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Medication Policy Manual

Policy No: dru012

Topic: Epogen[®], Procrit[®], epoetin alfa

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Epoetin alfa (erythropoietin) is a man-made protein that stimulates the production of red blood cells to treat anemia.

Policy/Criteria

I. Most contracts require prior authorization approval of erythropoietin therapy prior to coverage. Erythropoietin therapy may be considered medically necessary in patients with:

A. Anemia (hemoglobin less than 12 g/dL) associated with chronic kidney disease (CKD) when:

1. Erythropoietin is prescribed by a nephrologist.

OR

2. There is a diagnosis of Stage 3, 4 or 5 CKD as defined by the National Kidney Foundation.

OR

B. Anemia (hematocrit less than 30%) in AZT-treated HIV-infected patients when the dose of AZT is equal to or less than 4,200 mg per week.

OR

C. Limited acute severe anemia conditions (hematocrit equal to or less than 24%) when a blood transfusion would otherwise be needed, such as with blood loss after trauma.

OR

D. A high risk for perioperative transfusions with significant anticipated blood loss. Preoperative use is limited to individuals who meet all of the following:

1. Patient is undergoing pre-planned, noncardiac, nonvascular surgery such as major orthopedic hip or knee surgery.

AND

2. Hemoglobin is equal to or less than 13 g/dL.

AND

3. Patient is not a candidate for autologous blood transfusion. (Erythropoietin is not covered when used in conjunction with, prior to, or following phlebotomy for autologous blood transfusion, except in unusual circumstances where it is medically unsafe to delay surgery and significant autologous blood stores are necessary.)

AND

4. Patient is considered to be at high risk for perioperative transfusions with significant anticipated blood loss. For example, the patient is expected to lose more than 2 units of blood.

OR

- E. Anemia of chronic disease (characterized by hemoglobin less than 10 g/dL or hematocrit equal to or less than 30%) if:

1. The patient's own erythropoietin levels are 500 mU/mL or less;

AND

2. Patient's transferrin saturation is at least 20% and ferritin is at least 100 ng/mL.

OR

- F. Anemia (hemoglobin less than 10 g/dL or hematocrit less than 30%) when prescribed by an oncologist or hematologist for members currently receiving chemotherapy (current chemotherapy is defined as chemotherapy administration within 8 weeks).

OR

- G. Anemia (hemoglobin less than 12 g/dL) in patients infected with hepatitis C virus (HCV) receiving combination therapy with interferon alfa (INF- α) and ribavirin (RBV).

OR

- H. Anemia (hematocrit less than 32%) in low birth weight infants.

OR

- I.** Anemia (characterized by hemoglobin less than 10 g/dL or hematocrit equal to or less than 30%) associated with myelodysplastic syndrome (MDS).

II. Administration, Quantity Limitations, and Authorization Period

- A.** Regence considers epoetin alfa to be a self-administered medication or a medication that is administered in the provider office or hospital settings.
- B.** When prior authorization is approved, epoetin alfa may be authorized in doses of up to 20,000 units per day or up to 60,000 units per week for all indications other than anemia in HCV-infected patients receiving INF- α and RBV or anemia in low birth weight infants. When prior authorization is approved, epoetin alfa may be authorized in doses up to 40,000 units per week for HCV-infected patients or up to 1,000 units per week for low birth-weight infants.
- C.** Authorization may be reviewed at least once per treatment period or every six months, whichever is less, to confirm that the patient's recent (within the last 60 days) hemoglobin is less than 12 g/dL.

III. Erythropoietin is considered not medically necessary when used in all other conditions, including, but not limited to:

- A.** Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.
- B.** Anemia associated with the treatment of acute and chronic myelogenous leukemias (AML, CML) or erythroid cancers.
- C.** Anemia of cancer not related to cancer treatment.
- D.** Any anemia associated only with radiotherapy.
- E.** Prophylactic use to prevent chemotherapy-induced anemia.
- F.** Prophylactic use to reduce tumor hypoxia.
- G.** Patients with erythropoietin-type resistance due to neutralizing antibodies.

Position Summary

- Erythropoiesis-stimulating agents (ESAs) increase the risk of serious cardiovascular events and death when administered to target a hemoglobin of greater than 12 g/dL. ^[1, 75]
- A higher incidence of deep venous thrombosis was documented in patients receiving epoetin alfa who were not receiving prophylactic anticoagulation. ^[1, 75]
- These products have not been shown to improve or relieve the symptoms of anemia nor to improve quality of life in patients with cancer.
- The key safety issues that led to the new black box warnings of 2007 on ESA products were:
 - * Increased risk of thromboembolic events (MI, stroke, DVT, etc.)
 - * Increased risk of death
 - * Tumor progression
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of less than 12 g/dL. ^[1, 75]
- Anemia of myelodysplastic syndrome (MDS) is an FDA off-label use. It is listed in national compendia as an “accepted not established” indication. It is not included in the July 2007 CMS Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions. In the final rule CMS declared that MDS is not a neoplastic condition, and therefore exempt from the ruling.
- Prior to initiation of therapy and during therapy, the patient’s iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. ^[1, 75]
- Blood pressure should be adequately controlled prior to initiation of epoetin alfa therapy, and must be closely monitored and controlled during therapy. ^[1, 75]
- Erythropoietin is more effective, and therefore less expensive, if given subcutaneously (SC) instead of intravenously (IV). If given SC, dosing can be 2-3 times a week and occasionally once a week or every other week in the stable patient with chronic renal failure. However, if given IV, the pharmacokinetics indicate that there is no advantage in giving doses daily, and that 3 doses/week is appropriate.

- Erythropoietin is approved for the treatment of anemia of in: chronic renal failure, zidovudine-treated HIV-infected patients, cancer patients on chemotherapy, and reduction of allogenic blood transfusion in surgery patients.
- Off-label uses include: ACD, low birthweight infants, hepatitis C on ribavirin and interferon alfa.

Dialysis and End Stage Renal Disease

- Erythropoietin is FDA approved for the treatment of anemia. ^[1]
- The benefits of increasing hematocrit values from below 30 percent to 30 to 38 percent in patients undergoing dialysis with erythropoietin include a decrease in the need for transfusion and an improvement in the quality of life, cognitive function, cardiac function, exercise capacity, and immune function. ^[2-16]
- In retrospective studies, the mortality rate among patients with hematocrit below 30 percent was higher than that among patients with hematocrit of 30 to 35 percent. Hematocrit in excess of 35 to 42 percent was not associated with greater improvements. ^[17-19]
- Retrospective analysis has demonstrated that erythropoietin is associated with a decrease in morbidity and mortality in patients with end-stage renal disease. ^[20]
- Practice guidelines by the National Kidney Foundation for treatment of anemia associated with chronic kidney disease for recommends maintaining the hematocrit between 33 and 36 percent. ^[21]
- Recommended epoetin alfa dosing in anemia associated with chronic renal failure is 12.5-525 units/kg given three times weekly. ^[1]
- While uncontrolled observational studies suggest that improving hemoglobin levels in patients with ESRD with erythropoietins might improve cardiac function, double-blind, randomized controlled trials have not found a causal relationship. ^[52-55]
- Extended dosing schedules (up to every 4 weeks) of epoetin appear to be safe and effective for maintaining hemoglobin in patients with chronic kidney disease. ^[56]
- Erythropoietin is FDA approved for the treatment of anemia. ^[1]

Cancer

- Erythropoietin stimulates production of red blood cells. Erythropoiesis stimulating proteins increases hemoglobin levels and reduce the numbers of transfusions in patients with non-myeloid malignancies who receive concomitant chemotherapy. ^[22-36]
- In several studies, approximately 50% of anemic patients receiving chemotherapy alone required transfusions as compared to approximately 20-25% of patients who received ESAs concurrently with chemotherapy. NNT = 4.9 (95% CI 4.1, 6.1) ^[77]
- The recommended subcutaneous epoetin alfa dosing in anemia due to chemotherapy is 300 units/kg three times weekly or 40,000 – 60,000 units every week. ^[1]
- Administration of erythropoietins in larger doses less frequently generally results in similar clinical responses. ^[46,57-58]
- Doses of erythropoietins larger than recommended in the approved product labeling have been studied, but this is no direct useful evidence that these doses improve patient outcomes. ^[46,59]
- Head-to-head trials between epoetin and darbepoetin generally find little, if any, difference in clinical responses between the two agents. ^[46,60-62]

Human Immunodeficiency Virus (HIV) Infection

- HIV disease and its treatment, particularly with zidovudine, can cause anemia. Erythropoietin use in this patient population has been shown to increase hematocrit, decrease transfusions and increase energy. ^[37] Erythropoietin administration was associated with a decreased risk of dying among these patients with anemia. ^[38] Erythropoietin generally has not raised hemoglobin concentrations or decreased transfusion requirements in patients with erythropoietin concentrations higher than 500 mU/mL.
- The recommended epoetin alfa dosing in HIV-associated anemia is 100-300 units/kg administered subcutaneously three times weekly. ^[1]
- Administration of epoetin 40,000IU to 60,000IU every week to patients co-infected with HIV and HCV (concurrently receiving peg-interferon/ribavirin) improved mean hemoglobin levels at 16 weeks with and without concurrent AZT administration (p=0.001 and p<0.001 respectively). ^[63]

Chronic Hepatitis C Virus (HCV) Infection

- HCV-infected patients receiving combination therapy with interferon alfa (INF- α) and ribavirin (RBV) or pegylated INF- α /RBV experience anemia that prompts dose reduction leading to poor clinical response.
- Weekly doses of epoetin alfa 40,000 IU administered subcutaneously for 8 weeks in HCV-infected patients with hemoglobin less than 12 mg/dL improves clinical outcomes and does not necessitate dose reductions of INF- α /RBV. ^[39-41]

Surgery and Autologous Blood Donations

- Supplemental iron is important for optimal benefit, and providers are cautioned that some studies have shown a higher than normal incidence of pulmonary emboli.
- An erythropoietin dose of 600 IU/kg SC once per week for 3 weeks prior to surgery and on the day of surgery has been found to be as effective as 300IU/kg SC for 10 days prior to surgery, on the day of surgery, and 4 days postoperatively.
- Patients with a baseline hematocrit of less than or equal to 39 percent receiving erythropoietin before surgery were able to increase the number of units of blood they were able to pre-deposit, thereby decreasing the need for transfusions after surgery. ^[42]
- A placebo-controlled trial before major orthopedic surgery found that patients with a baseline hemoglobin of 10 to 13 gm/dL who were treated with erythropoietin required fewer transfusions. ^[43]
- Use of perioperative epoetin 300 IU/kg in cancer patients undergoing colorectal surgery significantly improved hemoglobin levels and hematocrit (p<0.02 and 0.05 respectively) and decreased the need for perioperative and postoperative transfusions. ^[64]
- Recommended epoetin alfa dosing to reduce the need for transfusion during or after surgery is 300 IU/kg per day or 600 units/kg per week administered subcutaneously. ^[1]

Anemia in Low Birth Weight Infants

- Epoetin alfa in low-birth weight infants less than 1,500 g was shown to increase hematocrit levels and reduce the need for transfusions compared to placebo. ^[49-50,65]

- Epoetin alfa doses in these trials used 200 IU/kg twice weekly, 400 IU/kg three times weekly, or 750 IU/kg once weekly administered subcutaneously. ^[49-50,65]
- A high-dose (5,000 IU/kg/week) regimen of epoetin beta was compared to standard dosing (1,250 IU/kg/week) in low birth-weight infants (<1,500 g). Hemoglobin levels and transfusion rates were similar between the two groups, but the high-dose group had significantly more intracranial hemorrhage (p<0.02). ^[66]

Safety

- ESAs increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population. ^[1]
- Uncontrolled hypertension is a contraindicated use in both the Epogen (epoetin) and Aranesp (darbepoetin alfa). ^[1]

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| Aranesp, darbepoetin dru076 |

| Codes | Number | Description |
|-------|--------|--|
| HCPCS | J0885 | Injection, epoetin alpha (for non-ESRD use), per 1,000 units |
| HCPCS | J0886 | Injection, epoetin alpha (for ESRD use), per 1,000 units (renal dialysis facilities and hospitals must use code Q4081 effective 1/1/07). |
| HCPCS | Q4081 | Injection, epoetin alpha (for ESRD use), per 100 units (renal dialysis facilities and hospitals must use code Q4081 effective 1/1/07). |

Appendix A: Stages of Chronic Kidney Disease ^[48]

| Stage | Description | GFR mL/min/1.73 m ² | Action* |
|-------|------------------------------------|-----------------------------------|---|
| 1 | Kidney damage with normal or ↑ GFR | ≥ 90 | Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction |
| 2 | Kidney damage with mild ↓ GFR | 60-89 | Estimating progression |
| 3 | Moderate ↓ GFR | 30-59 | Evaluating and treating complications |
| 4 | Severe ↓ GFR | 15-29 | Preparation for kidney transplant therapy |
| 5 | Kidney failure | < 15 (or dialysis) | Replacement (if uremia present) |

Chronic kidney disease is defined as either kidney damage OR GFR less than 60mL/min/1.73 m² for more than 3months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations:

GFR: glomerular filtration rate

CVD: cardiovascular disease