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Month/Year of Review: May 2014 **Date of Last Review:** June 2012
PDL Class: Erythropoeiesis Stimulating Agents **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

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

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.
- There is insufficient evidence to assess efficacy and safety of peginesatide relative to epoetin or darbepoetin.

Previous Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.
- Recommend listing peginesatide as non-preferred until more safety and efficacy data are available.
- Recommend modify the initial approval lengths for CKD associated anemia and chemotherapy induced anemia to 12 weeks to assess adequate response in concurrence with the Oregon Health Plan (OHP) list of covered services.
- Recommend the Health Evidence Review Commission reevaluate OHP guideline note 7. FDA labeling and current practice is 12 weeks.

PA Criteria: All ESAs require PA for clinical appropriateness according to OHP guidelines and current medical literature and to preferentially cover preferred products when feasible. Requests are authorized for 12 weeks initially, then up to 12 months with a quantity limit of 30 days per dispense. See Appendix 1.

Conclusions:

- 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.
- No further review of research needed at this time and review comparative costs.

Methods:

A Medline literature search ending March Week 4 2014 for meta-analyses, systematic reviews or randomized active-controlled trials (RCT's) comparing erythropoietin to 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. .

New Systematic Reviews and Guidelines

CKD:

The 2012 Kidney Disease Improving Global Outcomes (KDIGO)[1] guidelines recommend initiating ESA only for patients with hemoglobin <10 g/dL and balance the individuals risk of needing transfusion and risks of ESA therapy, as well as the prior response to iron therapy. The guidelines state there is no robust evidence to distinguish one brand ESA from another regulatory agency approved product.

Oncology:

Two new systematic reviews confirm previous conclusions about the risks and benefits of ESA use in oncology. Neither resolves the controversy of whether targeting hemoglobin levels less than 10 g/dl is less risky.

A 2013 AHRQ Comparative Effectiveness[2] update of managing anemia in chemotherapy patients found moderate level evidence that ESAs reduce the proportion of patients that need blood transfusions and there is no meaningful difference between darbepoetin and erythropoietin. Low strength evidence suggested that there was no effect on overall survival but moderate level evidence that ESAs increased on-study (short-term) mortality and thromboembolic events.

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A 2012 update[3] of a previously published 2007 Cochrane review of 91 RCTs evaluated erythropoietin or darbepoetin in 20,102 patients with anemia associated with cancer. It found Level 1 [likely reliable] evidence that ESAs reduce the need for blood transfusion (RR 0.65 95% CI 0.62 – 0.68, NNT 7-8). However, it found Level 2 [mid-level] evidence that ESAs may increase thromboembolic complications (RR 1.52 95% CI 1.34 – 1.74, NNH 29-64) and mortality (HR 1.05 95% CI 1-1.11). The morbidity results were limited by trial heterogeneity.

FDA warnings:
On February 24, 2013 the FDA issued a news release noticing health care providers of an immediate recall of all lots of Omontys injection due to 19 cases of anaphylaxis and subsequently, 3 deaths.[4] The drug is no longer marketed in the United States.

New Drugs or formulations:
None.

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References:

1. Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney international Supplement*. 2012;2(4):279-331.

2. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update - Research Review - Final | AHRQ Effective Health Care Program. Available at: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1480&ECem=130425. Accessed April 26, 2013.

3. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD003407.pub5/abstract. Accessed April 3, 2014.

4. Press Announcements > FDA alerts health care providers of recall of anemia drug Omontys. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm340899.htm. Accessed April 3, 2014.

Appendix 1: Prior Authorization Criteria

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

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

Length of Authorization:

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

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis?	Yes: Go to #**Error! Reference source not found.**	No: Pass to RPH; Deny (not covered by the OHP).
3. Is this continuation therapy?	Yes: Go to #12	No: Go to #4
4. Is the requested product preferred?	Yes: Go to #6	No: Go to #5
5. Will the Prescriber change to a preferred product?	Yes: Inform provider of covered alternatives in class. Go to #6	No: Go to #**Error! Reference source not found.**
6. Is the diagnosis anemia due to chronic renal failure[2] or chemotherapy[3,4] ?	Yes: Go to #7	No: Go to #8

Approval Criteria		
7. Is Hb < 10g/dl or Hct < 30% AND Transferrin saturation >20% and/or ferritin >100ng/ml?	Yes: Approve for 12 weeks with additional approval based upon adequate response.	No: Pass to RPH; Deny (not medically appropriate).
8. Is the diagnosis anemia due to HIV[5]?	Yes: Go to #9	No: Go to #10
9. Is the Hb < 10g/dL or Hct < 30% AND Transferrin saturation > 20% AND Endogenous erythropoietin < 500 iu/L AND If on Zidovudine is dose < 4200mg/week?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).
10. Is the diagnosis anemia due to ribavirin treatment[6]?	Yes: Go to #11	No: Pass to RPh; Deny, (not medically appropriate).
11. Is the Hb < 10g/dL or Hct < 30% AND Is the transferrin saturation >20% and/or ferritin >100ng/ml AND Has the dose of ribavirin been reduced by 200mg/day and anemia persisted > 2 weeks?	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh; Deny (not medically appropriate).
12. Has the patient responded to initial therapy?	Yes: Approve for length of Rx or 12 months, whichever is less.	No: Pass to RPh; Deny (not medically appropriate).

References:

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

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

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

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

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

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

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

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