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Literature Scan: Erythropoiesis Stimulating Agents

Date of Review: July 2016

Date of Last Review: May 2014
Literature Search: April 2014 – April 2016

Current Status of PDL Class: see **Appendix 1**

Conclusions:

- In controlled trials, patients with chronic kidney disease (CKD) experienced greater risk for death, serious adverse cardiovascular reactions and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. [1–3]
- For patients with CKD, consider ESA treatment when the hemoglobin level is less than 10 g/dL. This recommendation does not define how far below 10 g/dL is appropriate before an ESA is initiated. Individualize dosing and use the lowest effective dose of ESA sufficient to reduce the need for red blood cell transfusions. Adjust dosing as appropriate.[2]
- There is low quality evidence of no difference between ESAs for prevention of blood transfusions or all-cause mortality.[4] All ESA agents increase risk for hypertension equally, though evidence is imprecise.[4] The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis remain uncertain and analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness are not possible at this time.[4]

Recommendations:

- No further review or research needed at this time. No modification to the prior authorization (PA) clinical criteria is needed. After the executive session, no changes to the PDL were made.

Previous 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. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- For ESA 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. There are no differences in efficacy or safety between the epoetin and darbepoetin.

- Peginesatide was removed from the market in February 2013 due to 19 reports of anaphylaxis following first dose (including 3 deaths) in patients receiving dialysis. It is recommended it be removed entirely from the PDL.
- There is no new comparative evidence that changes the previous conclusions.

Previous Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review by the Cochrane Collaboration compared the efficacy and safety between ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and biosimilar ESAs), placebo, or no treatment in adults with chronic kidney disease (CKD).[4] Fifty-six eligible studies involving 15,596 adults with CKD were identified. Risks of bias in the included studies was generally high or unclear for more than half of studies. There was moderate to low confidence that epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycol-epoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo.[4] The authors could not determine if all ESAs were similar or different in their effects on preventing blood transfusions. Confidence in the comparative effectiveness of different ESAs was generally very low. The comparative effects of ESAs compared with another ESA, placebo or no treatment on all-cause mortality were imprecise.

All ESAs increased the odds of hypertension compared to placebo (epoetin alfa OR 2.31, 95% CI 1.27 to 4.23; epoetin beta OR 2.57, 95% CI 1.23 to 5.39; darbepoetin alfa OR 1.83, 95% CI 1.05 to 3.21; methoxy polyethylene glycol-epoetin beta OR 1.96, 95% CI 0.98 to 3.92). The authors' confidence in the comparative effects of ESAs on hypertension was low due to imprecision in treatment estimates. The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis were uncertain and analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness were not possible.[4]

The reviewers concluded there is insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data. Direct comparative data for the effectiveness of different ESA formulations based on patient-centered outcomes (such as quality of life, fatigue, and functional status)

are sparse and poorly reported. Comparative treatment effects of different ESA formulations on other patient-important outcomes such as survival, MI, stroke, breathlessness and fatigue are very uncertain.[4]

New Guidelines:
NICE guidelines on anemia management in Chronic Kidney Disease were partially updated in 2015.[5] The sections new or updated in 2015 include:
guideline development group and scope, methodology, diagnostic tests for the prediction of response to iron therapy, concurrent illness, iron therapies and treatment of ESA resistance. All other sections and recommendations from the 2011 guideline remain unchanged. The evidence reviewed by the guideline development group led to the conclusion that there is no difference between darbepoetin and epoetin alfa in terms of efficacy and safety.[5]

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. EPOGEN (Epoetin alfa).[Prescribing Information]. Thousand Oaks, CA: Amgen Inc., March 2016.

2. Research C for DE and. Drug Safety and Availability - FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm. Accessed April 12, 2016.

3. Aranesp (Darbepoetin alfa) [Prescribing Information]. Thousand Oaks, CA: Amgen Inc. July 2015.

4. Palmer SC, Saglimbene V, Mavridis D, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2014;12:CD010590. doi:10.1002/14651858.CD010590.pub2.

5. National Clinical Guideline Centre (UK). *Anaemia Management in Chronic Kidney Disease: Partial Update 2015*. London: Royal College of Physicians (UK); 2015. http://www.ncbi.nlm.nih.gov/books/NBK299242/. Accessed April 11, 2016.

6. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO*. 2010;28(33):4996-5010. doi:10.1200/JCO.2010.29.2201.

7. Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M. Anemia in HIV Infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis*. 2004;38(10):1454-1463. doi:10.1086/383031.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INJECTION	VIAL	PROCRIT	EPOETIN ALFA	Y
INJECTION	SYRINGE	ARANESP	DARBEPOETIN ALFA IN POLYSORBAT	Y
INJECTION	VIAL	ARANESP	DARBEPOETIN ALFA IN POLYSORBAT	Y
INJECTION	VIAL	EPOGEN	EPOETIN ALFA	N

Appendix 2: New Clinical Trials

A total of 21 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Search: ((("Hematinics"[Mesh]) AND "Hematinics" [Pharmacological Action]) AND ("Hematinics/administration and dosage"[Mesh] OR "Hematinics/adverse effects"[Mesh] OR "Hematinics/therapeutic use"[Mesh] OR "Hematinics/toxicity"[Mesh])) AND ("Epoetin Alfa"[Mesh] OR "Erythropoietin"[Mesh]) Filters: Clinical Trial, 5 years; adults; safety: efficacy

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

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

Length of Authorization:

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

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this continuation of therapy previously approved by the FFS program?	**Yes:** Go to #12	**No:** Go to #4
4. Is the requested product preferred?	**Yes:** Go to #6	**No:** Go to #5

Approval Criteria		
5. Will the prescriber change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the diagnosis anemia due to chronic renal failure[2] or chemotherapy[6,4] ?	**Yes:** Go to #7	**No:** Go to #8
7. Is Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% and/or ferritin >100 ng/mL?	**Yes:** Approve for 12 weeks with additional approval based upon adequate response.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis anemia due to HIV[7]?	**Yes:** Go to #9	**No:** Go to #10
9. Is the Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% **AND** Endogenous erythropoietin <500 IU/L **AND** If on zidovudine, is dose <4200 mg/week?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the diagnosis anemia due to ribavirin treatment[6]?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the Hgb <10 g/dL or Hct <30% **AND** Is the transferrin saturation >20% and/or ferritin >100 ng/mL **AND** Has the dose of ribavirin been reduced by 200 mg/day and anemia persisted >2 weeks?	**Yes:** Approve up to the length of ribavirin treatment.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Has the patient responded to initial therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:

1. Oregon Health Policy and Research Current Prioritized List of Health Services. Available at: http://cms.oregon.gov/oha/OHPR/pages/herc/current-prioritized-list.aspx Accessed September 12.2012
2. National Kidney Foundation. NKF KDOQI Guidelines. *NKF KDOQI Guidelines* 2006. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm . Accessed May 25, 2012.
3. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hermatology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO* 2010:28(33):4996-5010. Available at: www.asco.org/institute-quality/asco-ash-clinical-practice-guideline-update-use-epoetin-and-darbepoetin-adult. Accessed May 1, 2012.
4. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*. 2010:116(20):4045-4059.
5. Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis*. 2004:38(10):1454-1463. Available at: http://cid.oxfordjournals.org/content/38/10/1454. Accessed May 8, 2012.
6. Recombinant Erythropoietin Criteria for Use for Hepatitis C Treatment-Related Anemia. VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. April 2007

P&T Review: *7/16 (DM); 5/14; 11/12; 6/12; 2/12, 9/10*
Implementation: *1/1/13; 9/24/12; 5/14/12*