Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Erythropoiesis Stimulating Agents (ESA)

Date of Review: January 2019

Date of Last Review: July 2016
Literature Search: 04/01/2016 - 10/23/2018

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Literature Scan:
The erythropoiesis stimulating agents (ESA) literature scan was prompted by a new approval for epoetin alfa-epbx. New comparative evidence published since the last review for the ESA class will also be evaluated.

Conclusions:
- This literature scan identified 2 systematic reviews[1,2], 1 new formulation[3], 1 new indication[4], and 3 new safety alerts[4-6]. Identified literature supports current policy.
- In August 2017, a Cochrane Collaboration systematic review was completed comparing methoxy polyethylene glycol-epoetin beta to other ESAs in anemia of chronic kidney disease (CKD).[1] The review concluded that there is low certainty evidence that methoxy peg-epoetin beta has little or no effects on patient-centered outcomes compared with epoetin alfa or darbepoetin alfa in CKD.[1]
- In May 2018, Retacrit® (epoetin alfa-epbx) was approved as a new biosimilar to Epogen/Procrit.[3]
- In June 2018, Mircera® (methoxy polyethylene glycol-epoetin beta) was approved for the treatment of pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.[4]

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

Summary of Prior Reviews and Current Policy
Prior DURM reviews have demonstrated a lack of difference in safety and efficacy for darbepoetin and epoetin and determined that preference can be established based on cost.[7-9] Darbepoetin (Aranesp®) is the current preferred agent and epoetin alfa (Procrit® and Epogen®), epoetin alfa-epbx (Retacrit®), and methoxy peg-epoetin beta (Mircera®) are currently non-preferred agents. Current policy requires prior authorization (PA) for all agents. The PA ensures that ESAs are covered according to Oregon Health Plan guidelines and current medical literature. The Oregon Health Authority (OHA) Health Evidence Review Commission (HERC) has a Guideline Note in the Prioritized List (Guideline Note 7) regarding ESA use in indications of anemia induced by cancer chemotherapy, anemia associated with HIV/AIDS, and anemia associated with chronic renal failure.[10] The guidance describes what hemoglobin levels are required and when reassessment should occur.[10]

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. The Medline search strategy used for this review 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), 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 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.

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:
In January 2017, the Cochrane Collaboration published a systematic review evaluating short-acting ESAs for anemia in predialysis patients.[2] Primary outcomes included mortality, measures of correction of anemia (hemoglobin/hematocrit), and quality of life.[2] Of the included studies (n=14), 5 were comparative studies (n=794 participants) of epoetin alfa versus other epoetins.[2] However, no full published data were available which directly compared two FDA-approved agents.[2]

In August 2017, the Cochrane Collaboration published a systematic review evaluating continuous erythropoiesis receptor activator (CERA; methoxy poly ethylene-glycol epoetin beta) for anemia of CKD in patients with stage 3-5 CKD, patients requiring any form of long-term dialysis, and patients with a functioning kidney transplant.[1] Included interventions compared CERA to placebo, no treatment, darbepoetin alfa, epoetin alfa or beta, or CERA using differing administration strategies.[1] Primary clinical outcomes included one or more major adverse cardiovascular events, one of more hospital admissions, vascular access thrombosis, cardiovascular mortality, all-cause mortality, cancer, quality of life, and adverse events.[1] Of the 27 studies in the review, studies with direct comparative evidence included 9 studies of CERA versus epoetin (n=2339), 9 studies of CERA versus darbepoetin alfa (n=4143), and 2 studies of CERA versus epoetin versus darbepoetin alfa (n=552).[1] Risk of bias for the studies was generally unclear to high with high risk of performance bias due to open-label design and lack of blinding in the majority of the trials (n=23).[1] For all comparative evidence identified, the quality of evidence ranged from very low to low.[1] Low quality evidence is presented below in **Table 1** and included data on all-cause mortality, red cell transfusions, and hypertension, all of which showed no difference between CERA and the comparator.[1] The authors concluded there is low certainty evidence that CERA has little or no effects on patient-centered outcomes compared with epoetin alfa, epoetin beta, or darbepoetin alfa in CKD.[1]

Table 1. Low Quality or Greater Comparative Evidence for CERA in CKD Patients for Specified Outcomes (Adapted from Cochrane)[1]

Outcome	Intervention	Comparison	Relative Effect (95% Confidence Interval)	Number of Participants (Studies)	Quality of Evidence
All-cause mortality	CERA	Epoetin	1.07 (0.73-1.57)	1846 (5)	Low
	CERA	Darbepoetin	1.11 (0.75-1.65)	1657 (5)	Low
One or more red cell transfusions	CERA	Epoetin	1.02 (0.72-1.46)	1824 (5)	Low
Hypertension	CERA	Epotetin	1.01 (0.75-1.37)	1821 (5)	Low
	CERA	Darbepoetin	1.00 (0.79-1.28)	1752 (6)	Low

After review, 16 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11-26]

New Guidelines:
None identified.

New Formulations or Indications:
05/2018: Retacrit® (epoetin alfa-epbx) was approved as a new biosimilar to Epogen®/Procrit® for the treatment of anemia due to CKD for dialysis and non-dialysis patients, anemia due to zidovudine in patients with an HIV infection, anemia due to the effects of concomitant myelosuppressive chemotherapy (when there is a minimum of two subsequent months of planned chemotherapy), and for the reduction of allogenic red blood cell transfusions in patients undergoing noncardiac, nonvascular surgery.[3] Retacrit® was approved based on product characterization, animal data, human pharmacokinetic and pharmacodynamics data, and clinical immunogenicity.[27] Retacrit® is not interchangeable with Epogen®/Procrit®.[27]

06/2018: Mircera® (methoxy polyethylene glycol-epoetin beta) was approved for the treatment of pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.[4,28] This new approval was based on an open-label, multiple dose, multicenter, dose-finding trial in 64 patients age 5 to 17 years.[28] Patients with CKD on hemodialysis with stable hemoglobin levels while receiving another ESA were then administered Mircera® IV every 4 weeks for 20 weeks.[28] Safety evidence from this trial was consistent with previous adult safety data.[28]

New FDA Safety Alerts:
Table 1. Description of new FDA Safety Alerts[4-6]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
• Epoetin alfa • Darbepoetin alfa • Methoxy polyethylene glycol-epoetin beta	• Epogen/ Procrit • Aranesp • Mircera	• 9/2017 • 10/2017 • 6/2018	Warnings and Precautions	New subsection regarding blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) reported with ESA treatment. Discontinue immediately if suspected.
Epoetin alfa	Epogen/Procrit	9/2017	Contraindication	Added contraindication for use in lactating women
Epoetin alfa	Epogen/Procrit	9/2017	Warnings and Precautions	New subsection regarding risk of serious adverse reactions due to benzyl alcohol preservative. Both Epogen and Procrit from multiple-dose vials contain benzyl alcohol and are contraindicated for use in neonates, infants, pregnant women, and lactating women. They should also not be mixed with bacteriostatic saline (which also contains benzyl alcohol) when administering to these patients. Serious and fatal reactions including “gasping syndrome” can occur in neonates and infants treated with benzyl alcohol-preserved drugs.

				There is a similar potential risk to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.

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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
INJECTION	VIAL	ARANESP	darbepoetin alfa in polysorbat	Y
INJECTION	SYRINGE	ARANESP	darbepoetin alfa in polysorbat	Y
INJECTION	VIAL	EPOGEN	epoetin alfa	N
INJECTION	VIAL	PROCRIT	epoetin alfa	N
INJECTION	SYRINGE	MIRCERA	methoxy peg-epoetin beta	N
INJECTION	VIAL	RETACRIT	epoetin alfa-epbx	N

Appendix 2: New Comparative Clinical Trials

A total of 174 citations were manually reviewed from the initial literature search. After further review, 174 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy on 10/23/2018

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R): 1946 to October 22, 2018	
1 exp Darbepoetin alfa/	*1003*
2 exp Epoetin Alfa/	*1754*
3 exp Erythropoietin/	*22843*
4 Methoxy Polyethylene Glycol-Epoetin Beta.mp.	*57*
5 1 or 2 or 3 or 4	*22862*
6 limit 5 to (English language and humans and yr="2016 –Current")	*687*
7 limit 6 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv, or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews	*174*

Appendix 4: Key Inclusion Criteria

Population	United States population with FDA-approved indication for ESA use
Intervention	Any ESA in **Appendix 1**
Comparator	Active comparison of any ESA in **Appendix 1**
Outcomes	Symptom improvement Morbidity Mortality Serious adverse events Discontinuation from serious adverse events
Timing	Any duration of trial; literature search 4/1/2016-10/23/2018
Setting	Outpatient

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. • 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[1] or chemotherapy[2,3]?	**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[4]?	**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[5]?	**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

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P&T Review: *1/19 (JP); 7/16; 5/14; 11/12; 6/12; 2/12, 9/10*
Implementation: *10/13/16; 1/1/13; 9/24/12; 5/14/12*