

**Pharmacy Prior Authorization
Erythropoiesis – Stimulating Agents Clinical Guideline**

Aranesp[®] (darbepoetin alfa)
Procrit[®] (epoetin alfa)

Epogen[®] (epoetin alfa)

Authorization Guidelines:

For patients who meet all of the following:

- Does not have uncontrolled hypertension
- No known hypersensitivity to mammalian cell-derived products
- No known hypersensitivity to albumin (human)
- Diagnosis of anemia with underlying cause documented
- Other causes of anemia have been treated (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc)
- Iron Studies showing member has adequate iron stores to support erythropoiesis
 - Serum ferritin ≥ 100 ng/ml and transferrin saturation* (iron saturation) $\geq 20\%$, **or**
 - Normal serum iron, TIBC and serum ferritin, **or**
 - Reticulocyte hemoglobin content (CHR) >29 , **or**

Additional Criteria for Treatment of Anemia due to Chronic Kidney Disease (CKD):

- For initial therapy: Hemoglobin < 10 g/dL within the last 2 weeks
- For maintenance therapy: Hemoglobin < 11 g/dL within the last 2 weeks

Additional Criteria for Treatment of Anemia in Patients with HIV receiving zidovudine (Procrit and Epogen only):

- Zidovudine dose ≤ 4200 mg/week
- Endogenous erythropoietin levels ≤ 500 IU/L
- For initial therapy: Hemoglobin < 10 g/dL within the last 2 weeks
- For maintenance therapy: Hemoglobin < 11 g/dL within the last 2 weeks

Additional Criteria for Treatment of Anemia due to Cancer Chemotherapy:

- Anemia is due to the effect of concomitant myelosuppressive chemotherapy
- Diagnosis of non-myeloid malignancy (e.g., solid tumor)
- There is a minimum of two additional months of planned chemotherapy
- Provider and patient are enrolled in the ESA APPRISE REMS program
- For initial therapy: Hemoglobin < 10 g/dL within the last 2 weeks
- For maintenance therapy: Hemoglobin < 11 g/dL within the last 2 weeks

Additional Criteria for reducing transfusions in patients undergoing elective, noncardiac, nonvascular surgery (Procrit and Epogen only):

- Hemoglobin > 10 and ≤ 13 g/dL within 30 days prior to planned surgery date
- Member is at high risk for perioperative blood loss

**Pharmacy Prior Authorization
Erythropoiesis – Stimulating Agents Clinical Guideline**

Additional Criteria for off-label use[†] in Anemia associated with Myelodysplastic Syndrome (MDS) (Procrit and Epogen only):

- Recent erythropoietin level ≤ 500 IU/L
- For initial therapy: Hemoglobin < 10 g/dL within the last 2 weeks
- For maintenance therapy: Hemoglobin < 11 g/dL within the last 2 weeks

Additional Criteria for off-label use[†] in Anemia due to Peg-interferon and Ribavirin treatment for Hepatitis C (Procrit and Epogen only):

- Hemoglobin of 8.5-10 g/dL within the last 2 weeks
- Member was unresponsive to Ribavirin dosage reduction (decrease daily ribavirin dose by 200mg)

Other off-label indications:

- Requests can be reviewed on a case-by-case basis with appropriate clinical literature to support safety and efficacy[†]

[†]Off-label use included based on peer-reviewed clinical studies

Non-Coverage: ESA's are not currently recommended for treatment of anemia due to blood loss, folate, B-12 or iron deficiency, hemolysis, AML, CML or erythroid cancers, thalassemia, Castleman's disease, aplastic anemia, sickle cell disease, Gaucher's disease, or other conditions that are not supported by peer-reviewed medical literature.

Initial Approval:

- CKD on dialysis: 4 months to allow time for enrollment with Medicare Part B for dialysis coverage
- Perioperative: up to 21 days of therapy per surgery
- PEG/RBV for Hepatitis C: 8 weeks
- All other indications: 3 months

Renewals:

- 3 months
- Documentation Required:
 - Follow up iron studies showing member has adequate iron to support erythropoiesis
 - Hb < 11 g/dL within the last 2 weeks
 - For hepatitis C: treatment with PEG/RBV should be discontinued if Hb is < 8.5 g/dL
 - ESAs for Dialysis patients – Medicare Part B: Epoetin and Aranesp are covered under the Medicare Part B benefit for the treatment of anemia associated with ESRD for all patients who are receiving dialysis. Refer orders to the Dialysis Center.

Additional Information:

WARNING: ESAs increase the risk of death, myocardial infraction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. ***See full prescribing information for complete boxed warning.***

Pharmacy Prior Authorization Erythropoiesis – Stimulating Agents Clinical Guideline

2010 FDA Safety Announcement – ESA use in Cancer: The FDA is requiring all drugs called Erythropoiesis-Stimulating Agents (ESAs) to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs. FDA required Amgen, the manufacturer of these products, to develop a risk management program because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.

As part of the REMS, a *Medication Guide* explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs. In addition to the Medication Guide, Amgen was required to develop the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program for healthcare professionals who prescribe ESAs to patients with cancer.

Under the ESA APPRISE Oncology program, Amgen will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer. Amgen is also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program.

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers
- Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense ESAs to patients with cancer
- Use the lowest dose to avoid RBC transfusions
- Use ESAs only for anemia from myelosuppressive chemotherapy
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure
- Discontinue following the completion of a chemotherapy course.

Perioperative:

- Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended

Evaluating Iron stores:

Aetna Clinical Policy Bulletin: Erythropoiesis Stimulating Agents:
http://www.aetna.com/cpb/medical/data/100_199/0195.html

Pharmacy Prior Authorization Erythropoiesis – Stimulating Agents Clinical Guideline

Prior to initiation of therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. According to the literature, transferrin saturation should be at least 20% and ferritin at least 100 ng/ml. In addition, since ferritin is an acute phase reactant, it may be falsely elevated (to the normal range) in iron deficient **dialysis** patients. Therefore, the best guide for iron supplementation in this group of patients is iron saturation greater than 20%.

Normal Reference Range of Serum Iron and Serum Ferritin:

- **Serum Iron:**
 - Children: 50 to 120 µg/dL
 - Men: 65 to 176 µg/dL
 - Newborns: 100 to 250 µg/dL
 - Women: 50 to 170 µg/dL

- **Serum Ferritin:**
 - Female: 12 to 150 ng/mL
 - Male: 12 to 300 ng/mL

References:

1. Epogen, Procrit. In: Clinical Pharmacology Online. Tampa, FL: Gold Standard Inc. [Updated February 26,2015; Accessed August 23,2015]. <http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=227&n=Epogen&t=0>.
2. Aranesp. In: Clinical Pharmacology Online. Tampa, FL: Gold Standard Inc. [Updated July 27,2015; Accessed August 23,2015]. <http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=2571&n=Aranesp&t=0>.
3. KDIGO Clinical Practice Guideline for anemia in Chronic Kidney Disease. <http://www.guideline.gov/content.aspx?id=38245&search=anemia+due+to+chronic+kidney+disease#Section420>. Accessed August 23,2015.
4. U.S. Department of Veterans Affairs. Interferon and Ribavirin Treatment Side effects. <http://www.hepatitis.va.gov/provider/reviews/treatment-side-effects.asp#S2X>. Accessed August 23,2015.
5. Epogen (erythropoietin) [package insert]. Thousand Oaks, CA: Amgen Inc.; Revised June 2014.
6. Procrit (erythropoietin) [package insert]. Thousand Oaks, CA: Amgen Inc.; Revised December 2013.
7. Aranesp (darbepoetin alpha) [package insert]. Thousand Oaks, CA: Amgen Inc.; Revised July 2015.
8. NCCN: National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology: Myelodysplastic Syndromes. http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf. Version 2.2015. Accessed August 28, 2015.
9. Clinical Policy Bulletin. Erythropoiesis Stimulating Agent. <https://www.aetna.com/health-care-professionals/clinical-policy-bulletins/pharmacy-clinical-policy-bulletins/pharmacy-clinical-policy-bulletins-search-results.html?YearSelect=2015&query=epogen&cfg=wwwcpcpbext&years=2015>. Accessed August 23,2015.
10. US Food and Drug Administration. 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 August 27,2015.
11. Friel TJ, Scadden DT. Hematologic manifestations of HIV infection: Anemia. Waltham, MA: UptoDate; Last modified June 25, 2015. http://www.uptodate.com/contents/hematologic-manifestations-of-hiv-infection-anemia?source=search_result&search=hiv+anemia&selectedTitle=1%7E150#H30. Accessed September 15, 2015.