

Medical Affairs Policy & Procedure

Title/Service: Erythropoietin (Aranesp, Darbepoetin Alfa, EPO, Epoetin Alfa, Epogen, Procrit)

Revised	09/16/2011
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Description:

Erythropoietin is a hormone that stimulates the bone marrow to produce red blood cells. Some individuals may be unable to produce sufficient erythropoietin internally to increase red blood cell counts and administration of a biologically engineered erythropoietin is given to treat the low blood counts.

Indications of Coverage:

Administration of erythropoietin is considered medically necessary for any of the following conditions:

Note: Anemia is defined as a hematocrit less than 30% or hemoglobin less than 10 g/dL.

- A. Anemia related to therapy with Zidovudine (AZT) in acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC).
- B. Anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors (except for head and neck and breast cancers), multiple myeloma, and lymphocytic leukemia when **all** of the following conditions are met:
 - 1) The pretreatment erythropoietin level is 100 MU/ml or less
 - 2) The starting dose for erythropoietin treatment is (as recommended on the FDA-approved label) no more than 150 U/kg/3 times weekly for Epoetin (EPO, Epoetin Alfa, Epogen, Procrit) and 2.25 mcg/kg/1 time weekly for Darbepoetin Alfa (Aranesp). Equivalent doses may be given over other approved time periods.
 - 3) Treatment duration for each course of chemotherapy includes the first eight weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

- C. Anemia secondary to End Stage Renal Disease (ESRD) for individuals undergoing dialysis.
- D. Anemia of chronic kidney disease for individuals who are not on dialysis when one of the following conditions is met:
- 1) Serum creatinine is equal to or greater than 3
 - 2) Creatinine clearance less than 60 ml/min
 - 3) Glomerular filtration rate (GFR) less than 60 mL/min/1.73 m²
- E. Anemia secondary to chemotherapeutic medications which are medically necessary for a non-cancer diagnosis or following stem cell transplantation and associated immunosuppression.
- F. Anemia secondary to Myelodysplastic Syndrome (MDS) when all of the following criteria are met:
- 1) Bone marrow blast count of less than 10% blasts
 - 2) The individual's anemia is symptomatic
- G. Anemia secondary to chronic disease (anemia of inflammatory disease) when other causes of anemia have been ruled out and all of the following criteria are met:
- 1) The individual has been diagnosed with one of the following conditions:
 - a) Rheumatoid arthritis
 - b) Systemic lupus erythematosus
 - c) Chronic hepatitis C
 - d) Crohn's disease (regional enteritis)
 - e) Ulcerative Colitis
 - 2) The pretreatment erythropoietin level is 100 MU/ml or less
 - 3) One of the following is documented:
 - a) Low or normal serum iron
 - b) Low or normal iron binding capacity
 - c) Normal or elevated serum ferritin

d) Adequate iron stores in bone marrow.

H. Prophylactic pre-operative use for reduction of allogenic blood transfusions prior to elective hip and knee replacement surgery when **all** of the following are documented:

- 1) Documentation of a hematocrit level of 30 – 39% (hemoglobin of 10 - 13g/dL)
- 2) Treatment is started a minimum of three weeks (twenty one days) prior to surgery
- 3) The individual is not a candidate for autologous blood transfusion
- 4) Blood loss of more than two units of blood is expected
- 5) Other causes of anemia have been ruled out

I. Anemic individuals (hematocrit level of 30 – 39% or hemoglobin of 10 - 13 g/dL) scheduled to undergo elective, non-cardiac, nonvascular surgery or individuals at high risk for perioperative transfusions with significant, anticipated blood loss when the individual is not a candidate for an autologous blood transfusion.

J. Individuals with a special circumstance who will not (due to strongly held beliefs) or cannot receive whole blood or components as replacement for traumatic or surgical loss.

K. For all indications:

- 1) Subcutaneous erythropoietin injections should be self-administered unless contraindicated (for example, the individual is unable to inject themselves due to a functional limitation). One injection in the clinic for teaching is allowed for individuals who have not previously received instruction in self-administered injections. For individuals with functional limitations, home health assistance may be considered.
- 2) Treatment may be allowed when the disease-specific conditions above are met and the individual's hemoglobin is below 10 g/dL (or hematocrit of 30%) unless it is being used for the elective hip, knee, non-cardiac, non-vascular, or high risk for perioperative transfusion indication. Continuing treatment may be allowed to maintain the hemoglobin level between 10 and 11 g/dL (hematocrit between 30 and 33%); however, in all cases, the maintenance goal is to limit symptomatic anemia requiring a blood transfusion, not a specific hemoglobin level.

Limitations of Coverage:

- A. Review contract and endorsements for exclusions and prior authorization or benefit requirements.
- B. If used for a condition/diagnosis other than is listed in the Indications of Coverage, deny as experimental or investigative.
- C. If used for a condition/diagnosis that is listed in the Indications of Coverage, but the criteria are not met, deny as not medically necessary.
- D. The use of erythropoietin is considered not medically necessary for the treatment of any of the following conditions:
 - 1) Breast cancer, lymphoma, testicular cancer
 - 2) Head and neck cancers
 - 3) Severe anemia or as a substitute for an emergency blood transfusion
 - 4) Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
 - 5) Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid (red blood cell) cancers
 - 6) Anemia of cancer not related to cancer treatment
 - 7) Anemia associated only with radiotherapy
 - 8) Prophylactic use to prevent chemotherapy-induced anemia
 - 9) Prophylactic use to reduce tumor hypoxia (where oxygen supply to tumor cells is decreased) in an effort to increase the effectiveness of the chemotherapy
 - 10) Individuals with erythropoietin-type resistance due to neutralizing antibodies
 - 11) Anemia due to cancer treatment in individuals with uncontrolled hypertension
 - 12) Anemia due to cancer treatment in patients being treated for the cancer when the anticipated outcome is cure
- E. The use of erythropoietin for the maintenance of an average hematocrit greater than 33% (hemoglobin greater than 11 g/dL) is considered investigational.

Documentation Required:

- Office notes
- Lab reports

Rationale:

Erythropoietin is approved for limiting the need for blood transfusions in individuals with specific conditions. The US Food and Drug Administration (FDA) issued “black box” warnings regarding the use of erythropoietin in conjunction with certain conditions, including cancer. Studies have shown a decrease in overall survival and a decrease in the length of time for progression of some types of cancer in individuals being given erythropoietin. Erythropoietin has also been shown to decrease the survival rate in individuals with active malignant cancers, even when chemotherapy is not being administered. Studies have shown that a similar cancer will progress more rapidly in an individual using erythropoietin when compared to an individual who is not using erythropoietin. Recent studies have also documented an increased rate of cardiovascular complications as a result of using erythropoietin. Additional warnings regarding the use of erythropoietin in individuals with hemoglobin levels above ≥ 10 g/dL were also distributed. Current recommendations include prescribing the lowest dose possible to avoid blood transfusions and ending the use of erythropoietin when chemotherapy has been completed.

References:

1. American Society of Hematology. Practice Update: ODAC Recommends ESAs Continue to be Indicated for Treatment of Chemotherapy-Induced Anemia But with New Restrictions. Mar 14, 2008. Available at: www.hematology.org/Practice/Practice-Updates/2979.aspx. Accessed: 5 Jan 11.
2. Aranesp (darbepoetin alfa) For Injection. Thousand Oaks, CA.: Amgen, Inc. Available at: pi.amgen.com/united_states/aranesp/ckd/aranesp_pi_hcp_english.pdf. Revised: 06/2011. Accessed: 31 Aug 11.
3. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD): Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions. NCD 110.21. Baltimore, MD. Effective date: 07/30/07. Available at: www.cms.hhs.gov/mcd/index_list.asp?list_type=ncd. Accessed: 31 Aug 11.
4. Food and Drug Administration. Oncologic drugs advisory committee. FDA briefing document. Mar 13, 2008. Available at: www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4345b2-01-FDA.pdf. Accessed: 31 Aug 11.

5. Janecka IP. Erythropoietin to treat anaemia in patients with head and neck cancer. *Lancet*. 2004 Mar 20;363(9413):993-4.
6. Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. *N Engl J Med*. 2007 Jun 14;356(24):2445-8.
7. Leyland-Jones B; BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol*. 2003 Aug;4(8):459-60.
8. Mohyeldin A, Lu H, Dalgard C, Lai SY, Cohen N, Acs G, Verma A. Erythropoietin signaling promotes invasiveness of human head and neck squamous cell carcinoma. *Neoplasia*. 2005 May;7(5):537-43.
9. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Cancer and chemotherapy induced anemia. Version 2.2012. Available at: www.nccn.org. Accessed: 31 Aug 11.
10. Procrit (Epoetin alfa) for injection. Raritan, NJ: Centocor Ortho Biotech Products. Revised: 06/2011. Available at: www.procrit.com/sites/default/files/shared/OBI/PI/ProcritBooklet.pdf#page=1. Accessed: 31 Aug 11.
11. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE; American Society of Clinical Oncology; American Society of Hematology. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol*. 2008 Jan 1;26(1):132-49.
12. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, Bohlius J, Evanchuk D, Goode MJ, Jakubowski AA, Regan DH, Somerfield MR; American Society of Hematology and the American Society of Clinical Oncology. Practice Guideline Update Committee. 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. *Blood*. 2010 Nov 18;116(20):4045-59. Available at: bloodjournal.hematologylibrary.org/content/116/20/4045.long. Accessed: 31 Aug 11.
13. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006 Nov 16;355(20):2085-98.
14. Tefferi, A. Editorial. Pharmaceutical Erythropoietin Use in Patients With Cancer: Is It Time to Abandon Ship or Just Drop Anchor? *Mayo Clin Proc*, November 2007; 82(11): 1316-1318. Available at: www.mayoclinicproceedings.com/content/82/11/1316.full.pdf. Accessed: 31 Aug 11.



15. Wisconsin Physicians Service Medicare Local Coverage Determination (LCD).
Erythropoiesis Stimulating Agents Epoetin alfa (EPO), Darbepoetin alfa (DPA) (INJ-023). Effective date: 12/15/10. Available at:
www.wpsmedicare.com/part_b/policy/active/local/index.shtml. Accessed: 31 Aug 11.

Approved by the Medical Director