



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Hematopoietic Growth Factors:  
Epoetin Alfa (Epogen®, Procrit®)  
and Darbepoetin Alfa (Aranesp®)**

**Effective Date ..... 6/15/2011  
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Coverage Policy Number ..... 5016**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers epoetin alfa (Epogen®, Procrit®) as medically necessary for the treatment of anemia in the presence of adequate iron stores (i.e. normal transferrin or serum ferritin level) for any of the following indications:**

- chronic kidney disease in an individual who is predialysis or on dialysis, with a hemoglobin (Hgb) < 12.0 g/dl
- cancer chemotherapy-induced anemia with a Hgb approaching or < 10 g/dl when additional chemotherapy is anticipated for at least another 2 months
- elective surgery with preoperative anemia (Hgb greater than 10 g/ dL and less than or equal to 13 g/dL) except when the anemia is secondary to autologous blood donation (see below)
- HIV infected individual receiving zidovudine treatment with a Hgb less than 13 g/DL in a male and 12 g/dL in a female
- anemia with a Hgb < 10 g/dl due to any of the following:
  - myelodysplastic syndrome
  - ribavirin use in hepatitis C
  - rheumatoid arthritis and/or rheumatic disease

- individual who will not or cannot receive blood products for treatment of acute hemorrhage or blood loss

**CIGNA covers darbepoetin alfa (Aranesp<sup>®</sup>) as medically necessary for the treatment of anemia in the presence of adequate iron stores (i.e. normal transferrin or serum ferritin level) for any of the following conditions:**

- chronic kidney disease in an individual who is predialysis or on dialysis with the hemoglobin (Hgb) < 12.0 g/dL
- cancer chemotherapy-induced anemia with a Hgb approaching or < 10 g/dl when additional chemotherapy is anticipated for at least another 2 months

**Treatment duration to consist of the following:**

- the **initial authorization** period is six (6) months for anemia associated with chronic kidney disease and two (2) months for any other condition for which medical necessity has been established
- **continued authorization** is considered medically necessary when both of the following criteria are met:
  - hemoglobin (Hgb) is ≤12.0 g/dL (<13 g/dl for chronic kidney disease, HIV-infected males receiving zidovudine treatment, and individuals with scheduled elective surgery and persistent preoperative anemia)
  - measurable response to the administration of ESA (e.g. Hgb has increased by 1 g/dl in a two (2)-week period **OR** Hgb > 11 g/dl in chronic kidney disease during the initial six (6)-month authorization)

**CIGNA does not cover epoetin alfa (Epogen<sup>®</sup>, Procrit<sup>®</sup>) or darbepoetin alfa (Aranesp<sup>®</sup>) for the following indications because it is considered not medically necessary (this list may not be all- inclusive):**

- anemia associated with acute renal failure
- anemia associated with congestive heart failure
- anemia in chronic diseases, including:
  - lymphoproliferative disorders (i.e., multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia)
  - cancer
  - individual with a history of cancer who is not currently undergoing current chemotherapy but has anemia associated with **ANY** of the following:
    - prior chemotherapy
    - prior radiation therapy
    - current treatment with radiation therapy
    - malignancy
- anemia in a woman with postpartum iron deficiency anemia
- anemia secondary to autologous blood donation
- athletic performance enhancement
- Castleman disease
- chemotherapy-induced anemia beyond 8 weeks in the absence of response
- chronic kidney disease (CKD) target Hgb > 13.0
- Gaucher disease
- non-critically ill individual requiring correction of anemia
- paroxysmal nocturnal hemoglobinuria (PNH)
- pruritis (uremic) in the absence of anemia
- sickle-cell anemia

**When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Hematopoietic Growth Factor therapy.**

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## **FDA Approved Indications**

### **Epogen and Procrit**

#### **Treatment of Anemia of Chronic Renal Failure Patients**

Epogen and Procrit are indicated for the treatment of anemia associated with CRF, including patients on dialysis and patients not on dialysis. Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin level less than 10 g/dL. Epogen and Procrit are not intended for patients who require immediate correction of severe anemia. Blood pressure should be adequately controlled prior to initiation of Epogen and Procrit therapy and must be closely monitored and controlled during therapy.

#### **Treatment of Anemia in Zidovudine-treated HIV-infected Patients**

Epogen and Procrit are indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. Epogen and Procrit are indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. Epogen and Procrit are not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding which should be managed appropriately.

#### **Treatment of Anemia in Cancer Patients on Chemotherapy**

Epogen and Procrit are indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months. Epogen and Procrit are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. Epogen and Procrit are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Epogen and Procrit on progression-free and overall survival. Epogen and Procrit are not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding. Epogen and Procrit use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

#### **Reduction of Allogeneic Blood Transfusion in Surgery Patients**

Epogen and Procrit are indicated for the treatment of anemic patients (hemoglobin > 10 to ≤ 13 g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions. Epogen and Procrit are not indicated for anemic patients who are willing to donate autologous blood.

## **Aranesp**

### **Anemia With Chronic Renal Failure**

Aranesp is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

### **Anemia With Non-Myeloid Malignancies Due to Chemotherapy**

Aranesp is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies. Aranesp is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy. Aranesp is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Aranesp on progression-free and overall survival.

## **FDA Recommended Dosing**

Dosing varies considerably for each agent depending on clinical indication. When to initiate therapy according to hemoglobin level varies according to the clinical guideline consulted and the labeled indication.

In patients with chronic kidney disease, epoetin alfa is typically dosed one to three times per week, while darbepoetin is dosed between once per week and once every other week. Equivalent doses are approximately 200 units epoetin alfa = 1 mcg darbepoetin alfa. The FDA-labeled starting dose of epoetin alfa is 50 to 100 units/kg three times per week, given either IV or SC. The recommended starting dose of darbepoetin alfa is 0.45 mcg/kg once weekly, given either IV or SC. After initial conversion, doses should be individualized by titration, based on hemoglobin response.

The dose of epoetin alfa for the treatment of chemotherapy-induced anemia is either 150 units/kg SC three times per week or 40,000 units SC once weekly. If patients have not responded to 60,000 units/week after four weeks, it is unlikely that they will respond to higher doses and treatment should be discontinued. The dose of darbepoetin alfa for the treatment of chemotherapy-induced anemia is either 2.25 mcg/kg SC once weekly or 500 mcg SC once every three weeks. In clinical trials comparing epoetin alfa and darbepoetin alfa for anemia due to cancer chemotherapy, dose conversion ratios have ranged from 300:1 to 380:1 (see table 1 below). Darbepoetin alfa doses should be based on clinical data and patient response, rather than on fixed conversions.

**Table 1 - Comparison of Epoetin Alfa and Darbepoetin Alfa**

<b>Property</b>	<b>Darbepoetin alfa</b>	<b>Epoetin alfa</b>
<b>Equivalent Dose</b>	1 mcg of darbepoetin alfa	200–400 units epoetin alfa (note: this conversion is based on product labeling and clinical trial data)
<b>Administration Frequency</b>	Once per week Once every 2 weeks Once every 3 weeks	2–3 times/week Once per week Daily for surgical patients
<b>Route of Administration</b>	IV, Subcutaneous	IV, Subcutaneous
<b>Package Sizes Available</b>	Single dose vials: 25, 40, 60, 100, 150, 200, 300, or 500 mcg  Single dose prefilled syringes: 25, 40, 60, 100, 150, 200, 300, or 500 mcg  Available in 2 formulations that contain either polysorbate or albumin.	Single dose vials: 2,000, 3,000, 4,000, 10,000, or 40,000 units/mL.  Multidose vials: 20,000 units per 2 mL and 20,000 units per 1 mL.  All solutions contain albumin.
<b>Labeled Indications</b>	<ul style="list-style-type: none"> <li>• Treatment of anemia associated with chronic renal failure including patients on dialysis and not on dialysis.</li> <li>• Treatment of anemia due to cancer chemotherapy.</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment of anemia associated with chronic renal failure including patients on dialysis and not on dialysis.</li> <li>• Treatment of anemia due to cancer chemotherapy.</li> <li>• Treatment of anemia in zidovudine treated HIV patients.</li> <li>• Reduction of allogeneic blood transfusion in surgery patients.</li> </ul>

Property	Darbeipoetin alfa	Epoetin alfa
<b>Labeled Dose Range for Initiating Therapy</b>	<ul style="list-style-type: none"> <li>CRF patients: 0.45 mcg/kg IV or subcutaneously every one to two weeks.</li> <li>Cancer chemotherapy patients: 2.25 mcg/kg subcutaneously once weekly or 500 mcg subcutaneously every three weeks.</li> </ul>	<ul style="list-style-type: none"> <li>CRF in adults: 50 to 100 units/kg three times per week, subcutaneously or IV (recommended if receiving hemodialysis).</li> <li>CRF in pediatric patients: 50 units/kg three times per week, subcutaneously or IV.</li> <li>HIV infected patients receiving zidovudine (<math>\leq</math> 4,200 mg/week) and with serum erythropoietin concentrations <math>\leq</math> 500 mUnits/mL: 100 units/kg three times per week, subcutaneously or IV for 8 weeks.</li> <li>Cancer chemotherapy patients: 150 units/kg three times per week or 40,000 units once weekly, subcutaneously. Administer 600 units/kg IV to a maximum of 40,000 units for pediatric patients.</li> <li>Surgery patients to reduce transfusion requirements: 300 units/kg/day subcutaneously for 10 days prior to surgery, day of surgery, and 4 days after surgery, or 600 units/kg subcutaneously once weekly beginning 3 weeks prior to surgery, plus a 4<sup>th</sup> dose on the day of surgery.</li> </ul>
<b>Time to Increased Hemoglobin Levels</b>	2 to 6 weeks (due to time required for erythropoiesis and red cell half-life)	2 to 6 weeks (due to time required for erythropoiesis and red cell half-life)
<b>Dosage Adjustments</b>	<p><u>CRF patients</u> The dose should be reduced by ~25% as Hgb approaches 13 g/dL or increases by more than 1 g/dL in any 2 week period. If Hgb continues to rise, the dose should be withheld until the Hgb begins to decrease. Dose increases should not be made more frequently than once per month. Increase by ~25% of previous dose if less than 1 g/dL increase in Hgb after 4 weeks of therapy.</p> <p><u>Cancer chemotherapy patients</u> The dose should be reduced by 40% as Hgb exceeds 11 g/dL or increases by more than 1 g/dL in any 2 week period. If Hgb exceeds 10 g/dL, the dose should be withheld until the Hgb falls to 10 g/dL. Restart dose at 40% below previous dose. Increase the dose up to 4.5 mcg/kg if less than 1 g/dL increase in Hgb after 6 weeks of weekly therapy.</p>	<p><u>CRF patients</u> The dose should be reduced by ~25% as Hgb approaches 13 g/dL or increases by more than 1 g/dL in any 2-week period. If Hgb continues to rise, the dose should be withheld until the Hgb begins to decrease. Dose increases should not be made more frequently than once per month. Increase by ~25% of previous dose if less than 1 g/dL increase in Hgb after 4 weeks of therapy.</p> <p><u>Cancer chemotherapy patients</u> The dose should be reduced by ~25% as Hgb approaches 10 g/dL or increases by more than 1 g/dL in any 2-week period. If Hgb exceeds 10 g/dL, the dose should be withheld until the Hgb falls to &lt; 10 g/dL. Restart dose at 25% below previous dose. Dose increases may be made every 4 to 8 weeks for inadequate responses. Increase dose to 300 units/kg three times weekly or 60,000 units once weekly; increase dose to 900 units/kg once weekly to a maximum of 60,000 units for pediatric patients.</p> <p><u>Zidovudine-treated patients</u> The dose should be reduced by ~25% as Hgb approaches 12 g/dL or increases by more than 1 g/dL in any 2 week period. If Hgb exceeds 13 g/dL, the dose should be withheld until the Hgb falls to &lt; 12 g/dL. Restart dose at 25% below previous dose. Dose increases may be made every 4 to 8 weeks for inadequate responses. Increase dose in increments of 50–100 units/kg three times weekly to a maximum of 300 units/kg three times weekly.</p>

Abbreviations: CKD = chronic kidney disease; CRF = chronic renal failure; Hgb = hemoglobin

## **Black Box Warning**

### **Epogen, Procrit, and Aranesp**

#### **WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR EVENTS, THROMBOEMBOLIC EVENTS, STROKE and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE**

**Chronic Renal Failure** - In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. **Cancer** - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion. **Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen, Procrit, or Aranesp to patients with cancer.**

## **Drug Availability**

### **Epogen**

Epogen, containing Epoetin alfa, is available in the following packages: 1 mL Single-dose, Preservative-free Solution: 2000 Units/mL; 3000 Units/mL; 4000 Units/mL; 10,000 Units/mL; 40,000 Units/mL. Dispensing packs containing 10 single-dose vials: 2 mL Multidose, Preserved Solution - 10,000 Units/mL or 1 mL Multidose, Preserved Solution - 20,000 Units/mL.

### **Procrit**

Procrit, containing Epoetin alfa, is available in the following packages: 1 mL Single-Dose, Preservative-free Solution Cartons containing six (6) single-dose vials: 2000 Units/mL; 3000 Units/mL; 4000 Units/mL; 10,000 Units/mL. Cartons containing four (4) single-dose vials: 40,000 Units/mL. Trays containing twenty-five (25) single-dose vials: 2000 Units/mL; 3000 Units/mL; 4000 Units/mL; 10,000 Units/mL. 2 mL Multidose, Preserved Solution Cartons containing four (4) multidose vials: 10,000 Units/mL. Cartons containing six (6) multidose vials: 10,000 Units/mL. 1 mL Multidose, Preserved Solution Cartons containing four (4) multidose vials: 20,000 Units/mL. Cartons containing six (6) multidose vials: 20,000 Units/mL.

## **General Background**

### **Pharmacology**

Erythropoietin is an endogenous hormone that stimulates the production, maturation, and release of red blood cells. Erythropoietin is produced primarily by the kidneys and is secreted when the kidneys detect changes in oxygen delivery. Low levels of erythropoietin can lead to significant anemia. Treatment with exogenous erythropoietin is needed to increase serum levels. Increased hemoglobin levels are not generally observed until two to six weeks after initiating treatment with erythropoietic agents because of the time required for erythropoiesis and the red blood cell (RBC) half-life.

Two hematopoietic growth factors are currently available in the United States: epoetin alfa and darbepoetin alfa. Epoetin alfa (Epogen, Procrit) is a recombinant form of erythropoietin that is administered intravenously or subcutaneously from one to three times per week. Darbepoetin alfa is a long-acting erythropoiesis-stimulating protein. Like epoetin alfa, it can be administered either intravenously or subcutaneously. It differs from epoetin alfa in that it contains two more amino-linked oligosaccharide chains. This difference in structure is believed to prolong the half-life of the drug and therefore reduce the necessary administration frequency.

When given by intravenous (IV) administration, the elimination half-life of epoetin alfa in chronic renal failure (CRF) patients is 4–13 hours. When given by subcutaneous (SC) administration, the elimination half-life of epoetin alfa is 19–25.3 hours in CRF patients and 40 hours (range: 16–67 hours) in cancer patients. Peak concentrations of subcutaneous epoetin alfa occurred at five to 24 hours in CRF patients and at 13.3 to 14.2 hours in cancer patients. The bioavailability of epoetin alfa after subcutaneous administration was 30 to 36%.

When given by intravenous (IV) administration, the elimination half-life of darbepoetin alfa in CRF patients is 21 hours (range: 18–25.3 hours). Following subcutaneous administration, absorption is slow and the elimination half-life of darbepoetin alfa is 49 hours (range: 27 to 89 hours) in CRF patients. Peak concentrations of

subcutaneous darbepoetin alfa occurred at 34 hours (range: 24 to 72 hours) in CRF patients and at 90 hours (range: 71 to 123 hours) in cancer patients. The bioavailability of darbepoetin alfa after subcutaneous administration was 37% (range: 30% to 50%).

## **Guidelines**

### **National Comprehensive Cancer Network (NCCN)**

The NCCN recommends ESA's for the following (includes Epogen, Procrit, and Aranesp):

### **Cancer and Chemotherapy Induced Anemia**

#### **Grade 2A**

Consider for the treatment of patients receiving myelosuppressive chemotherapy without curative intent who have moderate to severe chronic kidney disease; who are undergoing palliative treatment; who have no identifiable cause of anemia; in combination with IV iron supplementation for functional iron deficiency.

### **Myelodysplastic syndromes**

#### **Grade 2A**

Initial treatment in lower risk patients with no del(5q) with or without other cytogenetic abnormalities for symptomatic anemia with serum erythropoietin levels less than or equal to 500 mU/mL as a single agent in patients with less than 15% ringed sideroblasts or in combination with filgrastim in patients with greater than or equal to 15% ringed sideroblasts. Target hemoglobin levels should be up to 12 g/dL.

### **American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)**

The ASCO/ASH updated their recommendations on the use of epoetin and darbepoetin in patients with cancer. The updated ASCO/ASH guidelines published in the Journal of Clinical Oncology on January 1, 2008, are based on review and analysis of data published since 2002 through July 2007. For patients with chemotherapy-associated anemia, the committee continues to recommend initiating an erythropoiesis-stimulating agent (ESA) when hemoglobin (Hb)  $\leq$ 10 g/dL, to increase Hb and decrease transfusions. ESA treatment continues to be recommended for patients with low-risk myelodysplasia for similar reasons. There is no evidence showing increased survival as a result of ESA treatment. In addition, the committee recommends that the ESA therapy should not be continued beyond 6 to 8 weeks in the absence of response. The committee recommends monitoring iron stores and supplementing iron intake for ESA-treated patients. ESAs should be used cautiously with chemotherapy, or in clinical states, associated with elevated risk for thromboembolic complications. The committee also cautions against ESA use for patients with cancer who are not receiving chemotherapy, since recent trials report increased thromboembolic risks and decreased survival under these circumstances.

### **National Kidney Foundation**

In September 2007, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) released an update to its 2006 clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease, which updated the sections on hemoglobin targets. The Hb target is the intended aim of erythropoiesis-stimulating agent (ESA) therapy for the individual patient with CKD. Both potential benefits and risks should be considered in selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient. Based on KDOQI current recommendations, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL, but not exceeding 13.0 g/dL, in dialysis and nondialysis patients with CKD receiving ESA therapy. Patients with Hgb concentrations  $\geq$  13 g/dL do not have improvements in survival, hospitalization, or left ventricular hypertrophy and may actually be more prone to excessive adverse cardiovascular events compared to individuals with lower target Hgb concentrations.

## **Clinical Efficacy**

### **Anemia Associated with Prematurity**

Therapy with epoetin alfa may be beneficial in the treatment of anemia of prematurity, a condition in premature neonates of unclear etiology and characterized by low hematocrit, decreased reticulocyte index, and an inappropriately low serum erythropoietin concentration relative to the severity of anemia. While asymptomatic premature neonates may require no treatment for this condition, those with pulmonary disease, tachypnea, tachycardia, apnea, and/or impaired growth may require transfusion of whole blood and/or red blood cells, which may further suppress endogenous erythropoietin production. Epoetin alfa combined with iron supplementation has reduced transfusion requirements and increased hematocrit during the first several weeks of life. In a limited number of premature neonates with a baseline hematocrit averaging 26.3% (range: 22-31%), hematocrit

increased to a mean value of 29.6% (range: 24-35%) following 3 weeks of therapy with epoetin alfa 25-100 units/kg subcutaneously 3 times weekly. Although it appears that epoetin therapy is beneficial in this condition optimal patient selection criteria remain to be more fully elucidated.

### **Cancers Not Treated with Chemotherapy**

The results of recent studies of erythropoiesis-stimulating agents (ESAs) [Aranesp (darbepoetin alfa) in cancer patients raise questions and concerns about their safety and efficacy. Analyses of four new studies in patients with cancer found a higher chance of serious and life-threatening side effects and/or death with the use of ESAs. These research studies were evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA. In another study, patients scheduled for orthopedic surgery had a higher rate of deep venous thrombosis when treated with Procrit at the approved dose. This new information is consistent with risks found in two clinical studies in patients with chronic renal failure treated with an unapproved regimen of an ESA, including the CHOIR study.

Use of an ESA in anemic cancer patients who are not on chemotherapy offered no benefit and may shorten the time to death. ESAs are not FDA approved to treat anemia in cancer patients not receiving chemotherapy. There is a potential risk of shortening the time to tumor progression or disease-free survival. ESAs are administered only to avoid red blood cell transfusions in cancer patients. ESAs do not improve the outcome of cancer treatment and do not alleviate fatigue or increase energy.

Published evidence on the use of hematopoietic growth factors in the management of anemia in patients with cancer not receiving chemotherapy is limited. It is difficult to separate studies on disease-related anemia from treatment-related anemia. Published clinical guidelines do not address the use of epoetin alfa or darbepoetin alfa in patients with nonmyeloid malignancies that have not been treated by chemotherapy. There is limited evidence about the use of either darbepoetin alfa or epoetin alfa in patients with cancer not receiving chemotherapy, and there are no data to assess whether one agent is more effective than the other for this indication.

### **Hepatitis C**

Small studies have indicated that hematopoietic growth factors may be useful in treating anemia associated with interferon and ribavirin therapy in patients with hepatitis C. Additional information regarding standardized dosing administration and frequency are needed. There are two randomized controlled trials and two open-label trials evaluating epoetin alfa in patients being treated with interferon and ribavirin. There is one abstract available of a study using darbepoetin alfa in this patient population.

### **Lymphoproliferative Diseases, Including Multiple Myeloma, Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia**

For the treatment of anemia in patients with lymphoproliferative diseases, the American Society of Clinical Oncology (ASCO) guidelines suggest treatment with chemotherapy or corticosteroids and observation of hematologic outcomes before considering epoetin alfa therapy. If a rise in hemoglobin is not observed after chemotherapy, epoetin alfa should be used according to the criteria outlined for chemotherapy-associated anemia. There have been no comparative trials between epoetin alfa and darbepoetin alfa in patients with lymphoproliferative malignancies not receiving chemotherapy. There is only one study in abstract form with darbepoetin alfa and no studies with epoetin alfa in patients with lymphoproliferative malignancies not receiving chemotherapy. The American Hospital Formulary Service (AHFS) Drug Information states that epoetin alfa has improved anemia, decreased transfusion requirements, and enhanced feelings of well-being in a limited number of patients with advanced multiple myeloma.

### **Myelodysplastic Syndromes (MDS)**

In patients with low-risk myelodysplastic syndrome, both darbepoetin alfa and epoetin alfa have been shown to produce response rates ranging from 36–55%. There are no data to indicate that one agent is more efficacious than another, and optimal dosing regimens have not been established with either agent.

### **Postpartum Iron Deficiency Anemia**

Epoetin alfa has been given to postpartum women with anemia to increase hemoglobin levels and reduce the need for transfusions. A meta-analysis and Cochrane systematic review have been published on this topic. Darbepoetin alfa has not been studied for this indication. Overall, there is little evidence to support the use of

epoetin alfa therapy in women with postpartum anemia. Darbepoetin alfa has not been studied in this population.

### **Rheumatoid Arthritis**

Epoetin alfa has been used to treat anemia in patients with rheumatoid arthritis, but darbepoetin alfa has not yet been studied for this indication. Epoetin alfa therapy has been associated with high non-responder rates, ranging from 10–80%. Sample sizes were small in all of the studies, ranging from 11–72 patients. Epoetin alfa doses varied considerably among studies, as did route of administration. The SC route was used in six trials and the IV route in two trials; one trial allowed either IV or SC administration. Two trials showed that epoetin alfa was better than placebo for increasing hemoglobin levels, and in five trials, reported response rates ranged from 17–81%. These response rates varied so much because of the different definitions of response and the epoetin alfa doses used.

### **Sickle-Cell Anemia**

Epoetin alfa use has been described in five case reports of 19 patients with sickle-cell anemia. In four of the case reports, epoetin alfa was also given with hydroxyurea. Three of the cases reports showed no benefit with epoetin alfa, and one case report indicated that epoetin alfa may be beneficial only in patients who have not responded to hydroxyurea. At this time, epoetin alfa therapy is not indicated for patients with sickle-cell anemia. Darbepoetin alfa has not been studied in this population.

### **Adverse Reactions/Contraindications**

The Black Box Warning for Epogen and Procrit were updated with the label information in Feb 2010 and are contained in the section Black Box Warning as listed above.

In November 2007, the results of six earlier studies led to revisions in the labeling of epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp) warning of the increased risk. As a result of the new studies' data, the Boxed Warnings section of the prescribing information states that ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancer when dosed to target hemoglobin of  $\geq 12$  g/dL. Erythropoiesis-stimulating agents targeted to an Hgb concentration of 12 g/dL also increase the risk of death in patients with active malignant disease who are not receiving chemotherapy or radiation therapy and should not be used in these patients. The black box warning also describes the increased incidence of deep venous thrombosis in patients receiving erythropoiesis-stimulating agents preoperatively for the reduction of allogeneic blood transfusions who are not receiving prophylactic anticoagulation therapy.

On March 12, 2008, the FDA notified healthcare professionals of changes to the Boxed Warnings based on the findings from two additional clinical studies, Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE) in patients with breast cancer, and the National Cancer Institute Gynecologic Oncology Group (COG-19) in patients with cervical cancer. Data from two additional trials examining use of erythropoiesis stimulating agents (ESA) in cancer patients show increased mortality and more rapid tumor progression when the therapies are used in patients with cancer who received an ESA compared to patients who did not receive an ESA. The Box Warnings clarify that ESAs should only be used in patients with cancer when treating anemia specifically caused by chemotherapy and not for other causes of anemia. Further, it states that ESAs should be discontinued once the patient's chemotherapy course has been completed.

The FDA Oncologic Drugs Advisory Committee (ODAC) convened on March 13, 2008 to discuss additional restrictions on the use of anemia drugs to treat cancer patients. The committee recommended that ESAs should remain available for the treatment of anemia for patients with certain types of cancer but should not be used by patients with breast cancer or head and neck cancer. In addition, they recommended that doctors should avoid using ESAs in patients with early stage cancer who are undergoing intensive chemotherapy aimed to completely eliminate the disease. On July 30, 2008, based on the ODAC recommendations, the FDA issued a letter ordering the additional changes to clarify the FDA-approved conditions for use of ESAs in patients with cancer and revised directions for dosing to state the hemoglobin level at which treatment with an ESA should not be initiated.

FDA continues to encourage healthcare professionals to discuss with their patients before starting or continuing therapy with ESAs, the benefits of treatment with ESAs and the potential and demonstrated risks of ESAs for thrombovascular events, shortened time to tumor progression or recurrence, and shortened survival time.

Epoetin alfa (Epogen/Procrit) and darbepoetin alfa (Aranesp) labeling were revised to strengthen the safety information for healthcare professionals and patients. The changes are summarized as follows:

- Safety-related labeling changes for cancer patients receiving chemotherapy: The prescribing information has been revised to clarify the FDA-approved conditions for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer and revised directions for dosing to state the hemoglobin level ( $\geq 10$  g/dL) at which treatment with an ESA should not be initiated. The new label states that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Medication Guide and Patient Instructions for Use for all indications: The new Medication Guide contains information that FDA has determined is necessary for patients' safe and effective use of ESAs, and that could affect patients' decision to take this drug. Federal regulations require that the Medication Guide be distributed to patients.
- Revision on dosage and administration in cancer patients receiving chemotherapy to include the following:
  - Therapy should not be initiated at hemoglobin levels  $\geq 10$  g/dL
  - Ensure use of the lowest dose needed to avoid transfusion and to discontinue treatment with ESAs if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required.
- Currently, the following are listed as Box Warnings regarding the use of these agents in cancer patients:
  - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers
  - To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
  - Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
  - ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
  - Discontinue following the completion of a chemotherapy course.

The FDA provides answers to questions about using ESAs and their FDA-approved Medication Guides. The Guides are designed to help patients make informed decisions about the risks and benefits of using ESAs and to give them a starting point for discussions with their doctors. ESAs are only used during chemotherapy to reduce the need for blood transfusions in cancer patients. They are not appropriate for anemic cancer patients who are not receiving chemotherapy, nor are they approved for chemotherapy patients whose treatment goal is cancer cure. In addition, the Medication Guides warn about the dangers of blood clots while using ESAs. There is also risk of serious heart problems such as heart attack, stroke, heart failure, and a higher chance of death if patients are treated with an ESA to a hemoglobin level above 12 g/dL.

No evidence of drug interactions with epoetin alfa was observed in the course of clinical trials. No formal drug interaction studies have been performed with darbepoetin alfa.

Erythropoietic agents are contraindicated in patients with uncontrolled hypertension. Blood pressure should be controlled adequately before initiation of therapy, and patients with uncontrolled hypertension should not be treated with erythropoietic agents. These agents may also increase the risk of cardiovascular events. There may be an association of a higher risk of cardiovascular events with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 10 g/dL. It is recommended that the dose of these agents be decreased if the hemoglobin increase exceeds 1 g/dL in any two-week period. An increased incidence of thrombotic events (i.e., pulmonary emboli, thrombophlebitis, and thrombosis) has been observed in patients treated with erythropoietic agents. Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with erythropoietic agents. These effects have been reported predominantly in patients with CRF receiving the erythropoietic agents subcutaneously. The safety and efficacy of erythropoietic agents have not been established in patients with a known history of a seizure disorder or underlying hematologic diseases (i.e., sickle cell anemia, hemolytic anemia, thalassemia, porphyria, and hypercoagulable disorders).

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary per the criteria indicated in this policy:**

### Epoetin Alfa (Epogen®, Procrit®)

HCPCS Codes	Description
J0885	Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0886	Injection, epoetin alfa, 1000 units (for ESRD on dialysis)

ICD-9-CM Diagnosis Codes	Description
285.1	Acute posthemorrhagic anemia
285.21	Anemia in chronic kidney disease
285.29	Anemia of other chronic disease
285.3	Antineoplastic chemotherapy induced anemia
285.9	Anemia, unspecified

### Darbepoetin Alfa (Aranesp®)

HCPCS Codes	Description
J0881	Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882	Injection, darbepoetin alfa, 1 mcg (for ESRD on dialysis)

ICD-9-CM Diagnosis Codes	Description
285.21	Anemia in chronic kidney disease
285.3	Antineoplastic chemotherapy induced anemia

**Experimental/Investigational/Unproven/Not Covered for both Epoetin Alfa (Epogen®, Procrit®) and Darbepoetin Alfa (Aranesp®) per the criteris indicated in this policy:**

ICD-9-CM Diagnosis Codes	Description
272.7	Lipidosis
280.9	Iron deficiency anemia, unspecified
282.60-282.69	Sickle-cell anemia
283.2	Hemoglobinuria due to hemolysis from external causes
428.0	Congestive heart failure
584.5-584.9	Acute kidney failure
	Multiple/varied

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	5/15/2008	5016	Hematopoietic Growth Factors: Epoetin Alfa (Epogen <sup>®</sup> , Procrit <sup>®</sup> ) and Darbepoetin Alfa (Aranesp <sup>®</sup> )
Great-West Healthcare	5/2007 5/2007	P01.106.2 P01.109.2	Aranesp EPO

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