

Drug Class Literature Scan: Erythropoiesis Stimulating Agents

Date of Review: December 2023

Date of Last Review: January 2019

Literature Search: 10/23/2018 – 8/14/2023

Current Status of PDL Class:

See **Appendix 1**.

Purpose: Evaluate new evidence published since the last review in 2019 and assess utilization of prior authorization (PA) criteria.

Plain Language Summary:

- Erythropoietin is a hormone produced in the kidneys that causes the body to make red blood cells in the bone marrow. Medicines that increase erythropoietin production are called erythropoiesis-stimulating agents. These medicines must be injected by a health care provider either under the skin (subcutaneously) or into a vein (intravenously). Some people can self-administer these medicines at home after they learn how to prepare and use the injection.
- Erythropoietin-stimulating agents treat people who do not make enough red blood cells (a condition called anemia). Red blood cells carry oxygen from the lungs to the rest of the body. Anemia can make people feel tired or out of breath and may increase the need for a blood transfusion. The Food and Drug Administration has approved erythropoietin-stimulating agents for anemia associated with kidney disease, cancer treatment, and human immunodeficiency virus (HIV) infection. Providers also prescribe them for certain patients having surgery to reduce the need for a blood transfusion.
- Administration of these medicines can increase the risk of blood clots, stroke, heart attack, and death. To reduce the risk of side effects, people getting these medicines must be closely monitored by their provider. Blood tests are frequently obtained to check how well the medicine is working and to decide the best dosing schedule.
- Providers must explain to the Oregon Health Plan (OHP) why someone needs epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta before the OHP fee-for-service program will pay for it when the prescription is picked up at the pharmacy. This process is called prior authorization.

Conclusions:

- Since the previous 2019 Pharmacy and Therapeutics (P & T) Committee review of the class of erythropoiesis-stimulating agents (ESAs), 2 systematic reviews^{1,2} and one guideline³ have been updated.
- A 2023 Cochrane review evaluated recent evidence for the use of ESAs to manage anemia in adults with chronic kidney disease (CKD).¹ This review concluded epoetin alfa and darbepoetin alfa may be superior to placebo for the prevention of blood transfusion based on moderate- to very low-quality evidence, but increased the odds of hypertension compared to placebo (moderate-quality evidence).¹ Effects on death (any cause), were generally uncertain

between any ESA formulation and placebo or other ESA product (low-quality evidence).¹ The other potential benefits of ESAs, such as reduction in fatigue and breathlessness, remain uncertain due to sparse data.¹

- A 2020 Cochrane review evaluated the efficacy of preoperative epoetin therapy administered with iron in reducing the need for red blood cell (RBC) transfusions in preoperatively anemic adults undergoing non-cardiac surgery.² Moderate-quality evidence suggests that preoperative epoetin administered with iron therapy to anemic adults prior to non-cardiac surgery reduces the need for RBC transfusion and, when given at higher doses, increases the hemoglobin (Hb) concentration preoperatively compared to control treatment (placebo, no treatment, or standard of care with or without iron).² The administration of epoetin and iron treatment did not decrease the mean number of units of RBC transfused per patient (moderate-quality evidence) compared with control treatment.² There were no important differences in the risk of adverse events or mortality within 30 days (moderate-quality evidence), nor in length of hospital stay between those who received epoetin with iron and those who did not (low-quality evidence) compared with control treatment.²
- In 2019, the American Society of Clinical Oncology and American Society of Hematology (ASCO/ASH) updated clinical practice guidelines recommendations for use of ESA therapy in patients with chemotherapy-induced anemia.³ Providers should offer an ESA to patients receiving cancer treatment that is not curative in intent and presenting with Hb less than 10 g/dL (High quality of evidence [QoE]; Strong recommendation).³ ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (High QoE: Strength of recommendation: strong).³
- Most ESA claims are processed as physician administered claims (PAD), there is very little point of sale (POS) processing.

Recommendations:

- Based on review of recent evidence, no changes to the Preferred Drug List (PDL) are recommended.
- Retire ESA PA criteria due to limited POS utilization.
- No PDL changes were recommended after review drug costs in executive session.

Summary of Prior Reviews and Current Policy

- Epoetin alfa is Food and Drug Administration (FDA) approved for the treatment of anemia due to CKD in children and adults, anemia due to zidovudine therapy in HIV-infected adults, and anemia due to the effects of concomitantly administered myelosuppressive chemotherapy in patients aged 5 years and older with nonmyeloid malignancies receiving chemotherapy.⁴ It is also indicated to reduce the need for allogeneic blood transfusions in adults electing noncardiac, nonvascular surgery.⁴ Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.⁴ Epoetin alfa is not indicated for use under the following conditions:
 - cancer patients receiving hormonal therapy, therapeutic biologic products, or radiation therapy unless also receiving concurrent myelosuppressive chemotherapy;
 - cancer patients receiving myelosuppressive chemotherapy when the expected outcome is curative;
 - cancer patients receiving myelosuppressive chemotherapy when anemia can be managed by transfusion;
 - surgery patients who are willing to donate autologous blood;
 - surgery patients undergoing cardiac or vascular surgery; or
 - as a substitute for RBC transfusion in patients requiring immediate correction of anemia.⁴

The manufacturer has issued a black boxed warning for epoetin alfa due to the increased risk for death, serious adverse cardiovascular reactions, and stroke in patients with CKD when epoetin is administered to a target hemoglobin (Hb) level greater than 11 g/dL.⁴ In patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers, epoetin is associated with increased risk of tumor progression or recurrence.⁴ In addition, due to the increased risk

of deep vein thrombosis (DVT) in perisurgical patients, DVT prophylaxis is recommended with administration of epoetin alfa.⁴ The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) anemia workgroup published guidance that recommends balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) when initiating and maintaining ESA therapy.⁵ For adult CKD, non-dialysis patients, ESA therapy should not be initiated when Hb concentrations are greater than or equal to 10 g/dL.⁵

- Darbepoetin alfa and methoxy polyethylene glycol-epoetin beta have the similar limitations of use and an identical black box warning as epoetin alfa.^{6,7} Darbepoetin is FDA-approved for treatment of anemia due to CKD in children and adults and anemia due to chemotherapy in adults with cancer.⁶ Methoxy polyethylene glycol-epoetin beta is only FDA-approved for management of anemia due to CKD in people aged 5 years and older.⁷
- Prior DURM reviews have demonstrated a lack of difference in safety and efficacy for darbepoetin alfa and epoetin alfa and determined that preference can be established based on cost.⁸⁻¹⁰ Darbepoetin alfa (ARANESP) is the current preferred agent. Epoetin alfa (PROCRIT and EPOGEN), epoetin alfa-epbx (RETACRIT), and methoxy peg-epoetin beta (MIRCERA) are currently non-preferred agents (see **Appendix 1**). Current policy requires prior authorization (PA) for all agents (see **Appendix 5**). The PA ensures that erythropoiesis-stimulating agents (ESAs) are covered according to Oregon Health Plan guidelines and current medical literature. The 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.¹¹ The guidance describes which Hb levels are required and when reassessment should occur.¹¹
- In the second quarter of 2023 (April 1 through June 30) there were no POS claims processed for ESAs, all the claims were processed as PAD claims, mostly for patients with end stage renal disease.

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** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, 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:

Cochrane: Erythropoiesis-Stimulating Agents for Anemia in Adults with Chronic Kidney Disease

A 2023 Cochrane review evaluated recent evidence for the use of ESAs to manage anemia in adults with CKD.¹ This was an update to a 2014 publication on the same topic. The objective was to compare the efficacy and safety of epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs against each other or versus placebo in adults with CKD. The review included people requiring dialysis, not needing dialysis, and those who received a renal transplant.¹ Epoetin beta is not FDA-approved in the United States (US), so evidence for its safety and efficacy is not included in the summary of this systematic review. Literature was searched through April 2022 for eligible RCTs.¹ Sixty-two new studies (n=9,237) were included in the 2023 update, for an overall total of 117 studies with 25,237 participants.¹ The prespecified outcomes included need for blood transfusion, incidence of hypertension and fatigue related to

anemia, and mortality rates. The recently published RCTs did not evaluate changes in fatigue as an outcome.¹ This review primarily included participants with kidney failure dependent on dialysis or those with moderate-to-advanced CKD [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²].¹ Data on the use of ESAs in kidney transplant recipients were relatively sparse, and the findings of this review may not be directly applicable to this clinical setting.¹

Many studies included in this review were at high or unclear risk of bias in most methodological domains.¹ Only 2 studies were at low risk of bias for allocation concealment, blinding of outcome assessment and attrition from follow-up.¹ Allocation concealment was reported using low-risk methods in 17 studies (15%), and blinding of outcome assessment was reported in seven studies (6%).¹ There was complete outcome data in only 25 studies (22%), with 40 studies (34%) reporting incomplete outcome data, and missing data were unclearly documented in 51 studies (44%).¹ Overall, results remain similar in this update compared to the previous 2014 review.¹ Due to a lack of direct comparative evidence, the authors completed a network meta-analysis. For the purposes of this review, only results from meta-analyses using direct comparative evidence are summarized.

Epoetin alfa and darbepoetin alfa were compared to placebo to assess prevention of blood transfusions in 6 RCTs.¹ For preventing blood transfusion, epoetin alfa may be superior to placebo (odds ratio [OR] 0.15, 95% confidence interval [CI] 0.04 to 0.58, 5 RCTs, n=385; I² = 81%; low-quality evidence) and darbepoetin alfa was probably superior to placebo (OR 0.53, 95% CI 0.46 to 0.63; 1 RCT, n=4038; moderate-quality evidence).¹ No study evaluated the impact of methoxy polyethylene glycol-epoetin beta on reducing blood transfusions compared to placebo.¹

When ESAs were compared with each other, epoetin alfa probably increased the odds of blood transfusion compared to darbepoetin alfa (OR 2.31, 95% CI 1.34 to 3.97; 3 RCTs, n=1191; I² = 0%; moderate-quality evidence).¹ There was no difference on the odds of blood transfusion with epoetin alfa compared to a biosimilar epoetin (OR 0.90, 95% CI 0.57 to 1.44, 7 RCTs, n=2335; I² = 0%; low-quality evidence) or biosimilar darbepoetin alfa (OR 0.68, 95% CI 0.34 to 1.34, 1 RCT, n=752; low-quality evidence).¹ Darbepoetin alfa had no difference on the odds of blood transfusion compared to methoxy polyethylene glycol-epoetin beta (OR 1.36, 95% CI 0.64 to 2.89; 4 RCTs, n=1191; I² = 46%; very low-quality evidence), a biosimilar epoetin (OR 0.31, 95% CI 0.01 to 7.79, 1 RCT, n=74; low-quality evidence), or a biosimilar darbepoetin alfa (OR 1.05, 95% CI 0.07 to 16.88, 1 RCT, n=385; low-quality evidence), but confidence in these results remains uncertain.¹

Three agents (epoetin alfa, darbepoetin alfa and biosimilar epoetin) were compared with placebo to evaluate risk of death for any cause in 8 RCTs.¹ Compared to placebo, effects on risk of death were uncertain for epoetin alfa (OR 0.57, 95% CI 0.15 to 2.26, 5 RCTs, n=455; I² = 0%; low-quality evidence), darbepoetin alfa (OR 1.00, 95% CI 0.84 to 1.19, 2 RCTs, n=4,854; I² = 31%; low-quality evidence), and biosimilar epoetin (no events, 1 RCT, n=40; low-quality evidence).¹ No study evaluated the impact of methoxy polyethylene glycol-epoetin beta on mortality compared to placebo.¹

When ESAs were compared to each other, the odds of death from any cause with epoetin alfa were uncertain when compared to darbepoetin alfa (OR 0.78, 95% CI 0.50 to 1.22, 9 RCTs, n=1913; I² = 0%; low-quality evidence) or biosimilar epoetin (OR 1.01, 95% CI 0.69 to 1.47; 13 RCTs, n=4154; I² = 22%; low-quality evidence).¹ The odds of death with darbepoetin alfa were uncertain when compared to methoxy polyethylene glycol-epoetin beta (OR 1.07, 95% CI 0.68 to 1.68, 5 RCTs, n=1498; I² = 0%; low-quality evidence) or a biosimilar darbepoetin alfa (OR 0.61, 95% CI 0.19 to 1.91, 3 RCTs, n=335; I² = 0%; low-quality evidence).¹

To evaluate risk of hypertension, epoetin alfa and darbepoetin alfa were assessed against placebo in 3 RCTs.¹ The odds of hypertension were probably increased with epoetin alfa (OR 4.10, 95% CI 2.16 to 7.76, 2 RCTs, n=251; I² = 0%; moderate-quality evidence) and darbepoetin alfa (OR 1.14, 95% CI 0.99 to 1.32, 1 RCT, n=4038; moderate-quality evidence) when compared to placebo.¹ No study evaluated the risk of hypertension for methoxy polyethylene glycol-epoetin beta versus placebo.¹

When ESAs were compared to each other, the odds of hypertension were uncertain for epoetin alfa compared to darbepoetin alfa (OR 0.93, 95% CI 0.68 to 1.25, 6 RCTs, n=2090; $I^2 = 32\%$; low-quality evidence), a biosimilar epoetin (OR 1.21, 95% CI 0.76 to 1.93, 7 RCTs, n=1940; $I^2 = 27\%$; low-quality evidence), or a biosimilar darbepoetin alfa (OR 0.72, 95% CI 0.15 to 3.44, 1 RCT, n=747; low-quality evidence).¹ The odds of hypertension were uncertain for darbepoetin alfa compared to methoxy polyethylene glycol-epoetin beta (OR 0.91, 95% CI 0.62 to 1.33, 6 RCTs, n=1568; $I^2 = 27\%$; low-quality evidence) or a biosimilar darbepoetin alfa (OR 0.93, 95% CI 0.51 to 1.70, 3 RCTs, n=609; $I^2 = 3\%$; low certainty evidence).¹

Despite the inclusion of 61 studies since the previous version of this review in 2014, few studies were adequately powered to detect differences in patient-level outcomes.¹ There was important clinical diversity in studies based on the age of the participants, stage of CKD and duration of treatment.¹ This review concluded epoetin alfa and darbepoetin alfa may be superior to placebo for the prevention of blood transfusion based on moderate- to very low-quality evidence, but increased the odds of hypertension compared to placebo (moderate-quality evidence).¹ Effects on death (any cause), were generally uncertain between any ESA formulation and placebo or other ESA product (low-quality evidence).¹ The other potential benefits of ESAs, such as reduction in fatigue and breathlessness, remain uncertain due to sparse data.¹ In summary, current data from RCTs are insufficient to evaluate comparative efficacy and safety of different ESA formulations.¹

Cochrane: Erythropoietin Plus Iron versus Control Treatment Including Placebo or Iron for Preoperative Anemic Adults Undergoing Non-Cardiac Surgery

A 2020 Cochrane review evaluated the efficacy of preoperative epoetin therapy (subcutaneous or parenteral) with iron (enteral or parenteral) in reducing the need for allogeneic RBC transfusions in preoperatively anemic adults undergoing non-cardiac surgery.² This was an update to a 2016 publication on this topic. Literature was searched through August 2019.² Twelve RCTs (n=1880) which compared preoperative epoetin and iron therapy to control treatment (placebo, no treatment, or standard of care with or without iron) met inclusion criteria.² The surgery types included hip joint arthroplasty or hip or knee replacement (5 trials), colorectal cancer surgery (4 trials), hysterectomy (2 trials), and gastrointestinal surgery (1 trial) and included participants with mild and moderate preoperative anemia (Hb from 10 to 12 g/dL).² The duration of preoperative treatment varied across the trials, ranging from once a week to daily or a 5-to-10-day period, and in one trial preoperative epoetin was given on the morning of surgery and for five days postoperatively.² Intravenous iron was administered in 4 RCTs and oral iron was used in 8 RCTs.² The primary outcome was need for RBC transfusion. Secondary outcomes included Hb concentration directly before surgery, number of RBC units transfused, mortality within 30 days of surgery, adverse events, and length of hospital stay.² The overall risk of bias for selection bias, performance bias, and attrition bias was low in more than 50% of the included studies.² For allocation concealment, detection bias, and other bias, the risk of bias was low for about 20% of the included studies.² Risk of reporting bias was low for only 10% of the included studies.²

Compared to control treatment, preoperative epoetin and iron given to anemic adults reduced the need for RBC transfusion (risk ratio [RR] 0.55, 95% CI 0.38 to 0.80, n=1880; 12 RCTs; $I^2 = 84\%$; moderate-quality evidence).² Preoperative high-dose epoetin (500 to 600 IU/kg body weight) and iron increased the Hb concentration (mean difference [MD] 1.87 g/dL, 95% CI 1.26 to 2.49; n=852; studies = 3; $I^2 = 89\%$; low-quality evidence) but not low-dose epoetin (150 to 300 IU/kg body weight) and iron (MD 0.11 g/dL, 95% CI -0.46 to 0.69, n=334, 4 RCTs; $I^2 = 69\%$; low-quality evidence) when compared to control treatment.²

For people who needed a RBC transfusion, there was probably little or no difference in the number of RBC units transfused when epoetin and iron were given preoperatively (MD -0.09, 95% CI -0.23 to 0.05, n=1420, 6 RCTs; $I^2 = 2\%$; moderate-quality evidence) compared to control treatment.² There was probably little or no difference in the risk of mortality within 30 days of surgery (RR 1.19, 95% CI 0.39 to 3.63, n=230, 2 RCTs; $I^2 = 0\%$; moderate-quality evidence) or of adverse events including local rash, fever, constipation, or transient hypertension (RR 0.93, 95% CI 0.68 to 1.28, n=1722; 10 RCTs; $I^2 = 0\%$; moderate-quality evidence).² The administration of epoetin with iron before non-cardiac surgery did not clearly reduce the length of hospital stay of preoperative anemic adults (MD -1.07, 95% CI -4.12 to 1.98, n=293, 3 RCTs; $I^2 = 87\%$; low-quality evidence) compared to control treatment.²

In summary, moderate-quality evidence suggests that preoperative epoetin and iron therapy administered to anemic adults prior to non-cardiac surgery reduces the need for RBC transfusion and, when given at higher doses, increases the Hb concentration preoperatively.² The administration of epoetin and iron treatment did not decrease the mean number of units of RBC transfused per patient (moderate-quality evidence).² There were no important differences in the risk of adverse events or mortality within 30 days (moderate-quality evidence), nor in length of hospital stay between those who received epoetin with iron (low-quality evidence) and those who did not.²

After review, 20 systematic reviews were excluded due to poor quality,¹²⁻¹⁶ wrong study design of included trials (e.g., observational),^{17,18} comparator (e.g., no control or placebo-controlled),¹⁹⁻³⁰ or outcome studied.³¹⁻³³

New Guidelines:

American Society of Clinical Oncology and American Society of Hematology: Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents

A 2019 clinical guideline from ASCO/ASH updated previous recommendations for the use of ESAs in patients with anemia due to cancer chemotherapy.³ The guideline is based on evidence from 15 meta-analyses and 2 RCTs published through 2018.³ A growing body of evidence suggests that adding iron to treatment with an ESA may improve hematopoietic response and reduce the likelihood of RBC transfusion.³ The biosimilar literature review suggests that biosimilars of epoetin alfa have similar efficacy and safety to reference products, although evidence in cancer remains limited.³ Erythropoiesis-stimulating agents (including biosimilars) may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose Hb has declined to less than 10 g/dL.³ Red blood cell transfusion is also an option in these patients.³ With the exception of selected patients with myelodysplastic syndromes, ESAs should not be offered to most patients with nonchemotherapy-associated anemia.³ During ESA treatment, Hb may be increased to the lowest concentration needed to avoid transfusions.³ Iron replacement may be used to improve Hb response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency.³

Strength of recommendations based quality of evidence include:

- Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose Hb has declined to less than 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (High QoE: Strength of recommendation: strong).³
- ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Moderate QoE: Strength of recommendation: strong).³
- ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤ 500 IU/L (Moderate QoE; Strength of recommendation: moderate).³
- ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (High QoE: Strength of recommendation: strong).³
- Iron replacement may be used to improve Hb response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Moderate QoE: Strength of recommendation: weak).³
- The authors of the guideline arrived at informal consensus that epoetin alfa, darbepoetin, and biosimilar epoetin alfa are equivalent with respect to effectiveness and safety based on low- to moderate-quality evidence.³

References:

1. Chung EY, Palmer SC, Saglimbene VM, Craig JC, Tonelli M, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2023;2:CD010590.
2. Kaufner L, von Heymann C, Henkelmann A, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2020;8:CD012451.
3. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *Blood Adv*. 2019;3(8):1197-1210.
4. EPOGEN (epoetin alfa) Injection Prescribing Information. Thousand Oaks, CA; Amgen, Inc. July 2018.
5. McMurray JJV, Parfrey PS, Adamson JW, et al. Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney International Supplements*. 2012;2(4):279-335.
6. ARANESP (darbepoetin alfa) Injection Prescribing Information. Thousand Oaks, CA; Amgen, Inc. January 2019.
7. MIRCERA (methoxy polyethylene glycol-epoetin beta) Injection Prescribing Information. 9014 St. Gallen, Switzerland; Vifor International. March 2023.
8. Oregon State University Drug Use Research and Management. Literature Scan: Erythropoiesis Stimulating Agents. July 2016. Available at: http://www.orpd.org/durm/meetings/meetingdocs/2016_07_28/archives/2016_07_28_Erythropoiesis.pdf. Accessed October 23, 2018.
9. Oregon State University Drug Use Research and Management. Literature Scan: Erythropoiesis Stimulating Agents. May 2014. Available at: http://www.orpd.org/durm/meetings/meetingdocs/2014_05_29/archives/2014_05_29_ESAScan2014.pdf. Accessed October 23, 2018.
10. Oregon State University Drug Use Research and Management. Abbreviated Update: Erythropoiesis Stimulating Agents. June 2012. Available at: http://www.orpd.org/durm/meetings/meetingdocs/2012_06_28/archives/2012_06_28_ESA_CU.pdf Accessed October 23, 2018.
11. Health Evidence Review Commission Prioritized-List. <https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx>. Accessed September 28, 2023.
12. Hung CM, Chen JJ, Zeng BY, et al. Efficacy of Different Interventions to Reduce Pre- or Perioperative Blood Transfusion Rate in Patients with Colorectal Cancer: A Network Meta-Analysis of Randomized Controlled Trials. *Current Oncology*. 2021;28(4):3214-3226.
13. Hemani S, Lane O, Agarwal S, Yu SP, Woodbury A. Systematic Review of Erythropoietin (EPO) for Neuroprotection in Human Studies. *Neurochemical Research*. 2021;46(4):732-739.
14. Kaur M, Khatri K, Kankaria A, Dhir T, Arora H. Efficacy and safety of combined administration of erythropoietin and iron in comparison to iron therapy alone in orthopaedic surgery: systematic review and metanalysis. *Acta Orthopedica Mexicana*. 2021;35(6):547-556.
15. Zhou J, Lu J, Cai D. Recombinant Human Erythropoietin for Kidney Transplantation: A Systematic Review and Meta-Analysis. *Urology Journal*. 2020;17(3):217-223.
16. Kei T, Mistry N, Curley G, et al. Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis. *Canadian Journal of Anaesthesia*. 2019;66(6):716-731.
17. Yang J, Yu S, Yang Z, et al. Efficacy and Safety of Supportive Care Biosimilars Among Cancer Patients: A Systematic Review and Meta-Analysis. *BioDrugs*. 2019;33(4):373-389.
18. Park S, Greenberg P, Yucel A, et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. *Br J Haematol*. 2019;184(2):134-160.

19. Ananthan A, Balasubramanian H, Rao S, Patole S. Clinical Outcomes Related to the Gastrointestinal Trophic Effects of Erythropoietin in Preterm Neonates: A Systematic Review and Meta-Analysis. *Advances in Nutrition*. 2018;9(3):238-246.
20. Cho BC, Serini J, Zorrilla-Vaca A, et al. Impact of Preoperative Erythropoietin on Allogeneic Blood Transfusions in Surgical Patients: Results From a Systematic Review and Meta-analysis. *Anesthesia & Analgesia*. 2019;128(5):981-992.
21. Li J, Zhang J, Hao Q, Chen H, Cheng X. Erythropoietin for preventing bronchopulmonary dysplasia in preterm infants: A systematic review and meta-analysis. *Pediatric pulmonology*. 2022;57(4):1051-1063.
22. Chang X, Li Q, Tang H. Use of preoperative erythropoietin therapy to facilitate autologous blood donation in orthopedic surgery: A meta-analysis. *Medicine (Baltimore)*. 2020;99(2):e18577.
23. Garg B, Sharma D, Bansal A. Systematic review seeking erythropoietin role for neuroprotection in neonates with hypoxic ischemic encephalopathy: presently where do we stand. *Journal of Maternal-Fetal & Neonatal Medicine*. 2018;31(23):3214-3224.
24. Lee J, Cho Y, Choi KS, et al. Efficacy and safety of erythropoietin in patients with traumatic brain injury: A systematic review and meta-analysis. *American Journal of Emergency Medicine*. 2019;37(6):1101-1107.
25. Li Y, Zhang J, Wang H, et al. Does erythropoietin affect the outcome and complication rates of patient with traumatic brain injury? A pooled-analysis. *Neurological Sciences*. 2022;43(6):3783-3793.
26. Liu C, Huang C, Xie J, et al. Potential Efficacy of Erythropoietin on Reducing the Risk of Mortality in Patients with Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2020;2020:7563868.
27. Tomlinson D, Robinson PD, Oberoi S, et al. Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis. *Current Oncology*. 2018;25(2):e152-e167.
28. Katiyar V, Chaturvedi A, Sharma R, et al. Meta-Analysis with Trial Sequential Analysis on the Efficacy and Safety of Erythropoietin in Traumatic Brain Injury: A New Paradigm. *World Neurosurgery*. 2020;142:465-475.
29. Liu TS, Yin ZH, Yang ZH, Wan LN. The effects of monotherapy with erythropoietin in neonatal hypoxic-ischemic encephalopathy on neurobehavioral development: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(5):2318-2326.
30. Liu M, Wang AJ, Chen Y, et al. Efficacy and safety of erythropoietin for traumatic brain injury. *BMC neurology*. 2020;20(1):399.
31. Aher SM, Ohlsson A. Late erythropoiesis-stimulating agents to prevent red blood cell transfusion in preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2019;2:CD004868.
32. Aher SM, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2020;2:CD004865.
33. Liang L, Yu J, Xiao L, Wang G. Sustained low-dose prophylactic early erythropoietin for improvement of neurological outcomes in preterm infants: A systematic review and meta-analysis. *Journal of Affective Disorders*. 2021;282:1187-1192.
34. Locatelli F, Hannedouche T, Fishbane S, Morgan Z, Oguey D, White WB. Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta and Other Erythropoiesis-Stimulating Agents in Anemia of CKD: A Randomized Noninferiority Trial. *Clinical Journal of The American Society of Nephrology: CJASN*. 2019;14(12):1701-1710.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
darbepoetin alfa in polysorbate	ARANESP	INJECTION	SYRINGE	Y
darbepoetin alfa in polysorbate	ARANESP	INJECTION	VIAL	Y
epoetin alfa	EPOGEN	INJECTION	VIAL	N
epoetin alfa	PROCRT	INJECTION	VIAL	N
epoetin alfa-epbx	RETACRT	INJECTION	VIAL	N
methoxy peg-epoetin beta	MIRCERA	INJECTION	SYRINGE	N

Appendix 2: New Comparative Clinical Trials

A total of 339 citations were manually reviewed from the initial literature search. After further review, 338 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstracts is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Locatelli, et al. ³⁴ MC, OL, NI RCT N= 2825 Duration: ~8.5 years	1.Methoxy polyethylene glycol-beta dosed per protocol n = 1412 2. ESAs (Epoetin alfa, epoetin beta, and darbepoetin dosed per approved label) n=1413	Adult CKD patients with anemia. Anemia defined as Hb < 11 g/dL.	Composite endpoint: incidence of death, nonfatal MI, or nonfatal stroke. Prespecified NI margin of 1.2 for the HR	Incidence of death, MI or stroke 1. 45.4% (n=640) 2. 45.7% (n=644) HR 1.03 95% CI 0.93 to 1.15 P=0.004 for NI In patients with anemia of CKD, once-monthly methoxy polyethylene glycol-epoetin beta was noninferior to conventional, shorter-acting ESAs with respect to rates of major adverse cardiovascular events or all-cause mortality.	-OL, NI study is less robust than blinded superiority RCT -Funded by manufacturer of methoxy polyethylene glycol-beta
Abbreviations: CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; dL = deciliter; ESAs = erythropoiesis stimulating agents; g = grams; Hb = hemoglobin; HR = hazard ratio; MC = multi-center; MI = myocardial infarction; OL = open-label; NI = noninferiority; RCT = randomized controlled trial					

Appendix 3: Abstracts of Comparative Clinical Trials

Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta and Other Erythropoiesis-Stimulating Agents in Anemia of CKD: A Randomized Noninferiority Trial³⁴

Background and objectives: Erythropoiesis-stimulating agents correct anemia of CKD but may increase cardiovascular risk. We compared cardiovascular outcomes and all-cause mortality associated with monthly methoxy polyethylene glycol-epoetin beta with those of the shorter-acting agents epoetin alfa/beta and darbepoetin alfa in patients with anemia of CKD.

Design, setting, participants, & measurements: We conducted a multicenter, open-label, noninferiority trial in which patients were randomized to receive methoxy polyethylene glycol-epoetin beta or reference erythropoiesis-stimulating agents, stratified by maintenance or correction treatment status and C-reactive protein level. The trial had a prespecified noninferiority margin of 1.20 for the hazard ratio (HR) for the primary end point (a composite of all-cause mortality, nonfatal myocardial infarction or stroke, adjudicated by an independent blinded committee). This trial is registered with ClinicalTrials.gov, number [NCT00773513](#).

Results: In total, 2818 patients underwent randomization, received methoxy polyethylene glycol-epoetin beta or a reference agent, and were followed for a median of 3.4 years (maximum, 8.4 years). In the modified intention-to-treat analysis, a primary end point event occurred in 640 (45.4%) patients in the methoxy polyethylene glycol-epoetin beta arm, and 644 (45.7%) in the reference arm (HR 1.03; 95% confidence interval [95% CI], 0.93 to 1.15, $P=0.004$ for noninferiority). All-cause mortality was not different between treatment groups (HR 1.06; 95% CI, 0.94 to 1.19). Results in patient subgroups on dialysis or treated in the correction or maintenance settings were comparable to the primary analysis.

Conclusions: In patients with anemia of CKD, once-monthly methoxy polyethylene glycol-epoetin beta was noninferior to conventional, shorter-acting erythropoiesis-stimulating agents with respect to rates of major adverse cardiovascular events or all-cause mortality.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to July Week 5 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to August 14, 2023

1	Darbepoetin alfa/	1126
2	Epoetin Alfa/	1595
3	Epoetin alfa-epbx.mp.	6
4	Erythropoietin/ or methoxy peg-epoetin beta.mp.	16284
5	1 or 2 or 3 or 4	16529
6	limit 5 to (english language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii 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 practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	339

Erythropoiesis Stimulating Agents (ESAs)—RETIRE 12/23

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 continuation of therapy previously approved by the FFS program?	Yes: Go to #14	No: Go to #3
3. Is this an OHP covered diagnosis?	Yes: Go to #4	No: Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #12
4. Is the requested product preferred?	Yes: Go to #6	No: Go to #5

Approval Criteria		
<p>5. Will the prescriber change to a preferred product?</p> <p><u>Message:</u></p> <ul style="list-style-type: none"> 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 ^{1,2} or chemotherapy ³ ?	Yes: Go to #7	No: Go to #8
<p>7. Is Hb <10 g/dL or Hct <30% AND Transferrin saturation >20% and/or ferritin >100 ng/mL?</p>	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
<p>9. Is the Hb <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?</p>	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
<p>11. Is the Hb <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?</p>	Yes: Approve up to the length of ribavirin treatment.	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the request for: 1) an FDA approved indication AND 2) is the request for a preferred product or has the patient failed to have benefit with, or have contraindications or intolerance to the preferred products?	Yes: Go to #13	No: Pass to RPh. Deny; medical appropriateness
13. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical necessity.
14. Has the patient responded to initial therapy?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness

References:

1. 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.
2. National Clinical Guideline Centre (UK). Anemia 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.
3. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *Blood Adv*. 2019;3(8):1197-1210.
4. 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.
5. 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: 12/23 (DM); 1/19 (JP); 7/16; 5/14; 11/12; 6/12; 2/12, 9/10
Implementation: 3/19; 10/13/16; 1/1/13; 9/24/12; 5/14/12