Drug Class Monograph

Class: Erythropoiesis-stimulating agents (ESAs)
Drugs: epoetin alfa (Procrit, Epogen), darbepoetin alfa (Aranesp), methoxypolyethylene glycol epoetin beta (Mircera)
Formulary Medication: N/A
Line of Business: Non-Medicare
Effective Date: November 16, 2016
Revision Date: November 16, 2016

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutic Subcommittee.

Policy/Criteria:

Code-1 Criteria:

1. Epogen (epoetin alfa)
   a. Restricted to use for the treatment of anemia due to: zidovudine therapy, cancer chemotherapy or chronic renal failure.

Prior Authorization Criteria:

1. Epogen (epoetin alfa)
   a. Patients undergoing elective, noncardiac, nonvascular surgery who are at high risk for perioperative blood loss, to reduce the need for allogeneic red blood cell transfusions
      • Perioperative hemoglobin level > 10 and ≤ 13 g/dL
      • Patient is unwilling to donate autologous blood preoperatively
   b. Diagnosis of anemia associated with myelodysplastic syndrome (MDS)
      • Initial authorization:
         ▪ Baseline hemoglobin level < 10 g/dL
         ▪ Baseline serum erythropoietin level ≤ 500 mUnits/mL
         ▪ Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
      • Re-authorization:
- Positive clinical response (e.g. improvement in hemoglobin level)
- If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

c. Diagnosis of anemia due to hepatitis C therapy (e.g. ribavirin and interferon-alfa)
   - Initial authorization:
     - Documented concurrent use of ribavirin and interferon alfa, or ribavirin and peginterferon alfa.
     - Baseline hemoglobin level < 10 g/dL
     - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
   - Re-authorization:
     - Positive clinical response (e.g. improvement in hemoglobin level)
     - If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

2. Procrit (epoetin alfa)
   
a. Diagnosis of anemia due to chronic kidney disease (CKD)
      - Initial authorization:
        - Baseline hemoglobin level < 10 g/dL
        - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
      - Re-authorization:
        - Positive clinical response (e.g. improvement in hemoglobin level)
        - If hemoglobin level > 11 g/dL, dosage should be reduced or interrupted

b. Diagnosis of anemia due to zidovudine in HIV-infected patients
   - Initial authorization:
     - Zidovudine administered at ≤ 4200 mg per week
     - Serum erythropoietin level ≤ 500 mUnits/mL
     - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
   - Re-authorization:
     - Positive clinical response (e.g. improvement in hemoglobin level)
     - If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

c. Diagnosis of anemia due to concomitant myelosuppressive chemotherapy in patients with non-myeloid malignancies
   - Initial authorization:
     - Baseline hemoglobin level < 10 g/dL
     - At least two additional months of planned chemotherapy
     - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
• Re-authorization:
  ▪ Positive clinical response (e.g. improvement in hemoglobin level)
  ▪ If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

d. Patients undergoing elective, noncardiac, nonvascular surgery who are at high risk for perioperative blood loss, to reduce the need for allogeneic red blood cell transfusions
  • Perioperative hemoglobin level > 10 and ≤ 13 g/dL
  • Patient is unwilling to donate autologous blood preoperatively

e. Diagnosis of anemia associated with myelodysplastic syndrome (MDS)
  • Initial authorization:
    ▪ Baseline hemoglobin level < 10 g/dL
    ▪ Baseline serum erythropoietin level ≤ 500 mUnits/mL
    ▪ Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
  • Re-authorization:
    ▪ Positive clinical response (e.g. improvement in hemoglobin level)
    ▪ If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

f. Diagnosis of anemia due to hepatitis C therapy (e.g. ribavirin and interferon-alfa)
  • Initial authorization:
    ▪ Documented concurrent use of ribavirin and interferon alfa, or ribavirin and peginterferon alfa.
    ▪ Baseline hemoglobin level < 10 g/dL
    ▪ Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
  • Re-authorization:
    ▪ Positive clinical response (e.g. improvement in hemoglobin level)
    ▪ If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

3. Aranesp (darbepoetin alfa)

a. Diagnosis of anemia due to chronic kidney disease (CKD)
  • Initial authorization:
    ▪ Baseline hemoglobin level < 10 g/dL
    ▪ Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
  • Re-authorization:
    ▪ Positive clinical response (e.g. improvement in hemoglobin level)
    ▪ If hemoglobin level > 11 g/dL, dosage should be reduced or interrupted
b. Diagnosis of anemia due to concomitant myelosuppressive chemotherapy in patients with non-myeloid malignancies
   - Initial authorization:
     - Baseline hemoglobin level < 10 g/dL
     - At least two additional months of planned chemotherapy
     - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
   - Re-authorization:
     - Positive clinical response (e.g. improvement in hemoglobin level)
     - If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

c. Diagnosis of anemia associated with myelodysplastic syndrome (MDS)
   - Initial authorization:
     - Baseline hemoglobin level < 10 g/dL
     - Baseline serum erythropoietin level ≤ 500 mUnits/mL
     - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
   - Re-authorization:
     - Positive clinical response (e.g. improvement in hemoglobin level)
     - If hemoglobin level ≥ 12 g/dL, dosage should be reduced or interrupted

4. Mircera (methoxypolyethylene glycol epoetin beta)

   a. Diagnosis of anemia due to chronic kidney disease (CKD)
      - Initial authorization:
        - Baseline hemoglobin level < 10 g/dL
        - Baseline adequate iron store should be demonstrated (i.e. serum transferrin saturation ≥ 20%, serum ferritin ≥ 100 ng/mL)
      - Re-authorization:
        - Positive clinical response (e.g. improvement in hemoglobin level)
        - If hemoglobin level > 11 g/dL, dosage should be reduced or interrupted

Clinical Justification:

U.S. Food and Drug Administration: Modified Dosing Recommendation for Erythropoiesis-Stimulating Agents (ESAs) (June 2011)

- FDA recommended more conservative dosing guideline for ESAs when used to treat anemia in patients with chronic kidney disease (CKD) because of the increased risks of cardiovascular events such as stroke, thrombosis and death.
- For patients with the anemia of CKD not on dialysis:
Consider starting ESA treatment only when the hemoglobin level is less than 10 g/dL and when certain other considerations apply
- If the hemoglobin level exceeds 10g/dL, reduce or interrupt the dose of ESA.

- For patients with the anemia of CKD on dialysis:
  - Initiate ESA treatment when the hemoglobin levels is less than 10g/dL
  - If the hemoglobin level approaches or exceeds 11g/dL, reduce or interrupt the dose of ESA

2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease

- For adult CKD nondialysis patients with Hb ≥ 10g/dL, it is recommended that ESA therapy not be initiated. (2D)
- For adult CKD nondialysis patients with Hb <10g/dL, treatment decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia (2C)
- For adult CKD 5D (dialysis-dependent) patients, it is recommended that ESA therapy be used to avoid having the Hb fall below 9.0 g/dL by starting ESA therapy when the Hb is between 9.0-10.0 g/dL.
- In general, it is recommended that ESAs not be used to maintain Hb >11.5 g/dL in adult patients with CKD.

U.S. Food and Drug Administration: Risk Evaluation and Mitigation Strategy (REMS) for Erythropoiesis-Stimulating Agents (ESAs)

- In April 2008, FDA requires that ESAs be prescribed and used under a risk management program to ensure that patients have been counseled on the risks and benefits of therapy
- As part of REMS for ESAs, prescribers are required to enroll in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program
- This is based on studies that found that ESAs caused tumors to grow faster and resulted in earlier deaths in some cancer patients

2010 American Society of Hematology/American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer

- It is recommended that ESAs not be used in treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy.
- The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and an Hb concentration that has decreased to less than 10 g/dL to decrease transfusions.
- An optimal level at which to initiate ESA therapy in patients with anemia and Hb between 10 and 12 g/dL cannot be definitively determined from available evidence.
- An optimal target Hb concentration cannot be definitively determined from the available literature. Modification to reduce the ESA dose is appropriate when Hb reaches a level sufficient to avoid transfusion or the increase exceeds 1g/dL in any 2-week period to avoid excessive ESA exposure.
- Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed.

**2015 National Comprehensive Cancer Network (NCCN) Guidelines: Cancer and Chemotherapy-Induced Anemia**

- For patients with cancer, the black box warning on the revised FDA label states that ESAs should only be used to treat CIA and should be discontinued once the chemotherapy course is complete.
- Randomized trial data suggest that ESAs may promote tumor growth in an off-target manner. For this reason, the FDA states that these agents should not be used when the anticipated outcome is cure.
- Epoetin alfa and darbepoetin alfa are considered equivalent by the NCCN Panel.
- Response to ESA therapy is assessed to determine whether the initial dose should be reduced, escalated or withheld. Decisions related to ESA dose adjustment are based on the goal of a gradual increase in Hb level that remains sufficient to avoid transfusion.
- ESA therapy should be discontinued in patients showing no response despite iron supplementation after 8 or 9 weeks of therapy, and PRBC transfusion should be considered.
- ESAs should be discontinued when chemotherapy is complete and anemia has resolved, usually within 6 weeks.


- An alternative option to lenalidomide for myelodysplastic syndrome associated symptomatic anemia is ESAs in patients with sEpo levels of 500 mU/mL or less. Patients with normal cytogenetics, less than 15% ring sideroblasts, and sEpo levels of 500 mU/mL or less may respond to relative high doses of ESA therapy, including epoetin doses at 40,000-60,000 units one to three times a week subcutaneously or darbepoetin doses at 150-300 mcg/kg/week subcutaneously.
- Clinical trial results in patients with MDS have suggested that the overall response rates to darbepoetin are similar or possibly higher than epoetin.
**2011 American Association for the Study of Liver Diseases: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection**

- Dose reduction of antiviral medications should be considered as the initial response to manage anemia.
- Potential risks for anemia is likely to be greater with longer duration of antiviral therapy.
- Potential benefit should be weigh against the potential risks when considering the use of ESAs

**References:**


