hybrid method. The LOCF/BOCF method demonstrated a statistically significant difference in the primary efficacy endpoint.[6]

This randomized double-blind, 3-week study took place in adults with moderate to severe pain of at least six weeks in duration due to a chronic anal fissure and compared nitroglycerin ointment to placebo. A total of 247 patients were randomized and 219 completed the trial, resulting in a total attrition of 11.3% (13.8% in the nitroglycerin group vs. 8.9% in the placebo group). The primary efficacy endpoint was the change from baseline in the 24-hour average pain intensity, using the visual analog scale (VAS). There is limited information to assess the quality and risk of bias included in this randomized controlled trial. A statistically significant change from baseline VAS score was seen comparing nitroglycerin ointment to placebo (p=0.038).[6]

Table 1. Primary Outcome Results for Study REC-C-001 using the LOCF/BOCF hybrid analysis

Change from baseline in visual analog scale (VAS) score	**Nitroglycerin ointment 0.4% (n=123)**	**Placebo (n=124)**
Change from Baseline Adjusted Means (SE)	-44 (3)	-37 (3.0)
Difference from Placebo (SE)	-7 (3.3); 95% CI (-14 to -0.4)	
p-value	0.038	

Safety: The most common adverse events reported in this study were headache, dizziness, diarrhea, and nausea. There were more discontinuations due to adverse events in the NTG group compared to the placebo group (7.3% vs. 2.4%, RR 3.02; 95% CI 0.78-14.0, p=0.074) and the most common reason within that group was headache, occurring in 64% of patients.[1,6] It is contraindicated with the use of phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, vardenafil, and tadalafil), as these are shown to potentiate the hypotensive effects of nitrates.

Mechanism of Action: Nitroglycerin forms nitric oxide which regulates the contractile state in smooth muscle and results in vasodilation. Intra-anal application of nitroglycerin reduces sphincter tone and resting intra-anal pressure.[1]

Dose and administration: Apply 1 inch of ointment (1.5mg of nitroglycerin) intra-anally every 12 hours for up to 3 weeks.[1]

Special Populations: There are no adequate and well-controlled studied in pregnant women, pediatrics, or in the geriatric populations.[1]

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Appendix 1 : Suggested PA Criteria

Suggested PA

Nitroglycerin Ointment 0.4% (Rectiv)

Goal(s):

- Cover for only OHP covered diagnoses.
- Restrict to indications supported by medical literature.

Length of Authorization: 3 weeks

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis for moderate to severe pain associated with chronic anal fissure?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness).
3. Is the diagnosis an OHP covered diagnosis?	Yes: Approve for 3 weeks	No: Pass to RPH; Deny, (Not covered by the OHP).

P&T Board Action: June 2012
Revision(s):
Initiated:

Drug Class Review

Targeted Immune Modulators

Final Update 3 Report
Executive Summary

March 2012

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

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Targeted Immune Modulators", dated March 2012. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 2: November 2009
Update 1: January 2007
Original Report: December 2005
The literature on this topic is scanned periodically

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INTRODUCTION

Targeted immune modulators, commonly referred to as biological response modifiers or simply *biologics*, are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the biologics (infliximab) in 1998 and approved 12 additional agents since that time for treating various rheumatic conditions, inflammatory bowel diseases, and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), certolizumab pegol (2008), golimumab (2009), ustekinumab (2009), and tocilizumab (2010).

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of targeted immune modulators. Included drugs are shown in Table 1.

Table 1. Included interventions

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Abatacept	Orencia® Bristol Myers Squibb	CTLA 4-Ig	Rheumatoid arthritis	Intravenous infusion dosed according to body weight (<60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter. Following single intravenous loading dose according to body weight specified above, the first 125 mg subcutaneous injection within 1 day, followed by 125 mg once weekly. Patients unable to receive an infusion may initiate weekly subcutaneous injections without an intravenous loading dose. Patients transitioning from intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of next scheduled intravenous dose.
			Juvenile rheumatoid arthritis[a] (6 years and older)	See Canadian product label
			Juvenile idiopathic arthritis (6 years and older)	10 mg/kg for patients <75 kg; adults schedule for patients >75kg (maximum dose 1000 mg) on weeks 0, 2, and 4 and then every 4 weeks thereafter.
Adalimumab	Humira® Abbott	TNF Inhibitor	Rheumatoid arthritis	40 mg every other week as subcutaneous injection; may increase to 40 mg weekly for adalimumab monotherapy.
			Psoriatic arthritis, ankylosing spondylitis	40 mg every other week as subcutaneous injection.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Juvenile idiopathic arthritis[b] (4 years of age and older)	15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week. ≥ 30 kg (66 lbs): 40 mg every other week.
			Crohn's disease	Initial subcutaneous dose (Day 1) 160 mg (four 40 mg injections in 1 day or two 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
			Plaque psoriasis	80 mg initial subcutaneous dose followed by 40 mg every other week starting 1 week after initial dose.
Alefacept	Amevive® Astellas	CD2 antagonist	Plaque psoriasis	15 mg given once weekly as an intramuscular injection. Treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are >250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle.
Anakinra	Kineret® Biovitrum/ Amgen	IL-1 receptor antagonist	Rheumatoid arthritis	100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency.
Certolizumab pegol	Cimzia® UCB, Inc	TNF Inhibitor	Rheumatoid arthritis	400 mg subcutaneous injection initially and at weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
			Crohn's disease[b]	400 mg subcutaneous injection initially and at weeks 2 and 4. If response occurs 400 mg subcutaneously every 4 weeks.
Etanercept	Enbrel® Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg once weekly as subcutaneous injection.
			Juvenile idiopathic arthritis (2-17 years)[c]	0.8 mg/kg weekly (maximum 50 mg weekly), given as 1 or 2 subcutaneous injections.
			Plaque psoriasis	50 mg given twice weekly as a subcutaneous injection for 3 months, followed by 50 mg weekly.
Golimumab	Simponi® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	50 mg subcutaneous injection once a month in combination with methotrexate.[d]
			Psoriatic arthritis, ankylosing spondylitis	50 mg subcutaneous injection once a month with or without methotrexate or other DMARDs.[e]
Infliximab	Remicade® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	*Adult:* 3 mg/kg intravenous induction at 0, 2, and 6 weeks with methotrexate followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treating as often as every 4 weeks.
			Crohn's disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg. *Pediatric* [f,g]: 5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Psoriatic arthritis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter, with or without methotrexate.
			Ankylosing spondylitis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 6 weeks thereafter.
			Active ulcerative colitis	5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. *Pediatric*[f]: 5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by maintenace regimen of 5 mg/kg every 8 weeks.
			Plaque psoriasis	5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.
Natalizumab	Tysabri® Biogen-Idec	Anti-alpha-4 integrin subunit	Crohn's disease[b]	300 mg intravenous infusion every 4 weeks.
Rituximab	Rituxan® Genentech Hoffman-La Roche[h]	Anti-CD 20a	Rheumatoid arthritis	Two 1000 mg intravenous infusion on days 1 and 15 in combination with methotrexate. Subsequent courses administered every 24 weeks or based on clinical evaluation but not sooner than every 16 weeks.
Tocilizumab	Actemra® Genentech	IL-6 receptor monoclonal antibody	Rheumatoid arthritis	Start dose 4 mg/kg, increase up to 8 mg/kg given every 4 weeks with or without DMARD. Increase to 8 mg/kg based on clinical response. Dose exceeding 800 mg/ infusion not recommended.
			Systemic juvenile idiopathic arthritis[b] (2 years and older)	Body weight <30 kg: 12 mg/kg intravenous infusion every 2 weeks. Body weight ≥30 kg: 8 mg/kg every 2 weeks.
Ustekinumab	Stelara® Janssen Biotech	IL-12 and IL-23 monoclonal antibody	Plaque psoriasis	Body weight ≤100 kg (220 lbs), recommended dose 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks by subcutaneous injection Body weight >100 kg (220 pounds), recommended dose 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Abbreviations: AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.
[a] Approved only in Canada
[b] Not approved in Canada
[c] In Canada, pediatric: 4-17 years
[d] Not approved in combination with methotrexate in Canada
[e] Not approved in combination with methotrexate/other DMARDs in Canada
[f] In United States., pediatric: 6-17 years
[g] In Canada, pediatric: ≥9 years
[h] Manufacturer in Canada
Note: Table 1 provides manufacturer and approved indications in the United States and Canada and dosage and administration information in the United States relative to indications covered in this report. Readers should refer to the Health Canada product monograph of individual drug products for dosing information for Canada.

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

1. How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?

2. What are the comparative incidence and severity of harms associated with the use of these drugs?

3. Do the included drugs differ in effectiveness or harms in the following subgroups:
   - Different genders or different racial, age, or socioeconomic groups?
   - Patients with comorbidities?
   - Patients taking other commonly prescribed drugs?
   - Patients with early aggressive compared with persistent rheumatoid arthritis?

METHODS

For Update 3 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2009 (January) to 2011 (October) using included drugs, indications, and study designs as search terms. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches.

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

RESULTS

Overview

For Update 3, literature searches identified 1589 citations. We received dossiers from five pharmaceutical manufacturers: Abbot, Amgen, Centocor Ortho Biotech, Genentech, and UCB Inc. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 436 citations. After re-applying the criteria for inclusion, we ultimately included 78 new publications, representing 68 unique studies.

Key Question 1. Efficacy and Effectiveness

Rheumatoid Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab.

We included 16 trials, 21 systematic reviews and meta-analyses, and seven observational studies. Only one randomized controlled trial was a double-blinded head-to-head trial. One study was characterized as an effectiveness trial. Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

The only double-blinded head-to-head trial that we found on the comparative efficacy of targeted immune modulators was a fair randomized controlled trial that compared abatacept with infliximab in patients with inadequate response to methotrexate. At 6 months, no differences in efficacy were apparent between patients treated with abatacept or infliximab. The strength of evidence is moderate. After 1 year, however, abatacept was statistically significantly more efficacious on most outcome measures than infliximab (American College of Rheumatology 20 response 72.4 compared with 55.8%; $P<0.001$; American College of Rheumatology 50 response 45.5 compared with 36.4%; $P<0.001$). It has to be noted though, that infliximab was administered at a fixed dose throughout the entire study. Infliximab efficacy trials have shown that up to 30% of patients require dose increases.

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis were limited to one small randomized controlled trial and multiple nonrandomized or observational studies rendering evidence of low strength. These studies indicated no differences in efficacy between adalimumab and etanercept but greater response rates for adalimumab and etanercept compared with infliximab.

Overall, seven studies indicated that etanercept is more efficacious than infliximab. The only study with a randomized allocation of patients, however, was a fair, small (n=32) open-label trial. Results indicated greater response rates in patients treated with etanercept than with infliximab (74.4% compared with 60% after 54 weeks; P=NR). Six head-to-head observational studies and one nonrandomized trial also reported similar findings of greater efficacy of etanercept than infliximab. The strength of evidence was moderate.

Two prospective cohort studies based on Dutch and a Danish registries reported greater efficacy with adalimumab than infliximab. In the Danish (n=1452), 35% of patients treated with adalimumab achieved a LUNDEX-corrected American College of Rheumatology 50 response at 12 months, compared with 25% of patients on infliximab ($P< 0.001$). The strength of evidence was low.

Indirect comparisons of placebo-controlled randomized controlled trials suggest that etanercept is statistically significantly more efficacious than abatacept, anakinra, infliximab, and tocilizumab (range of relative risks from 2.31 to 3.30). No statistically significant differences in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab. The strength of evidence was low, except for the comparison of etanercept with infliximab for which the strength of evidence was moderate.

Data were too heterogeneous to conduct indirect comparisons of certolizumab pegol, golimumab, and rituximab with other targeted immune modulators.

Good to fair evidence was found from meta-analyses and large randomized controlled trials that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab are statistically significantly more efficacious than placebo for the treatment of rheumatoid arthritis. Treatment effects were large and consistent across studies.

Juvenile Idiopathic Arthritis

Currently abatacept, adalimumab, etanercept, and tocilizumab are approved by the US Food and Drug Administration for the treatment of juvenile idiopathic arthritis.

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of juvenile idiopathic arthritis exists. Five randomized controlled trials provided fair evidence that abatacept, adalimumab, etanercept, infliximab, and tocilizumab are more efficacious than placebo for the treatment of juvenile idiopathic arthritis. Except for the infliximab trial, however, the highly selected study populations were likely to compromise the external validity of these studies. Some of these studies did not meet our formal eligibility criteria. Because these studies are the only available randomized controlled evidence on some drugs, we are still presenting main findings.

Ankylosing Spondylitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis: adalimumab, etanercept, golimumab, and infliximab. We did not find any head-to-head trials of biologics for ankylosing spondylitis. We located one systematic review and meta-analysis that presented pooled results from nine randomized, placebo-controlled trials of adalimumab, etanercept, and infliximab. In addition we located four randomized placebo-controlled trials that were not included in the systematic review as they have been published more recently: two assessed etanercept, one assessed golimumab, and one assessed infliximab. We did not detect any studies on abatacept, alefacept, anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab. We did not include studies on early ankylosing spondylitis (nonradiological axial spondyloarthritis).

No direct evidence on the comparative effectiveness of targeted immune modulators for the treatment of ankylosing spondylitis exists. The strength of the evidence is insufficient. Good-to-fair evidence exists for the general efficacy of adalimumab, etanercept, golimumab, and infliximab compared with placebo.

Psoriatic Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of psoriatic arthritis: adalimumab, etanercept, infliximab, and golimumab.

We included two systematic reviews and meta-analyses that analyzed the same six trials of adalimumab, etanercept, and infliximab. The reviews provided comparisons between the three biologics using two different statistical methods of indirect comparisons. In addition, we included four placebo-controlled randomized controlled trials assessing the efficacy of abatacept, alefacept, golimumab, and ustekinumab. The studies ranged in duration from 12 to 22 weeks. Finally, we included one open-label registry study of adalimumab, etanercept, and infliximab for

data on quality of life. We did not find any studies on anakinra, certolizumab pegol, natalizumab, rituximab, or tocilizumab.

No direct evidence from head-to-head randomized controlled trials on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in adults or children exists.

Two systematic reviews and meta-analyses conducted indirect comparisons of adalimumab, etanercept, and infliximab for the treatment of psoriatic arthritis in adults. Both analyses suggested that the three treatments are more efficacious than placebo but no statistically significant differences among adalimumab, etanercept, and infliximab could be detected. One prospective observational registry study of 595 patients with psoriatic arthritis showed that adalimumab, etanercept, and infliximab have similar positive effects on quality of life. The strength of the evidence for the comparative effectiveness of adalimumab, etanercept, and infliximab was low.

In addition, evidence indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone and that abatacept, golimumab, and ustekinumab are more efficacious than placebo.

At this time there are no studies, placebo or head-to-head, that evaluate the use of targeted immune modulators in children with psoriatic arthritis.

Psoriatic Arthritis in Children

No evidence on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in children exists. In addition, no placebo-controlled trials on children with psoriatic arthritis are evident in the literature.

Crohn's Disease

The following drugs are currently approved by the US Food and Drug Administration for the treatment of Crohn's disease: adalimumab, certolizumab pegol, infliximab, and natalizumab.

Overall, the strength of evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease was insufficient. We did not find any head-to-head randomized controlled trials or observational studies comparing one targeted immune modulator to another and evidence was insufficient to make indirect comparisons.

We included one recent, good-quality systematic review and meta-analysis of all four targeted immune modulators approved by the US Food and Drug Administration for Crohn's disease. The review assessed two outcomes, failure of remission and relapse of disease activity, and analyzed the subgroup of patients with fistulizing disease separately. Overall, the review included 27 randomized controlled trials: eight on adalimumab, seven on certolizumab pegol, seven on infliximab, and six on natalizumab.

Pooled results regarding the general efficacy of targeted immune modulators for Crohn's disease showed consistent results. Infliximab demonstrated statistically significant greater efficacy than placebo for inducing remission and preventing relapse in all patients and in healing and maintaining remission in fistulizing Crohn's disease. Natalizumab was superior to placebo in inducing remission and preventing relapse in patients with Crohn's disease. Adalimumab demonstrated statistically significant greater efficacy than placebo for inducing remission. Both single trials on evaluating the efficacy of adalimumab for maintaining response demonstrated

statistically significant greater efficacy than placebo. Certolizumab pegol was superior to placebo only in preventing relapse but there was a trend showing a greater efficacy than placebo in inducing remission. Overall, Adalimumab and certolizumab pegol were not shown to be more efficacious compared with placebo for inducing remission and healing in fistulizing Crohn's disease. In particular, the evidence from currently available trials on investigating the efficacy of targeted immune modulators in patients with fistulizing Crohn's disease was insufficient.

We did not find any evidence that met our eligibility criteria on the general efficacy of abatacept, alefacept, anakinra, etanercept, golimumab, rituximab, tocilizumab, or ustekinumab for the treatment of Crohn's disease.

Although some studies allowed stable doses of other immunomodulatory agents, no conclusive evidence exists to determine whether combination treatment of targeted immune modulators with other agents (azathioprine, 6-mercaptopurine or methotrexate) leads to clinically and statistically greater improvements than monotherapy. We did not include studies of targeted immune modulators compared with active therapies for Crohn's disease.

We found no studies that met our eligibility criteria assessing the comparative or general efficacy of any targeted immune modulator in pediatric populations.

Crohn's Disease in Children

The only drug which is currently approved by the US Food and Drug Administration for the treatment of Crohn's disease in children is infliximab.

No new studies meeting our eligibility criteria were identified during the updated search. No evidence on the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease in children exists. We identified one systematic review of the evidence base for the medical treatment of pediatric inflammatory bowel disease. Due to the short time frame of the literature research the systematic review was rated poor. In addition, no placebo-controlled trials on children with Crohn's disease met our eligibility criteria.

We identified one randomized controlled trial ("A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNFα chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease" ortho REACH study) comparing two different dosing regimens of infliximab. We briefly described the REACH study because it is the only study we found that included children. In this study, 112 patients with a Pediatric Crohn's Disease Activity Index score greater than 30 were treated with 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 10, patients who responded to treatment (88.4% of treated patients) were randomized to 5 mg/kg every 8 or 12 weeks through week 46. Pediatric patients were more likely to be in clinical response and remission at week 54 when given infliximab every 8 weeks rather than every 12 weeks.

Ulcerative Colitis

Infliximab is the only drug currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in adults and children.

No head-to-head evidence on the comparative effectiveness of targeted immune modulators for the treatment of ulcerative colitis exists. The strength of the evidence is insufficient.

We located one recent, good-quality systematic review and meta-analysis of targeted immune modulators for inducing remission in ulcerative colitis. This review pooled the results of

five randomized controlled trials of 5 mg/kg infliximab compared with placebo. Patients were allowed stable doses of corticosteroids in all trials. The reviewers calculated a relative risk of 0.72 (95% CI, 0.57 to 0.91) for a *failure* to achieve remission, i.e., infliximab is more efficacious than placebo.

Ulcerative Colitis in Children

Infliximab is the only targeted immune modulator currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in children. We did not locate any randomized controlled trials of targeted immune modulators in the pediatric population of patients with ulcerative colitis.

Plaque Psoriasis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of plaque psoriasis: adalimumab, alefacept, etanercept, infliximab, and ustekinumab. We did not review trials of efalizumab because it was withdrawn from the market.

We located one fair-quality, randomized, head-to-head trial of etanercept compared with ustekinumab for the treatment of severe plaque psoriasis. In the trial 903 patients were randomized to 50 mg etanercept twice weekly or two doses of ustekinumab (45 mg or 90 mg) in a 12-week period. Significantly more patients in both ustekinumab groups achieved the primary outcome of a PASI 75 response compared with etanercept. The strength of evidence for this comparison was low.

Fair to good evidence from multiple placebo-controlled randomized controlled trials demonstrated the general efficacy of adalimumab, alefacept, etanercept, infliximab, and ustekinumab for achieving a Psoriasis Area and Severity Index 75 response in adults with plaque psoriasis. Specifically, we located 17 placebo-controlled trials that assessed the efficacy of targeted immune modulators for the treatment of plaque psoriasis in adults: five on adalimumab, three on alefacept, five on etanercept, one on infliximab, and three on ustekinumab. The studies on alefacept and etanercept were pooled in a meta-analysis. We did not find any studies on other targeted immune modulators. In addition, one study assessed the efficacy of etanercept in children and adolescents. Significantly more children in the etanercept group than in the placebo group experienced a response.

Key Question 2. Adverse Events

Eighteen head-to-head studies (almost exclusively observational studies) provided direct evidence on the harms associated with targeted immune modulators. Other evidence came from indirect comparisons of over 200 randomized controlled trials with placebo or disease-modifying antirheumatic drug controls (including two head-to-head randomized controlled trials). We located evidence on serious infection, malignancy, cardiovascular harms, rates of serious harms, withdrawal due to harms, and specific adverse events such as injection site reactions.

Evidence on the comparative risk of serious infections with targeted immune modulators was low strength. Evidence from short-term trials (median 6 months), using indirect comparison meta-analyses, indicated serious infections are less common with abatacept than with certolizumab, infliximab, and tocilizumab while certolizumab appeared to have a higher risk than

adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, or placebo. Analyses of only the antitumor necrosis factor monoclonal antibodies (adalimumab, certolizumab, golimumab, and infliximab) indicated that as a group, they have an increased risk compared with control groups (odds ratio, 1.49; 95% CI, 1.17 to 1.90), while the other targeted immune modulators, including etanercept (which blocks tumor necrosis factor by blocking receptors), did not. Limited observational evidence indicated an increased risk with antitumor necrosis factor drugs etanercept, infliximab, and adalimumab (hazard ratio, 1.2; 95% CI, 1.1 to 1.5) compared with disease-modifying drugs and that among the targeted immune modulators the risk of hospitalization with infection was higher with infliximab than anakinra, adalimumab, and etanercept. These studies found that and that the risk was highest in the first 6 months of treatment and among those with other risk factors for infection. The risk of tuberculosis appeared to be elevated with the use of targeted immune modulators as a group (odds ratio, 4.68; 95% CI, 1.18 to 18.60) based on trial data. Comparisons between the drugs were more limited, with low strength evidence indicating increased risk of tuberculosis with adalimumab compared with etanercept (adjusted incidence rate ratio, 4.1; 95% CI, 1.4 to 12.4) and a nearly statistically significant increased risk with infliximab compared with etanercept (3.1; 95% CI, 1.0 to 9.5). The median time to diagnosis of tuberculosis (anywhere, including reactivation of tuberculosis) was 13.4 months from start of therapy. While there was a small increase in risk of herpes zoster with antitumor necrosis factor drugs as a group (pooled hazard ratio 1.42 (95% CI, 1.14 to 1.78), risk was not increased with etanercept. The strength of this evidence was low. The evidence on adalimumab and infliximab was insufficient to draw conclusions. The strength of evidence comparing the risk of serious infections with targeted immune modulators was low strength. Evidence on the risk of other specific serious infections was insufficient strength to make conclusions.

On the whole, a broad range of evidence did not indicate a clear increase in risk of malignancy in general with the use of targeted immune modulators. There was evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the antitumor necrosis factor drugs adalimumab, infliximab, and etanercept (relative risk, 2.02; 95% CI, 1.11 to 3.95). Observational evidence supported these findings, although the risk estimates were somewhat lower magnitude. The strength of evidence comparing the risk of malignancy with targeted immune modulators is low strength. Although the US Food and Drug Administration issued a warning about the potential increased risk of malignancy in children, evidence in children is insufficient for making conclusions.

While case reports have indicated potential risk of various other serious adverse events, strength of evidence on the comparative risk of heart failure, autoimmunity, demyelination, and serious hepatic events with targeted immune modulator drugs is insufficient at this time.

Comparative evidence on overall adverse events, discontinuation of drug due to adverse events, and other measures of short-term tolerability was low to moderate strength, depending on the specific outcome. The rates of overall adverse events occurring with targeted immune modulators did not differ statistically significantly between the drugs. In short-term trials, abatacept and anakinra had lower risk of a serious adverse event compared with other targeted immune modulators. Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with abatacept, adalimumab, etanercept, and golimumab. Infusion or allergic reactions contributed to the increased risk of discontinuation with infliximab (hazard ratio, 2.11; 95% CI, 1.23 to 3.62).

Evidence on the comparative risk of adverse events associated with targeted immune modulators in children is very limited and was insufficient strength to make conclusions. The adverse event profiles appeared similar to those seen in adults, with small numbers of children experiencing serious adverse events including serious infections and injection site or infusion reactions.

Key Question 3. Subgroups

Overall, the strength of evidence to determine differences between targeted immune modulators in effectiveness or adverse events among subgroups was insufficient. The majority of the studies were not specifically designed to compare the effectiveness and safety of targeted immune modulators in one subgroup of patients compared with another or compared with the general population. Subgroup analyses and indirect evidence from placebo-controlled trials provided evidence for some targeted immune modulator drugs in certain subpopulations.

Evidence on the effect of age was mixed. Indirect evidence from three studies indicated that age is not associated with greater or lesser clinical response rates or adverse events in ankylosing spondylitis, rheumatoid arthritis psoriatic arthritis, or plaque psoriasis, while two studies on rheumatoid arthritis patients found treatment response to be better in younger patients than older patients and adverse events found to be significantly higher in patients 70 years and older.

Limited evidence on the effect of race on differences in effectiveness or harms of targeted immune modulators exists. Similar to findings in predominantly white populations, indirect evidence from placebo-controlled trials showed that adalimumab and ustekinumab had better response rates compared with placebo in Asian patients with plaque psoriasis and rheumatoid arthritis. Patients of non white ethnicity had a six-fold increased risk of tuberculosis compared with white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.

The evidence on differences between men and women is sparse: one study reported on efficacy and one study reported on adverse events. A pooled analysis of nine efficacy studies of alefacept did not detect any differences in efficacy and safety for obese or diabetic patients with plaque psoriasis.

Findings in studies evaluating effectiveness and safety in patients with comorbid conditions (respiratory disease, diabetes, cardiovascular disease) are mixed. Two studies reported no differences in adverse events in patients with comorbidities while three studies reported an increased risk of the occurrence of adverse events.

SUMMARY

The main findings of this review are summarized in Table 2. The applicability of the results are limited by the scope of the key questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented.

Table 2. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Moderate	Based on 1 randomized controlled trial, no difference in efficacy between abatacept and infliximab.
	Low	Based on 2 observational studies similar effectiveness between adalimumab and etanercept
	Low	Based on 2 observational studies, greater effectiveness of adalimumab than infliximab
	Moderate	Based on 2 trials and 5 observational studies, greater effectiveness of etanercept than infliximab.
	Low	Based on indirect comparisons, greater effectiveness of etanercept than abatacept; etanercept than anakinra; and etanercept than tocilizumab.
	Low	Based on indirect comparisons, similar efficacy between abatacept and adalimumab; abatacept and anakinra; abatacept and tocilizumab; adalimumab and anakinra; adalimumab and tocilizumab; anakinra and infliximab; anakinra and tocilizumab; and infliximab and tocilizumab.
	Insufficient	No evidence available for all other comparisons.
1. Comparative effectiveness for juvenile idiopathic arthritis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for ankylosing spondylitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for psoriatic arthritis	Low	Based on indirect comparisons and a prospective registry study, no difference in effectiveness between adalimumab, etanercept and/or infliximab.
1. Comparative effectiveness for Crohn's disease	Insufficient	No comparative evidence available.
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for plaque psoriasis	Low	Based on one randomized controlled trial, ustekinumab is more efficacious than etanercept
2. Comparative harms	Low	*Serious Infections (as a group)* Less common with abatacept based on indirect comparisons and one randomized controlled trial. Certolizumab pegol associated with greater odds than adalimumab, anakinra, etanercept, golimumab, infliximab, and rituximab. The antitumor necrosis factor drugs adalimumab, etanercept, and infliximab have higher risk than DMARDs based on observational studies. Tuberculosis: risk of higher with adalimumab than etanercept based on one observational study. Herpes Zoster: risk is not increased with etanercept based on 2 observational studies, but risk with other drugs is unclear or insufficient.
	Low	*Malignancy:* Based on three observational studies and indirect comparisons, risk of non melanoma skin cancer is greater with the antitumor necrosis factor drugs adalimumab, etanercept, and infliximab than non targeted immune modulator therapy, but no increased risk of any malignancy or differences between drugs found.
	Low	*Overall adverse events:* Based on one randomized controlled trial, adalimumab has lower rate than

Key question	Strength of evidence	Conclusion
		infliximab or etanercept. Based on seven observational studies, the rate is greater with infliximab than adalimumab or etanercept. Based on one randomized controlled trial, rates similar between etanercept and ustekinumab: Injection-site reactions more frequent with etanercept than ustekinumab. In short-term trials, abatacept and anakinra have lower risk of a serious adverse event than other targeted immune modulators.
	Low	*Discontinuations due to adverse events*: Based on seven observational studies and indirect comparisons, the rate is greater with infliximab than abatacept, anakinra, etanercept and golimumab. Infusion or allergic reactions contributed to the difference in risk.
	Insufficient	*Children*: No comparative evidence available.
3. Subgroups – age	Insufficient	The evidence on the effect of age is contradicting and insufficient to draw conclusions.
3. Subgroups – sex	Insufficient	The evidence is mixed and insufficient to draw conclusions.
3. Subgroups – ethnicity	Insufficient	No direct comparisons available. Based on indirect evidence, adalimumab and ustekinumab had better efficacy than placebo in Asian patients with plaque psoriasis and rheumatoid arthritis. Based on one observational study, non white patients had increased risk of tuberculosis than white patients treated with antitumor necrosis factor drugs in patients with rheumatoid arthritis.
3. Subgroups – comorbidities	Insufficient	The evidence is mixed and was insufficient to draw conclusions.

CONCLUSION

Overall, targeted immune modulators are highly effective medications for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis that substantially improve the burden of disease and are generally safe for short-term treatment.

For rheumatoid arthritis, low-and moderate-strength evidence indicated that some targeted immune modulators are more efficacious than others. These results were based on three head-to-head trials, several large observational studies, and indirect comparisons of placebo-controlled trials. The evidence is currently insufficient to reliably determine the comparative effectiveness for other indications and in subgroups.

Low-strength evidence indicated that serious infections are less common with abatacept than the other drugs and that the rate of adverse events is greater with infliximab than adalimumab or etanercept. Likewise, more patients receiving infliximab withdrew due to adverse events than abatacept, adalimumab, etanercept, and golimumab. Infusion or allergic reactions contributed to the difference in risk.

P&T Committee Brief

Targeted Immune Modulators:
Comparative Drug Class Review

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This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on Targeted Immune Modulators" dated March 2012, which is a product of the UNC-RTI Evidence-based Practice Center at the University of North Carolina at Chapel Hill. You can find the original report online at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Although at least one of the authors of this report reviewed and commented on the brief, its contents and conclusions are those of the Center and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

Targeted Immune Modulators

Targeted immune modulators (TIMs), commonly referred to as biological response modifiers, or simply *biologics*, are a relatively new category of medication used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Chrohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (PP). The US Food and Drug Administration (FDA) approved the first of the biologics (infliximab) in 1998. Since then, the FDA has approved 12 additional agents for treating various rheumatic conditions, inflammatory bowel disease (IBD), and psoriasis. TIMs work by selectively blocking a variety of different mechanisms involved in the inflammatory and immune response. Biologics available in the US and Canada, and their indications, route, and frequency of administration are listed in Table 2.

Purpose

The purpose of this review is to compare the efficacy, effectiveness, safety, and tolerability of the included drugs in patients with RA, JRA, AS, PsA, CD, UC, and PP.

Methodology

The Drug Effectiveness Review Project (DERP) reviews all pertinent studies, solicits and accepts public input, and updates reviews frequently. The original TIMs review was completed in 2005 and has been updated twice previously. Literature searches for this update identified 1,589 additional citations, and five dossiers were received from manufacturers. Study eligibility is determined by pre-set criteria, and studies which did not meet these criteria with respect to study design or duration, patient population, interventions, outcomes, language of publication, or appraised quality were excluded. Included health outcomes are listed in Table 1.

Table 1. *Included Health Outcomes*

Health Outcomes	▪ Quality of life (QOL) ▪ Functional capacity ▪ Pain ▪ Reduction in # of swollen or tender joints ▪ Response ▪ Remission ▪ Reduction of affected body surface area (Psoriasis Area & Severity Index) ▪ American College of Rheumatology scales (ACR 20/50/70) ▪ Hospitalizations ▪ Mortality ▪ Steroid withdrawal
Radiological Outcomes	Considered only if no studies of other health outcomes were found
Safety Outcomes	▪ Overall serious and specific adverse events (AEs) ▪ Withdrawals due to AEs

Evidence Available

Relevant information for this topic consists of 163 unique studies, 68 of them new in this update: 70 randomized controlled trials (RCTs), 51 observational studies, 31 systematic reviews, and 11 trials of other design.

Table 2. *Biologics Available in US & Canada*

Generic Name	Trade Name	Indication	Route & Frequency of Administration
abatacept[1]	Orencia®	RA JIA	IV infusion Q 2-4 weeks, *or* SQ injection Q week
adalimumab[2,3]	Humira®	RA PsA AS JIA CD PP	SQ injection Q 1-2 weeks
alefacept	Amevive®	PP	IM injection Q week
anakinra	Kineret®	PP	SQ injection Q week
certolizumab pegol[3]	Cimzia®	RA CD[4]	SQ injection Q 2-4 weeks
etanercept[1,3]	Enbrel®	RA PsA AS JRA PP	SQ injection 1-2X/week
golimumab[3]	Simponi®	RA PsA AS	SQ injection Q month
infliximab[1,3]	Remicade®	RA CD PsA AS active UC PP	IV infusion Q 4-8 weeks
natalizumab	Tysabri®	CD[4]	IV infusion Q 4 weeks
rituximab	Rituxan®	RA	IV infusion at 0 and 15 days, then Q 16-24 weeks
tocilizumab[1]	Actemra®	RA JIA[5]	IV infusion Q 2-4 weeks
ustekinumab	Stelara®	PP	SQ injection at 0 and 4 weeks, then Q 12 weeks

[1] *approved for use in children in the US & Canada*
[2] *approved for use in children in the US only*
[3] *TNF inhibitor*
[4] *not approved for CD in Canada*
[5] *not aoproved for JIA in Canada*

Key Questions & Findings

Question 1 *How do the included drugs compare in their effectiveness for alleviating symptoms and stabilizing the disease in patients with RA, JRA, AS, PsA, Crohn's disease, UC, and plaque psoriasis?*

Rheumatoid Arthritis

Currently, the following drugs are approved by the FDA and Health Canada (HC) for the treatment of RA: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab. The only double blind head-to-head study found compared abatacept to infliximab in patients with inadequate response to methotrexate. At six months no differences in efficacy were apparent, but after one year abatacept was significantly more efficacious on most outcome measures than infliximab. ***Of note: infliximab was administered at a fixed dose throughout the entire study, even though infliximab efficacy trials have shown that up to 30% of patients require dose increases.***

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis were limited to one small RCT and multiple non-randomized or observational studies rendering evidence of low strength. These studies indicated no differences in efficacy between adalimumab (two observational studies) and etanercept (five observational studies, one RCT, and one non-randomized trial) compared with infliximab.

Table 3. *Comparative Efficacy for RA*

Based on Direct Evidence
abatacept > infliximab
adalimumab ~ etanercept
adalimumab > infliximab
etanercept > infliximab
Based on Indirect Evidence
etanercept > abatacept/anakinra/infliximab/tocilizumab
adalimumab ~ anakinra/infliximab/tocilizumab

> = more efficacious than
~ = has similar efficaciousness to
< = less efficacious than

Indirect comparisons of randomized placebo-controlled trials suggest that etanercept is statistically more efficacious than abatacept, anakinra, infliximab, and tocilizumab (range of relative risks from 2.31 to 3.30). No statistically significant differences in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab. Data were too heterogeneous to conduct indirect comparisons of certolizumab pegol, golimumab, and rituximab with other TIMs. Good to fair evidence exists from meta-analyses and large RCTs that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab are statistically significantly more efficacious than placebo for the treatment of RA. Treatment effects are large and consistent across studies.

Juvenile Idiopathic Arthritis

Currently, abatacept, adalimumab, etanercept, and tocilizumab are approved by the FDA and HC for the treatment of JIA. No evidence on the comparative effectiveness of any TIM for the treatment of JIA exists. Five RCTs provide fair evidence that abatacept, adalimumab, etanercept, infliximab, and tocilizumab are more efficacious than placebo for the treatment of JIA.

Ankylosing Spondylitis

Adalimumab, etanercept, golimumab, and infliximab are currently approved by the FDA for the treatment of AS (only etanercept and infliximab are approved for the treatment of AS in Canada). No direct evidence on the comparative effectiveness of TIMs for the treatment of AS exists. The strength of the evidence is insufficient. Good to fair evidence exists for the general efficacy of adalimumab, etanercept, golimumab, and infliximab compared with placebo for the treatment of AS, based on one systematic review of nine RCTs (adalimumab, etanercept, and infliximab), and four other RCTs (etanercept, golimumab, and infliximab). No studies on abatacept, alefacept, anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab for the treatment of AS were found.

Psoriatic Arthritis

The following drugs are currently approved by the FDA and HC for the treatment of PsA: adalimumab, etanercept, golimumab, and infliximab. No head-to-head trials comparing one TIM to another were found, nor were any studies on anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab. Two systematic reviews conducted indirect comparisons of adalimumab, etanercept, and infliximab for the treatment of PsA in adults. Both analyses suggested that the three treatments are more efficacious than placebo, but no statistically significant differences among them could be detected. One prospective observational registry study of 595 patients with PsA showed that adalimumab, etanercept, and infliximab have similar positive effects on QOL. The strength of evidence for this comparison is considered low. In addition, evidence from one phase II study indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone and that abatacept, golimumab, and ustekinumab are more efficacious than placebo. No studies that evaluate the use of TIMs in children with PsA were found.

Ulcerative Colitis

Only infliximab is currently approved by the FDA and HC for the treatment of UC. No comparative evidence was found for TIMs in the treatment of UC, and the evidence is considered insufficient. One systematic review (five RCTs) found that infliximab is significantly more efficacious than placebo for the treatment of UC. No trials in children were found.

Plaque Psoriasis

Adalimumab, alefacept, etanercept, infliximab, and ustekinumab are currently approved by the FDA and HC for the treatment of plaque psoriasis. One head-to-head RCT comparing etanercept to ustekinumab found that significantly more patients in the ustekinumab group achieved the primary outcome of a PASI 75 response compared to etanercept. The strength of the evidence for this comparison is low. Multiple placebo controlled trials (17) provide good to fair evidence of the general efficacy of adalimumab, alefacept, etanercept, infliximab, and ustekinumab for the treatment of plaque psoriasis. No studies on the other TIMs were found. One study of etanercept in children found a greater response compared to placebo.

Question 2 *What are the comparative incidence and severity of complications associated with the use of these drugs?*

Eighteen head-to-head studies provided direct evidence on the harms associated with TIMs, which was supplemented by indirect comparisons of over 200 RCTs (placebo or active control). Evidence on the comparative risks of serious infection with TIMs was low strength. Evidence from short-term trials (median six months duration) using indirect comparison meta-analyses indicated serious infections are less common with abatacept than with certolizumab pegol, infliximab, and tocilizumab, while certolizumab pegol appeared to have a higher risk than adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, or placebo. Analyses of only the antitumor necrosis factor (anti-TNF) drugs (adalimumab, certolizumab pegol, golimumab, and infliximab) indicated as a group they have an increased risk compared to control groups, while the other TIMs, including etanercept (which works via a different mechanism to antagonize anti-TNF than the previous group) did not. Limited observational evidence indicates an increased risk of serious infection with anti-TNF drugs etanercept, infliximab, and adalimumab, and that the risk was highest in the first six months of treatment. The risk of tuberculosis appeared to be elevated with the use of TIMs as a group based on trial data. Comparisons between the drugs are more limited, with the best evidence indicating increased risk of tuberculosis with adalimumab compared with etanercept, and a nearly statistically significant increased risk with infliximab compared with etanercept.

On the whole, a broad range of evidence did not indicate a clear increase in risk of malignancy in general with the use of TIMs. There was evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the anti-TNF drugs adalimumab, infliximab, and etanercept. Observational evidence supported these findings, although the risk estimates are somewhat lower magnitude. The strength of evidence comparing the risk of malignancy with TIMs is low. Although the FDA has issued a warning about the potential increased risk of malignancy in children, evidnce in children is insufficient for making conclusions. While case reports have indicated potential risk of various other

serious adverse events, strength of evidence on the comparative risk of heart failure, autoimmunity, demyelination, and serious hepatic events with TIMs is insufficient at this time.

Table 4. *Comparative Harms*

Infections
abatacept > certolizumab pegol/infliximab/tocilizumabnfliximab (serious infection)
certolizumab > adalimumab/anakinra/etanercept/golimumab/infliximab/rituximab (serious infection)
TIMs [in general] > control groups (TB)
adalimumab > etanercept (TB)
infliximab > etanercept (TB)
Malignancy
adalimumab/infliximab/etanercept > control groups (nonmelanoma skin cancer)
Overall AE/Discontinuation Due to AE
abatacept/anakinra < other TIMs (serious AE)
infliximab > abatacept/adalimumab/etanercept/golimumab (discontinuation due to AE)

> = higher risk than
< = lower risk than

Comparative evidence on overall AEs, discontinuation of drug due to AEs, and other measures of short-term tolerability was low to moderate strength, depending on the specific outcome. The rates of overall AEs occurring with TIMs did not differ statistically significantly between the drugs. In short-term trials abatacept and anakinra had lower risk of a serious AE compared to other TIMs. Infliximab had a higher risk of patients discontinuing treatment due to AEs compared with abatacept, adalimumab, etanercept, and golimumab at least partially due to the increased risk of infusion or allergic reactions. Evidence on the comparative risk of AEs associated with TIMs in children is very limited and was of insufficient strength to make conclusions. The AE profiles appeared similar to those seen in adults.

Question 3 *Do the included drugs differ in effectiveness or AEs in the following subgroups: racial groups, genders, age groups; or in patients taking other commonly prescribed drugs?*

Overall, the strength of evidence to determine differences between TIMs in effectiveness or AEs among subgroups was insufficient. The majority of the studies were not specifically designed to compare the effectiveness and safety of TIMs in one subgroup of patients compared to another. However, subgroup analyses and indirect evidence provided evidence for some TIMs in certain subpopulations. Evidence on the effect of age was mixed. Indirect evidence from three studies indicated that age is not associated with greater or less clinical response rates or AEs in AS, RA, PsA, or PP. However, three other studies found differences; in one case, response to treatment of RA with etanercept and infliximab was better in those over less than 65 years, in two others there was a higher risk of AEs in older patients.

Regarding race, indirect evidence showed that adalimumab and ustekinumab had better response rates compared with placebo in Asian patients with PP, while patients of non-white ethnicity had a six-fold increased risk of tuberculosis compared with white patients treated with anti-TNF drugs for RA. The evidence on gender differences is limited to two studies, one reporting on efficacy and the other on AEs. A pooled analysis of nine efficacy studies of alefacept did not detect any differences in efficacy and safety for obese or diabetic patients with PP. Two studies reported no differences in AEs in patients with comorbidities while three studies reported an increased risk of the occurrence of AEs.

Conclusion

In summary, insufficient evidence exists for the comparative effectiveness of TIMs for the treatment of JIA, AS, CD, and UC. For RA there is a moderate strength of evidence that there is no difference in efficacy between abatacept and infliximab, but that etanercept is more effective than infliximab. In addition, there is low strength of evidence that etanercept is more efficacious than abatacept, anakinra, and tocilizumab, and that the following comparisons have similar efficacy:

- Abatacept is similar to adalimumab, anakinra & tocilizumab
- Adalimumab is similar to anakinra & tocilizumab
- Anakinra is similar to infliximab & tocilizumab
- Infliximab is similar to tocilizumab

For the treatment of PsA there is low strength of evidence that there is no difference in effectiveness between adalimumab, etanercept, and infliximab; and for the treatment of PP there is also low strength of evidence that ustekinumab is more efficacious than etanercept.

For harms there is low strength of evidence that serious infections are less common with abatacept than with the other drugs, and that certolizumab pegol has greater odds of serious infection than adalimumab, anakinra, etanercept, golimumab, infliximab, and rituximab. In addition, adalimumab, etanercept, and infliximab have a higher risk of serious infection than non-TIM therapies, and the risk of tuberculosis is higher with adalimumab than etanercept. There is also low strength of evidence that the risk of non-melanoma skin cancer is greater with adalimumab, etanercept, and infliximab compared to non-TIM therapies, but no differences between TIM drugs was found. For other AEs the following comparisons had a low strength of evidence:

- Adalimumab has a lower rate compared to infliximab & etanercept for overall AEs
- Infiximab has a higher rate compared to adalimumab & etanercept for overall AEs
- Etanercept has similar rates of overall AEs to ustekinumab, although injection site reactions are higher for etanercept
- Abatacept and anakinra have lower risk of serious AEs than other TIMs in the short-term
- Discontinuations due to AEs are higher with infliximab compared to abatacept, anakinra, etanercept & golimumab, due in part to a higher rate of infusion reactions

There was insufficient evidence for all other comparisons, including efficacy and harms in children and subpopulations.

Conclusions and Recommendations:
Targeted Immune Modulators (TIMS)

Current Status of PDL Class:

- Preferred Agents: ADALIMUMAB (HUMIRA®), ETANERCEPT (ENBREL®), INFLIXIMAB (REMICADE®)
- Non Preferred: ABATACEPT (ORENCIA®), ALEFACEPT (AMEVIVE®), ANAKINRA (KINERET®), CERTOLIZUMAB (CIMZIA®), EFALIZUMAB (RAPTIVA®), NATALIZUMAB (TYSABRI®), RITUXIMAB (RITUXAN®)
- Prior authorization is required for non-preferred PDL drugs to ensure that non-preferred drugs are used for an above-the-line condition.

Research Questions:

- Does any of the new information from the Drug Effectiveness Review Project (DERP) class update[1] or clinical guidelines change previous conclusions regarding effectiveness, safety, and current management of TIMs?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- Three new TIMs were approved and included in the third DERP update. Golimumab (Simponi®) is a tumor necrosis factor (TNF) inhibitor FDA approved for rheumatoid arthritis, psoriatric arthritis, and ankylosing spondylitis. Tocilizumab (Actemra®) is an interleukin (IL)-6 monoclonal antibody approved for rheumatoid arthritis and juvenile idiopathic arthritis. Ustekinumab (Stelara®) is an IL-12 and IL-23 monoclonal antibody FDA approved for plaque psoriasis.
- For the treatment of rheumatoid arthritis (RA), there is low strength evidence that abatacept is more effective than infliximab in patients with an inadequate response to methotrexate at 1 year (1 fair quality head to head trial), although infliximab was administered at a fixed dose.[1]
- For the treatment of RA, there is low strength evidence that there is no difference between adalimumab and etanercept and that adalimumab and etanercept are more efficacious than infliximab.[1]
- For the treatment of RA, the majority of studies enrolled patients who had failed at least one disease-modifying antirheumatic drug (DMARD) treatment or were on a stable dose of methotrexate (MTX) with unsatisfactory response.
- The American College of Rheumatology recently updated their recommendations (2012) for biologic agents in treating RA and recommend starting an anti-TNF medication with or without methotrexate only in RA with high disease severity and features of poor prognosis (after 3 months of methotrexate monotherapy or DMARD combination therapy) with the level of evidence A for infliximab with methotrexate and B for etanercept, adalimumab, golimumab, and certolizumab with or without methotrexate.[2]
- There is no evidence on the comparative effectiveness of TIMS for treatment of juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, or crohns disease.[1]

- Studies included patients who had disease despite treatment with corticosteroids and methotrexate in juvenile idiopathic arthritis, and DMARD failure for plaque psoriasis.
- Only infliximab is currently approved for the treatment of ulcerative colitis.
- There is low quality evidence based on one 16 week head-to-head trial that ustekinumab produced a significantly better response than etanercept in patients with plaque psoriasis (67.5-73.8% vs. 56.8%, p<0.001).[1]

Recommendations:

- Maintain the most recently approved TIMS, golimumab, tocilizumab, and ustekinumab as non-preferred TIMS due to limited comparative evidence and lack of clinical benefit compared to currently available TIMS.
- Based on new clinical evidence, recommend no changes to current preferred TIMS on the PDL.
- Consider additional clinical criteria for prior authorization of non-preferred TIMS including a step therapy requirement with a trial of methotrexate first for RA and limited to the appropriate FDA indications for each non-preferred drug.
- Consider a DUE to evaluate preferred products for off-label use or use inconsistent with current clinical guidelines.

Guidelines:

The American College of Rheumatology published 2012 revised updates in select topic areas.[2] This update separates recommendations for early and established RA which are defined as disease duration < 6 months and > 6 months, respectively. For early RA, the guidelines recommend DMARD monotherapy initially and the use of an anti-TNF biologics with or without MTX only in patients who have high disease activity and with poor prognostic features.[2] They designated a level of evidence A for infliximab in combination with MTX, and level of evidence B for etanercept, adalimumab, golimumab, and certolizumab with or without MTX. In established RA, the panel recommends DMARD monotherapy and combination therapy before switching to an anti-TNF biologic.[2] IF a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, an alternative is switching to an anti-TNF biologic, or to abatacept or rituximab in TNF-naïve patients. This included level of evidence A for etanercept, infliximab, adalimumab, golimumab, certolizumab, abatacept, and rituximab all in combination with MTX. These same agents are given a level of evidence C when given without MTX.[2]

The national clinical guidelines on the management of early RA from the Scottish Intercollegiate Guidelines Network (SIGN) from 2011 state that the use of the TNF inhibitors for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate or other DMARDs is not recommended.[3] Clinical guidelines from the National Institute for Clinical Excellence (NICE) recommend that adalimumab, etanercept, and infliximab are options for adults with active RA and for those who have undergone trials of two DMARDS, including MTX (defined as 6 months).[4]

For the treatment of juvenile idiopathic arthritis, the American College of Rheumatology recommends the initiation of TNF-inhibitors in patients who have received glucocorticoid joint injections and 3 months of MTX at the maximum tolerated dose (level of evidence C).[5] For systematic arthritis, level C evidence supports the initiation of anakinra in all patients with active fever and features of poor prognosis.

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5. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken).* 2011;63(4):465–482.

Month/Year of Review: June 2012
New Drug: Deferiprone
Brand Name: Ferriprox®
Dossier: Yes

End date of literature search: March 5, 2012
Manufacturer: ApoPharma
Comparator Therapies: Deferasirox (PO) and deferoxamine (IV)

FDA Approved Indications:
Deferiprone is indicated for "the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate." Safety and effectiveness have not been established in other chronic anemias.

Research Questions:
1. How does deferiprone compare to other iron chelation therapy—deferoxamine and deferasirox—in the treatment of iron overload in patients with thalassemia syndromes?
2. Is deferiprone safer than deferoxamine or deferasirox?
3. Does deferiprone or the iron chelators reduce morbidity and mortality associated with iron overload in thalassemia?

Conclusions:
Significant morbidity and mortality are associated with iron overload in patients with thalassemia syndromes. Presently, deferiprone represents the only option for patients for whom deferoxamine and deferasirox are contraindicated or prove to be inadequate in reducing iron burden. There is insufficient evidence to compare the efficacy of deferiprone with the other oral agent, deferasirox.

There is insufficient evidence to determine whether deferiprone is more effective than currently available therapy. Italian guidelines indicate there is no strong evidence deferiprone in monotherapy or in combination with deferoxamine is superior to deferoxamine alone.[1,2] Accordingly, the FDA has approved deferiprone as second-line therapy for patients with thalassemia syndromes who have had inadequate response with deferoxamine or deferasirox. Italian and U.S. and Italian guidelines recommend that clinicians consider deferiprone in combination with deferoxamine as an option in patients with cardiac symptoms or cardiomyopathy.

The adverse reactions of greatest concern for deferiprone are agranulocytosis and neutropenia that may result in severe infection or death. Adverse outcomes due to these conditions can be mitigated by regular monitoring. Furthermore, deferiprone's place in iron chelation therapy is as a final recourse, so the alternative to deferiprone would be entry into a clinical trial for an experimental iron chelator, if available, or almost certain disability or death from iron overload.

There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related sequelae, functioning, or increased survival. FDA approval is based on a reduction in serum ferritin level (primary end point), reduction in liver iron concentration (LIC), and increase in MRI T2* (secondary end points) as determined by reviewing pre-existing clinical data. Only LIC by liver biopsy is considered standard reliable surrogate for measuring iron burden and is considered to be related to clinical benefit. The analysis of pre-existing clinical data showed 52%, 42%, and 62% of patients responded to deferiprone therapy defined as a ≥20% reduction in serum ferritin, ≥20% reduction in LIC, or ≥20% increase in MRI T2*, respectively. However, whether these results translate into clinical benefit remains unclear.

Recommendation:

- Recommend adding deferoxamine as a preferred agent on the PDL.
- Recommend making the oral agents deferasirox and deferiprone non-preferred and using the default non-preferred PA criteria to utilize them as second line agents.

BACKGROUND/CURRENT LANDSCAPE

Deferiprone is one of three FDA-approved drugs to treat iron overload. Deferoxamine (Desferal) was approved in 1968 and deferasirox (Exjade) in 2005 for the treatment of chronic iron overload due to transfusion-dependent anemias or blood transfusions, respectively.[3,4] While the U.S. approved deferiprone in 2011, the European Union approved the drug in 1999. Most of the more than 60 countries that have approved deferiprone have limited its use to treating iron overload in patients with thalassemia major for whom deferoxamine therapy has been contraindicated or inadequate. The FDA also has limited deferiprone so that it will serve as second-line therapy in patients with transfusion-dependent thalassemia syndromes.[5]

Thalassemia is a hereditary disorder characterized by decreased hemoglobin production and red blood cell survival. Patients with severe manifestations of thalassemia require red blood cell transfusions and iron chelation therapy or allogeneic bone marrow transplant.[6,7]

Patients with transfusion-dependent thalassemia develop iron overload because the body is unable to excrete excess iron. This problem is more pronounced in patients with thalassemia because their gastrointestinal tracts absorb more iron than normal. The excess non-transferrin-bound iron deposits in tissues as free iron, damaging and disrupting the normal function of organs such as the liver, pancreas, heart, and endocrine glands. Iron toxicity can cause diabetes, hypogonadism, hypothyroidism, adrenal insufficiency, hepatic fibrosis, cardiac arrhythmias and failure, and more.[7]

Iron overload in thalassemia is treated using chelators that bind iron in the blood and organs. Deferoxamine often is used as first-line therapy for iron overload in thalassemia; however, not all patients can tolerate deferoxamine because of its side effects. About 32% of thalassemia patients report complications with deferoxamine requiring modifications of dose or route of administration.[11] The rate of compliance with deferoxamine has been estimated to be 70% due to complex dosing and administration.[12] As a once daily orally administered iron chelator, deferasirox overcomes the administration-related noncompliance associated with deferoxamine. Its accelerated approval was based on LIC, considered a measure of clinical benefit, and serum ferritin levels, a surrogate endpoint; however, increased survival has yet to be demonstrated or clinical benefit confirmed.[4,13] As with deferoxamine, patients may experience deferasirox-associated side effects resulting in dose reduction or discontinuation, and some patients may have inadequate iron elimination for unexplained physiologic reasons.

Laboratory tests for assessing iron levels include serum ferritin, imaging, and LIC by liver biopsy.[7] Liver biopsy is the generally accepted standard for assessing LIC, because 90% of excess iron is deposited in the liver.[13] The suggested optimal range for LIC for chelation therapy in transfusional overload is 3.2 to 7 mg Fe/g dry weight. An LIC value of 7 mg Fe/g dry weight is considered the threshold for increased risk of sequelae due to iron overload.[14] Because liver iron does not linearly correlate with cardiac iron, alternative methods of accessing iron have been employed for the heart.[15] MRI T2* detects cardiac iron deposition, which is indicated by a decrease in T2* relaxation values measured in milliseconds (msec). In adults with thalassemia major, left ventricular dysfunction increases as the T2* falls below 20 msec.[7,14] The most commonly used test of iron burden is serum ferritin level. However, ferritin is an acute-phase reactant whose level is influenced by a variety of factors that limit its accuracy, such as the presence of inflammation, infection, and vitamin C deficiency.[7,16] Also, the relationship between serum ferritin level and treatment for iron excess is non-linear.[7] Nevertheless, serum ferritin levels <2500 µg/L with deferoxamine is associated with lower risk of cardiac dysfunction and death.[14]

The Standards of Care Guidelines for Thalassemia published by the Children's Hospital and Research Center Oakland (CHRCO), one of seven thalassemia treatment centers funded by the CDC, has not been updated since deferiprone's approval.[15] However, the guidelines do address deferiprone's use as an investigational drug and states the following with regard to the presence of cardiac symptom and cardiomyopathy, respectively:

- Presence of cardiac symptoms (arrhythmia or decreased left ventricular ejection fraction): *the patient must be exposed to chelator 24 hours per day, 7 days per week. This treatment is considered to be emergent. Multiple drug therapy—in particular, therapy involving deferiprone—should be considered in this circumstance. . . Patients whose cardiac T2* is less than 10 ms and who do not have cardiomyopathy should receive maximum therapy (see Table 5.1). Consultation with an iron chelation specialist is strongly recommended in the management of all patients with an abnormal cardiac T2*.*

- From Table 5.1, presence of iron-induced cardiomyopathy T2* <20 ms; or T2* <10 ms without cardiomyopathy: *Maximum chelation: 24-hour deferoxamine therapy; consider deferiprone . . . . Monitor intensively with cardiology consulation and iron chelation specialist.*

Recommendations for deferiprone's use as an approved drug in the EU are presented in Italian guidelines:

From the Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders:[1] *For patients with evidence of non-compliance to deferoxamine, or with severe adverse effects from deferoxamine which preclude its use, but without existing or pending severe iron overload, an oral iron chelator should be used as an alternative to deferoxamine therapy (level D). The lack of studies comparing deferiprone with deferasirox in thalassemia major or related disorders did not allow the panel to recommend one of them on the basis of scientific evidence on long-term efficacy. The panel felt justified in recommending deferasirox as the alternative therapy to deferoxamine on the basis of its better safety profile compared with deferiprone (level D). Deferiprone should be considered in the case of resistance or intolerance to deferasirox (level D).Patients who develop severe iron overload (serum ferritin higher than 3,000 ng/mL maintained for three months at least, liver iron content higher than 15 mg/g d.w., or heart T2* <12 msec) or overt iron-related cardiomyopathy (left ventricular ejection fraction <55%, arrhythmias, cardiac failure) should receive "intensive" or "combined" iron chelation therapy. The panel judged that the first choice for combined therapy is deferoxamine associated with deferiprone (level B). Patients who develop life-threatening cardiomyopathy should receive continuous intensive or combined chelation therapy.*

From the Society for the Study of Thalassemia and Hemoglobinopathies Guideline recommendations for heart complications in thalassemia major:[2]

- For prevention of iron-induced cardiac dysfunction: *The ability of iron chelating efficacy of desferrioxamine and deferiprone (L1) at the standard dosage (50 mg/kg over 8–10 h/5 days per week and 75 mg/kg/7 days per week, respectively) appears to be superimposable after 1 year of treatment in terms of ferritin reduction (I,A . . . . In summary (IIa,B):. . . . (2) The choice of the drug to be used must be individualized; intolerance, low compliance, onset of side effects, and not least, personal evaluations of the physician or of the patient, can lead to the choice of one of the most important drugs; (3)The combined or associated use of deferiprone plus desferrioxamine improves chelation, but also the risk of more marked side effects; (4) The dosages of the drugs or of their combination must be suited to obtain therapeutic targets that are seen as valid.*

- For chelation treatment in iron-induced myocardial dysfunction: *When clinically suggested, the modalities of administration are (1) continuous subcutaneous administration of desferroxamine (40–60 mg/kg every day) (I,B); (2) In selected cases, continuous administration of desferrioxamine through the peripheral venous pathway or through a central catheter . . . . . .(I,C); (3) Combined or associated desferrioxamine (40–50 mg/kg) and deferiprone (70–80 mg/kg) treatment has been reported in clinical practice (IIb,C).*

Efficacy:

Deferiprone provides another oral option for iron chelation. Although deferiprone has been approved in the EU since 1999, studies with deferiprone have been inconsistent and adequate, prospective, randomized, well-controlled clinical trials to assess the clinical benefit of deferiprone are still lacking.[1,2,12]

The FDA based accelerated approval for deferiprone on reduction in serum ferritin levels (primary outcome) and LIC and MRI T2* (secondary outcomes) as demonstrated by an open-label, unpublished, uncontrolled, retrospective analysis of pre-existing clinical data from 12 studies (n=264 patients) of deferiprone in

patients with transfusional iron overload for whom previous chelation therapy had been inadequate (LA36-0310). This study was completed after the original New Drug Application submission failed to achieve FDA approval. The initial NDA was based on a controlled trial of 61 adult patients with thalassemia randomized to deferiprone or deferoxamine therapy, with change in cardiac iron burden assessed by MRI T2* as the primary efficacy end point and serum ferritin and LIC as secondary end points. The FDA cited several deficiencies in the NDA, including insufficient evidence of efficacy, insufficient information to establish the clinical benefit of incremental changes in cardiac MRI T2* (e.g., improved survival, symptoms, functional status), lack of survival data, absence of pediatric patients, and more. Finally, the FDA stated "published literature does not consistently support the efficacy or safety of deferiprone. Some studies have suggested loss of effectiveness over expanded time periods and others have suggested increased liver toxicity among patients who remain on prolonged deferiprone therapy. . . . We note that other reports have not cited these problems."[13] Treatment success for the primary and secondary end points were defined as ≥20% decline in serum ferritin, ≥20% increase in cardiac MRI T2*, and ≥20% decline in LIC. Most patients included in the study had β-thalassemia (94.3%) and had been previously treated with deferoxamine (94.6%).

The vast majority of patients included in the study had β-thalassemia (94.3%) and had been previously treated with deferoxamine (94.6%). Only 27% of patients had been treated with deferiprone for 1 year or longer and 76% had been treated for at least 6 months. Most patients had received a deferiprone dose of 75 mg/kg/day (76.9%), while 17.8% and 5.3% of patients had received 100 mg/kg/day or 50 mg/kg/day, respectively.

The analysis showed 52% (n=136/264) of patients had a ≥20% decline in serum ferritin from baseline to end of study (up to 1 year of deferiprone therapy). The mean change in serum ferritin was a decrease of 962 µg/L (range 10385 µg/L decrease to 10002 µg/L increase). Fifty percent of patients achieved a ≥20% decline in serum ferritin in each of three subanalyses that excluded patients who had taken both deferiprone and deferoxamine or taken pediatric deferiprone solution or been at one study site that had questionable data quality. The success rate also was achieved for the secondary analyses, with 42% of patients (n=49/117; CI: 33% to 51%) achieving a ≥20% decline in LIC and 62% (n=24/39; CI: 45% to 77%) a ≥20% increase in cardiac MRI T2*. The mean change in LIC was a decrease of 1.7 mg Fe/g dry weight. The mean change in MRI T2* was an increase of 3.3 msec (range 2 msec decrease to 12.7 m sec increase).

This study was rated as "poor" and presented numerous limitations to the evaluation of the efficacy of deferiprone as follows:

- Serum ferritin is not an optimal end point, as serum ferritin is an inaccurate as a measure of body iron stores.
- Data are lacking on the clinical benefit of a ≥20% decrease in ferritin.
- The better measure, LIC, showed the weakest results for efficacy, and LIC was available for only 117 patients.
- The change in MRI T2* was small (3.3 msec), and data are lacking on the relationship between incremental changes in MRI T2* and cardiac function.
- Data were limited with regard to duration of response and dose-response relationship.
- Treatment compliance was not assessed.
- The population for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin, as 228 could be evaluated for serum ferritin only, 68 for LIC only, 9 for MRI T2* only, 31 for ferritin and LIC, 12 for ferritin and MRI T2*, 25 for LIC and MRI T2*, and 7 for all three tests.
- The study was non-randomized and single-arm with missing data.
- The studies used in the analysis were heterogeneous, differing in treatment regimens studied, end points and objectives, methods, follow-up periods, patient selection criteria and baseline characteristics, and more.
- Patient information was incomplete with regard to prior therapies.
- The reasons for response or non-response are unclear and may include dose prescribed, adherence to treatment, or blood transfusion rate, in addition to deferiprone pharmacology. According the FDA Statistical Review, "It is unclear whether the efficacy shown in the study is solely due to the Ferriprox therapy, and the interpretation of these analysis results should be taken cautiously."[13]

Several questions remained unaddressed by the study, including:

- What are deferiprone's effects on morbidity and mortality?
- What are the clinical benefits of long-term use?
- How can deferiprone be used in prophylaxis?
- What are the optimum treatment regimens for deferiprone in adults and in pediatric patients?
- How does deferiprone's efficacy in monotherapy or in combination compare to that of deferoxamine or deferasirox?

Safety:

The most serious adverse reaction reported in pooled data collected from 642 patients who participated in single arm or active-controlled clinical studies with deferiprone were agranulocytosis (1.7%; NNH 59) and neutropenia (6.2%; NNH 16), for which deferiprone carries a black box warning noting the potential for death from agranulocytosis or neutropenia. Thirteen deaths due to agranulocytosis-associated sepsis have been reported in the European Union's post-marketing surveillance database. The most common adverse reactions reported during clinical trials were chromaturia (14.6%), nausea (12.6%), vomiting (9.8%), and abdominal pain (10.4%). Gastrointestinal upset caused 1.6% of patients to discontinue therapy in clinical trials. Another noted concern was deferiprone's potential to cause hepatotoxicity. Elevations in ALT or AST were observed in 7.5% (NNH 13) patients and resulted in 0.78% discontinuing therapy.

Unanswered Safety Questions: What are the relationships between exposure to deferiprone (Cmax and AUC) to response and safety? Does deferiprone cause QT prolongation? What are the effects of age, gender, race, and renal and hepatic impairment on exposure to deferiprone and its metabolite? What drugs interact with deferiprone? What is the incidence of agranulocytosis leading to the death because of deferiprone? What is the incidence of hepatotoxicity? Is deferiprone excreted in breast milk and, if so, does it cause harm to infants? What are the adverse effects of long-term use?

COMPARATIVE CLINICAL EFFICACY
Relevant Endpoints:

1) **E*fficacy***: Increased survival, improvement in disease-related sequelae, prevention of iron-induced sequelae
2) ***Safety:*** Agranulocytosis and neutropenia

Study Endpoints:

1) **E*fficacy:*** the change in serum ferritin from baseline to completion of up to one year of therapy, defined as the observation closest to one year in a period of 15 months or at 12 ± 3 months. For subjects that stopped the study early, the value closest to the stopping date was used. Patients who had a decline in serum ferritin of at least 20% over that time period were considered successfully treated, and the trial would be deemed to show evidence of efficacy if at least 20% of patients achieved the described efficacy endpoint
2) ***Safety*:** None

Evidence Table[13]

Ref./Study Design	Drug Regimens	Patient Population[1]	N^, a	Duration	Efficacy Results[2] (CI, p-values)	ARR/ NNT[2,3]	Safety Results (CI, p-values)	ARR/ NNH[2,3]	Quality Rating/Comments[4]
LA36-0310									Poor
open-label, uncontrolled, retrospective analysis of pre-existing clinical data	35 to 100 mg/kg/day administered orally as a tablet or oral solution (The great majority of patients received tablets at a dose of 75 mg/kg/d in 3 divided doses, although some patients received higher or lower doses)	Inclusion criteria: • Treatment with deferiprone • At least a single baseline value for serum ferritin, LIC or MRI T2* available • Follow-up assessment of serum ferritin, LIC or MRI T2* after initiation of deferiprone and within one year of therapy • Had been receiving standard iron chelation therapy with either deferoxamine or deferasirox and before receiving deferiprone had one or more of the following: o Serum ferritin > 2,500 µg/L o Cardiac MRI T2* < 20 ms o LIC > 7 mg/g dry weight Exclusion criteria: • Naïve to iron chelation therapy • Never received deferiprone • No data on serum ferritin, LIC or MRI T2* either while receiving standard chelation therapy or after initiation of deferiprone, or both • Had had an improvement in any of the measures of iron burden of ≥ 20% related to chelator therapy within the year prior to consideration for enrollment Demographics of ITT	264 ferritin 117 LIC 39 T2*	up to 12 months	Primary analysis: % patients with ≥20% reduction in serum ferritin: 52% (CI: 45–58%) Secondary analysis: % patients with ≥20% reduction in LIC: 42% (CI: 33–51%) % patients with ≥20% increase in MRI T2*: 62% (CI: 45–77%)	N/A N/A N/A	Not assessed	N/A	Internal Validity RoB: Selection- The study is non-randomized and single-arm with missing data Performance- The studies used in the analysis were heterogeneous, differing in treatment regimens studied, end points and objectives, methods, follow-up periods, patient selection criteria and baseline characteristics, and more. Attrition- Last observation carried forward (LOCF) used for drop-outs. External Validity: Patient Characteristics- Patient information was incomplete with regard to prior therapies. There were only 2 black subjects in serum ferritin group and 0 in LIC and MRI groups. Setting- Outcomes- • Serum ferritin is a surrogate end point and lacks specificity as a measure of body iron stores. • The better measure, LIC, showed the weakest results for efficacy, and LIC was available for only 117 patients. • For serum ferritin endpoint: There was a wide variability of success rate (26-100%) among the various trials.

		population for primary endpoint: White 73% Asian 17% Black 1% Unknown 8% Multiracial 0.4% Male 45% Mean age 20.1 + or - 12.3 Underlying disease: Β-thal syndrome: 94.3% Sickle cell: 1.1% Myelofibrosis: 1.9% Deferiprone dose: 75 mg/kg/d: 76.9% 100 mg/kg/d: 17.8% 50 mg/kg/d: 5.3% Prior chelator: Deferoxamine: 94.6% Deferasirox: 3% Deferox+deferasirox: 2.2% Deferiprone treatment duration: ≥ 1 year: 27% ≥6 months< 1 year: 76% Mean serum ferritin: 4416 µg/L							• The change in MRI T2* was small (3.3 msec) and data are lacking on the relationship between incremental changes in MRI T2* and cardiac function. • Data were limited with regard to duration of response and dose-response relationship. • Treatment compliance was not assessed. • The population for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin, as 228 could be evaluated for serum ferritin only, 68 for LIC only, 9 for MRI T2* only, 31 for ferritin and LIC, 12 for ferritin and MRI T2*, 25 for LIC and MRI T2*, and 7 for all three tests. • The reasons for response or non-response are unclear and may include dose prescribed, adherence to treatment, or blood transfusion rate, in addition to deferiprone pharmacology

[1]Tests: MRI T2*: magnetic resonance imaging T2-star, LIC: liver iron concentration
[2]Results abbreviations: 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)
^Modified ITT: patients that had taken at least one dose of deferiprone and had at least one post-baseline measurement of an efficacy variable
[a]264 (from 12 studies) were eligible for the serum ferritin criterion, 117 (from 10 studies) were eligible for the LIC criterion and 39 (from 5 studies) were eligible for the cardiac MRI T2* criterion

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY
Deferiprone is a chelator with an affinity for ferric ion (iron III), binding with ferric ions to form neutral 3:1 (deferiprone:iron) complexes.

DRUG SAFETY

Data used for the deferiprone's safety profile for came from the European Union's post-approval adverse event reporting and pooled data from the patients who participated in the individual studies used in study LA36-0310. Both the pooled data and the database reported chromaturia, nausea, vomiting, and arthralgia as the most frequent adverse drug reactions. Agranulocytosis, the clinically most important adverse reaction, was reported in 1.7% (NNH 59) of patients in the database and 1.3% in the study. Thirteen reports of death due to agranulocytosis-associated sepsis and 94 reports of agranulocytosis appear in EU surveillance. Five to 10% of patients participating in the studies used for LA36-0310 developed neutropenia. Of the 642 patients in the clinical trials safety database, three experienced serious hepatobiliary reactions (cholelithiasis, hepatitis, and hepatic congestion), one torsades de pointes, one seizure, and one Henoch-Schönlein purpura. Hepatotoxicity is difficult to assess as liver disease can occur in thalassemia patients without chelation therapy and a large percentage of patients have hepatitis C [13]

Serious (REMS, Black Box Warnings, Contraindications):[5]

Black box warning:

- Deferiprone can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis.
- Measure the absolute neutrophil count (ANC) before starting deferiprone and monitor the ANC weekly on therapy. Interrupt deferiprone therapy if neutropenia develops.
- Interrupt deferiprone if infection develops and monitor the ANC more frequently.
- Advise patients taking deferiprone to report immediately any symptoms indicative of infection."

Contraindications: Hypersensitivity to the deferiprone product. Periorbital edema with skin rash, Henoch-Schönlein purpura, and urticaria have been reported post-marketing.

Precautions:

Agranulocytosis that may result in death, neutropenia, decreased plasma zinc concentrations, and increased ALT and AST values have been observed with Ferriprox therapy. Although a QT study has not been conducted, one patient with a history of QT prolongation experienced Torsades de Pointes with deferiprone therapy. Therefore, deferiprone should be used cautiously in patients who may have increased risk for QT interval.

Monitoring[5]

Monitor for symptoms of arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizure) and symptoms of infection. Measure the absolute neutrophil count (ANC) before starting deferiprone therapy. Monitor ANC weekly while on therapy and more frequently if infection develops. Monitor serum ALT monthly. Discontinue deferiprone if agranulocytosis (ANC < 0.5 x 10^9/L) or neutropenia (ANC <1.5 x 109/L and > 0.5 x 10^9/L) occur unless the benefits outweigh

the risks. Interrupt deferiprone therapy if infection occurs, and consider interruption if a persistent increase in serum transaminase levels develops. Monitor plasma zinc levels and prescribe zinc supplementation if deficiency is evident.

Should neutropenia occur, obtain complete blood cell, absolute neutrophil, and platelet counts daily until recovery.

Tolerability (Drop-out rates, management strategies)[5]

The most frequent adverse reactions reported in clinical trials were gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, which resulted in 1.6% of patients discontinuing therapy. .In clinical trials, 1.7% of patients experienced agranulocytosis. There have been reports of agranulocytosis leading to death. In clinical studies, 7.5% of 642 subjects developed increased ALT values, resulting in five (0.78%) subjects discontinuing the drug due to increased serum ALT or AST levels.

Pregnancy/Lactation rating[5]
Category D. Animal studies indicate deferiprone can cause fetal harm, including malformation at doses equivalent to 3% to 4% of the maximum recommended human dose (MRHD) based on body surface area and embryofetal death, as well as maternal toxicity, at doses equivalent 32% of the MRHD. Pregnancy should be avoided when taking deferiprone.

It is unknown whether deferiprone is excreted in human milk.

Carcinogenesis, Mutagenesis, Impairment of Fertility[5]
Although carcinogenicity studies have not been performed, finding tumor formation in carcinogenicity studies is considered likely given genotoxicity results and the findings of mammary gland hyperplasia and mammary gland tumors in rats treated in a 52-week toxicology study. Deferiprone was positive in an in vitro mouse lymphoma cell assay. Deferiprone was clastogenic in chromosomal aberration tests and bone marrow micronucleus assays. Deferiprone was negative in the Ames bacterial reverse mutation test. Deferiprone had no effects on male or female fertility or reproductive function at 25% of the MRHD.

Unanswered safety questions:
What are the relationships between exposure to deferiprone (Cmax and AUC) to response and safety? Does deferiprone cause QT prolongation? What are the effects of age, gender, race, and renal and hepatic impairment on exposure to deferiprone and its metabolite? What drugs interact with deferiprone? What is the incidence of agranulocytosis leading to the death because of deferiprone? What is the incidence of hepatotoxicity? Is deferiprone excreted in breast milk and, if so, does it cause harm to infants? What are the adverse effects of long-term use?

Dose Index (efficacy/toxic)[5]
Children receiving 2.5 to 3 times the recommended dose for more than one year have developed reversible neurological disorders such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements, and axial hypotonia.

No cases of acute overdose have been reported. No specific antidote for deferiprone overdose exists.

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

NME Drug Name	Lexicomp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for deferiprone	deferoxamine deferasirox	Not available		None	None

LA/SA for Ferriprox	None	Not available		None	None

PHARMACOKINETICS[5]

Parameter	Result
Oral Bioavailability	Not given
Cmax	20 mcg/mL*
Protein Binding	<10%
Elimination	75% to 90% in urine primarily as metabolite
Half-Life	1.9 hours
Metabolism	UGT 1A6

*Although administration with food decreased Cmax by 38% and AUC by 10%, dose adjustment is unnecessary.

ALLERGIES/INTERACTIONS[13]

Drug-Drug:

Separate by at least 4 hours the administration of deferiprone and other medications or supplements containing polyvalent cations such as iron, aluminum, and zinc

Avoid concomitant use with drugs associated with neutropenia or agranulocytosis, otherwise closely monitor the absolute neutrophil count.

Closely monitor patients for adverse reactions when deferiprone is used concomitantly with a UGT 1A6 inhibitor, such as silymarin (milk thistle), as the effect of coadministration with UGT 1A6 inhibitors has not been evaluated. Coadministration with such drugs may require lowering the dose of or interrupting deferiprone.

Food-Drug: Not studied

Allergy/Cross Reactive Substances: None

ADVERSE REACTIONS[5]

The following table represents pooled data from 642 patients who participated in single-arm or active-controlled clinical studies.

Table 2: Adverse drug reactions occurring in ≥ 1% of 642 Ferriprox-treated patient

Body System Preferred Term	% Subjects
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine Aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate Aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5
URINARY DISORDERS	
Chromaturia	14.6

DOSE & AVAILABILITY[5]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
25 mg/kg to a maximum of 33 mg/kg	500 mg tablets	oral	Three times daily	Efficacy and safety not evaluated	Efficacy and safety not evaluated	Efficacy and safety not established	Efficacy and safety not established. Start at the low end of the dosing range.	• Round dose to the nearest 250 mg (half-tablet). • Tailor dose to patient's response and therapeutic goals (maintenance or reduction of body iron burden). • Monitor serum ferritin concentration every two to three months. Consider temporarily interrupting deferiprone therapy if serum ferritin consistently falls below 500 mcg/L. • The relationship between deferiprone dose and the amount of iron eliminated from the body has not been assessed. • Dose proportionality over the labeled dosage range has not been studied.

Appendix 2: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.

5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf