

Evidence Based Guideline

Erythropoiesis-Stimulating Agents (ESAs)

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Description of Procedure or Service

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor synthesized at the cellular level by cells near the renal tubules in response to changes in the blood oxygen concentration. When a patient is anemic, the ability of the blood to carry oxygen is decreased. An oxygen-sensing protein in the kidney detects the decrease in blood oxygen concentration and induces the production of EPO, which then acts upon the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood hemoglobin (Hb) concentrations. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin results in anemia in several disease processes, including chronic kidney disease (CKD), many types of cancer treatment, other chronic diseases and use of certain drugs. The severity of anemia is defined by blood Hb concentration. Normal ranges are 12–16 g/dL in women and 14–18 g/dL in men. Mild anemia is defined as Hb from 10 g/dL to the lower limit of normal ranges, while moderate anemia is 8-10 g/dL. Severe anemia is defined as Hb 8 g/dL or below.

Erythropoiesis-stimulating agents (ESAs) are produced using recombinant DNA technologies. They were initially developed as replacement therapy to treat anemia due to endogenous erythropoietin deficiency that commonly occurs in individuals with chronic renal failure (CRF) secondary to CKD. Patients with CRF will become severely anemic, experience severe fatigue, and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia with ESA treatment results in reduced need for red blood cell transfusions and enhanced physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, and vitamin B-12) essential for the red cell production. Antibodies in certain tumor types may cause increased erythrocyte destruction through hemolysis. Tumors may cause blood loss via tissue invasion, for example gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. Marrow dysfunction can occur, however, even in the absence of frank invasion. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization as well as a direct suppression of red cell production. The treatment of cancer may also cause anemia. Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

Red blood cell (RBC) transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, it is not risk free, with several potential associated adverse events. The highest

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adverse event risk (1 per 432 whole blood units) is that for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (for example, type mismatch) are estimated to occur at a rate of 1 per 5,000–10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), human immunodeficiency virus (HIV) (<1 in 1,000,000), and bacterial contaminants (1 per 10,000–100,000) have fallen dramatically since the early 1990s. Therefore, while the initial impetus for commercialization of erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those. Nonetheless, blood shortages, transfusion errors, and the risk for alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Two ESA products have been licensed in the U.S. Epoetin alfa is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name, Epogen. The same epoetin alfa product manufactured by Amgen, Inc. is also marketed and distributed by Ortho Biotech, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit. Under a contractual agreement with Amgen, Ortho Biotech LP has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all U.S. Food and Drug Administration (FDA) -approved indications. The other ESA, darbepoetin alfa, is marketed by Amgen solely under the proprietary name, Aranesp.

The epoetins have the same amino acid sequence as endogenous erythropoietin, while darbepoetin alfa has two additional oligosaccharide chains; however, the epoetins and darbepoetin all have pharmacologic actions identical to those of the endogenous hormone. They increase the number of red blood cells, and thus the blood concentration of hemoglobin, when given to individuals with functioning erythropoiesis. Both currently marketed ESAs have been approved for use in the treatment of anemia associated with CRF, as well as other indications.

The major regulatory time line for approval actions pertaining to new indications is summarized below:

Epoetin alfa (Epogen/Procrit):

- 1989: approved for use among anemic CRF patients
- 1991: approved for use among zidovudine-treated HIV-infected patients
- 1993: approved for use among chemotherapy-induced anemia in patients with non-myeloid malignancies
- 1996: approved for presurgical use among certain patients undergoing surgery

Darbepoetin alfa (Aranesp):

- 2001: approved for use among anemic CRF patients
- 2002: approved for use among chemotherapy-induced anemia in patients with non-myeloid malignancies

Throughout this Guideline, unless otherwise stated, the term “ESA” refers to epoetin alfa (Epogen®, Procrit®) and to darbepoetin alfa (Aranesp®).

******Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Evidence Based Guideline for Erythropoiesis-Stimulating Agents (ESAs)

The use of an ESA may be appropriate for:

- treatment of anemia associated with chronic kidney disease ^{1,2};

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- treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy ^{1,2};
- treatment of anemia related to therapy with AZT (zidovudine) in HIV-infected patients ¹;
- reduction of allogeneic blood transfusion in surgery patients ¹;
- treatment of patients following allogeneic bone marrow transplantation; and
- treatment of patients with myelodysplastic syndromes to reduce transfusion dependency.

In the conditions noted above, the following criteria should be considered:

- The lowest dose of ESAs should be used in order to avoid red blood cell transfusions;
- ESAs should not be used to raise the Hb level above 12 g/dL; and
- ESA therapy should not be administered without adequate iron stores.

For the use in cancer patients, these additional FDA criteria should be considered:

- ESA therapy should not be initiated at Hb levels ≥ 10 g/dL and
- ESA treatment should be discontinued following the completion of a myelosuppressive chemotherapy course.

ESA treatment is to be administered according to current FDA-approved labeling for each product, using recommended starting, stopping, and dose adjustment points. This includes decreasing the dose of ESA as the Hb approaches the target level.

Prior to commencing ESA therapy, the patient's iron stores, blood ferritin, and transferrin saturation should be evaluated, adjusted, and maintained within normal physiological limits. ESA therapy should not be administered without adequate iron stores.

Blood pressure should be adequately controlled prior to initiation of ESA therapy and closely monitored and controlled during treatment.

Patients with myelodysplastic syndromes should be initially limited to a 3-month trial period with ESA. If no response to ESA is observed, ongoing therapy would not be merited.

¹ FDA-approved label for epoetin alfa (Epogen®, Procrit®)

² FDA-approved label for darbepoetin alfa (Aranesp®)

Medical Evidence regarding Erythropoiesis-Stimulating Agents (ESAs) indicates it is not recommended in the following situations

The use of an ESA is not recommended for:

- treatment of patients following high-dose chemotherapy with autologous stem-cell support;
- treatment of non-iatrogenic chronic anemia of cancer;
- other cancer-associated anemia excepted as noted above.

Benefits Application

This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

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Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J0881, J0882, J0885, J0886, Q4081

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.04, 5/12/2011

Medical Director 8/2011

Policy Implementation/Update Information

8/30/11 New Guideline implemented. ESA may be appropriate for: treatment of anemia associated with chronic kidney disease; treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy; treatment of anemia related to therapy with AZT (zidovudine) in HIV-infected patients; reduction of allogeneic blood transfusion in surgery patients; treatment of patients following allogeneic bone marrow transplantation; and treatment of patients with myelodysplastic syndromes to reduce transfusion dependency. Medical Director review 8/6/2011. (btw)

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