



Topic: Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (Epogen®, Procrit®)
Darbepoetin alfa, (Aranesp®)

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Note: Although the services described in this position statement are not subject to routine medical necessity review, utilization may be audited.

Clinical Position Statement: Epoetin alfa (erythropoietin), Darbepoetin

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

- 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.
- There is no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy or strength, in patients receiving Erythropoiesis-Stimulating Agents (ESA)s as compared to those receiving placebo.
- Key safety issues that led to the black box warnings on ESA products include:
 - Increased risk of thromboembolic events (MI, stroke, DVT, etc.)
 - Increased risk of death
 - Tumor progression
- Even when ESAs are dosed to target a hemoglobin of less than 12 g/dL, the risks of shortened survival and tumor progression are still present. [1,75]

- Anemia of myelodysplastic syndrome (MDS) is an FDA off-label use that has limited evidence. The data does suggest that ESAs lower the number of transfusions in MDS patients, however the magnitude of benefit and exactly who will benefit is unclear. 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. [74]
- 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: anemia of chronic disease (ACD) [44, 51], low birthweight infants, [49,50,65,66] hepatitis C on ribavirin and interferon alfa [39-41].

Dialysis and End Stage Renal Disease

- Erythropoiesis-Stimulating Agents (ESA) are used to treat anemia associated with chronic renal failure, and anemia in patients with non-myeloid cancers where anemia is due to the concomitantly administered chemotherapy. [1, 75]
- 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]

Myelodysplastic Syndrome (MDS)

- The actions of darbepoetin are similar to erythropoietin. Both stimulate the production of red blood cells. It is likely that darbepoetin will work in MDS.
- Anemia of MDS is an FDA off-label use. 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.

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, 46] Administration of erythropoietin has been shown to increase hemoglobin levels and reduce the numbers of transfusions in patients with non-myeloid malignancies who receive concomitant chemotherapy. [22-28,31,34,46,89-103]
- 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]

Anemia of Chronic Disease (ACD)

- ACD is a condition of impaired iron utilization where hemoglobin is low (greater than 9 mg/dL, target 12 mg/dL) but tissue iron (such as in storage) is normal or high. ACD is seen in a wide range of chronic malignant, autoimmune (juvenile rheumatoid arthritis, rheumatic fever, etc.), leukemic, inflammatory (Crohn's disease, and ulcerative colitis, etc.), and infectious disease (chronic bacterial endocarditis, osteomyelitis, etc.) conditions. [44]
- Treatment of ACD in rheumatoid arthritis with epoetin alfa 240 IU/kg three times weekly after 6 weeks was shown to restore normal hemoglobin levels.[51]

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] Patients with uncontrolled hypertension should not be treated with ESAs; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment.
- Hypertensive encephalopathy and seizures have been observed in patients with chronic renal failure treated with ESA's.
- The FDA requires 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. It comprises of the following:

- A medication guide explaining the risks and benefits to patients
- An educational training program for healthcare professionals who prescribe or dispense ESAs to cancer patients. It is called APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program

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Cross References

Erythropoiesis – Stimulating Agents (ESAs), BlueCross BlueShield Association Medical Policy, #5.01.04, Issue 2/2008.