



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans 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 6/15/2009
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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 as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant'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 participant'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 participant'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 group 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. Proprietary information of CIGNA. Copyright ©2009 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 conditions:

- chronic kidney disease, including individuals who are predialysis or on dialysis, with a Hemoglobin (Hgb) < 12.0 g/dL
- cancer chemotherapy induced anemia with Hemoglobin (Hgb) approaching or < 10 g/dl
- anemia with a Hemoglobin (Hgb) < 10 g/dl due to any of the following conditions:
 - human immunodeficiency virus (HIV) infection in individuals receiving zidovudine therapy
 - surgical patients
 - chronic disease including:
 - myelodysplastic syndrome
 - ribavirin use in individuals infected with hepatitis C
 - rheumatoid arthritis and rheumatic disease
 - prematurity
 - critically-ill (ICU-hospitalized) individuals
 - individuals who will not or cannot receive blood products for treatment of acute hemorrhage or blood loss

CIGNA covers darbepoetin alfa (Aranesp[®]) 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, including individuals who are predialysis or on dialysis with the Hemoglobin (Hgb) < 12.0 g/dL
- cancer chemotherapy induced anemia with Hemoglobin (Hgb) approaching or <10 g/dl
- anemia with a Hemoglobin (Hgb) < 10 g/dl due to any of the following conditions:
 - prematurity
 - critically-ill (ICU-hospitalized) individuals
 - individuals who will not or cannot receive blood products for treatment of acute hemorrhage or blood loss

Treatment duration to consist of the following:

- the **initial authorization** period is six (6) months for anemia associated with chronic kidney disease and eight weeks for all other conditions 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 individuals with chronic kidney disease)
 - measurable response to the administration of the ESA (e.g., Hgb has increased by 1 g/dl in a two-week period **OR** Hgb > 11 g/dl in chronic kidney disease during the initial six-month authorization)

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

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

General Background

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. Studies to determine whether Aranesp® increases mortality or decreases progression-free/recurrence-free survival are ongoing. 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. Aranesp® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

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

Property	Darbepoetin alfa	Epoetin alfa
Equivalent Daily Dose	1 mcg of darbepoetin alfa	200–400 units epoetin alfa (note: this conversion is based on product labeling and clinical trial data)
Administration Frequency	Once per week Once every 2 weeks Once every 3 weeks	2–3 times/week Once per week Daily for surgical patients
Route of Administration	IV, Subcutaneous	IV, Subcutaneous
Package Sizes Available	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.
Labeled Indications	<ul style="list-style-type: none"> • Treatment of anemia associated with chronic renal failure including patients on dialysis and not on dialysis. • Treatment of anemia due to cancer chemotherapy. 	<ul style="list-style-type: none"> • Treatment of anemia associated with chronic renal failure including patients on dialysis and not on dialysis. • Treatment of anemia due to cancer chemotherapy. • Treatment of anemia in zidovudine treated HIV patients. • Reduction of allogeneic blood transfusion in surgery patients.

Property	Darbeпоetin alfa	Epoetin alfa
Labeled Dose Range for Initiating Therapy	<ul style="list-style-type: none"> CRF patients: 0.45 mcg/kg IV or subcutaneously every one to two weeks. Cancer chemotherapy patients: 2.25 mcg/kg subcutaneously once weekly or 500 mcg subcutaneously every three weeks. 	<ul style="list-style-type: none"> CRF in adults: 50 to 100 units/kg three times per week, subcutaneously or IV (recommended if receiving hemodialysis). CRF in pediatric patients: 50 units/kg three times per week, subcutaneously or IV. HIV infected patients receiving zidovudine (\leq 4,200 mg/week) and with serum erythropoietin concentrations \leq 500 mUnits/mL: 100 units/kg three times per week, subcutaneously or IV for 8 weeks. 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. 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 4th dose on the day of surgery.
Time to Increased Hemoglobin Levels	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)
Dosage Adjustments	<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 < 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 < 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

The National Comprehensive Cancer Network (NCCN) recommends ESA's for the following: cancer and chemotherapy induced anemia - consider for the initial treatment, with or without IV iron supplementation, of patients receiving myelosuppressive chemotherapy without curative intent who have: asymptomatic anemia and risk factors for the development of symptomatic anemia requiring red blood cell transfusion and with functional iron deficiency or symptomatic anemia requiring transfusion; following initial response assessment, consider for the continued initial treatment of anemia by dose escalation, with or without IV iron supplementation, for patients not responding to 4 weeks of epoetin alfa therapy: for patients responding to erythropoietic therapy (hemoglobin increased by 1 g/dL) at 8 to 9 weeks, dosage should be titrated to avoid red blood cell transfusion or for patients with stable hemoglobin (within 1 to 2 g/dL of baseline) while receiving chemotherapy, erythropoietic therapy should be continued or for patients with no hemoglobin response at 8 to 9 weeks, erythropoietic therapy should be discontinued. Transfuse as indicated based upon symptoms and institutional guidelines. Myelodysplastic syndromes - 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. Analyses of eight studies in patients with cancer found decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels greater than 12 g/dL. Erythropoiesis-stimulating agents (ESAs) should only be used in the setting of myelosuppressive chemotherapy-related anemia when the intent of chemotherapy is not curative. ESAs should be discontinued when chemotherapy treatment is complete and anemia has resolved, usually within 6 weeks. Patients should be counseled regarding the risks and benefits of ESAs prior to initiation of ESA therapy. Target hemoglobin levels should be up to 12 g/dL.

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (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) ≤ 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.

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 ≥ 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.

The National Cancer Institute (NCI) and the World Health Organization (WHO) have different rating scales for anemia. The NCI has a more conservative definition of grades 0, 1, and 2 anemia. The National Comprehensive Cancer Network (NCCN) uses a different scale and defines mild anemia as Hgb 10–11 g/dL, moderate anemia as Hgb 8–10 g/dL, and severe anemia as Hgb < 8 g/dL. The NCCN guidelines recommend erythropoietin therapy if patients are symptomatic and Hgb level is 10–11 g/dL and to strongly consider therapy if Hgb is < 10 g/dL. Most clinical trials begin treatment of anemia when Hgb is 11 g/dL or less. The target Hgb value for the initiation of erythropoietin therapy depends on the goal of treatment. If the goal is to prevent a blood transfusion, then an Hgb level of 10 g/dL or less is acceptable. However, if the goal is to improve patient function and QOL, then an Hgb of 11g/dL is considered the appropriate level for intervention. The largest incremental gain in QOL occurs when Hgb is between 11 and 12 g/dL.

These differences in definitions of anemia and target levels of Hgb for treatment between the ASCO/ASH, NKF-KDOQI, and NCCN guidelines and clinical practice recommendations result in different practices by oncologists and hematologists across the country.

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 (Epoen[®], 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%).

Fifteen trials comparing darbepoetin alfa to epoetin alfa have been conducted on patients with anemia due to kidney disease or cancer chemotherapy. Results indicate that these agents probably have comparable efficacy regarding their effects on hematological indices and the number of red blood cell transfusions required for anemia of kidney disease. A study released in May 2006 by the Agency for Healthcare Research and Quality (AHRQ) finds there is no clinically significant difference in the medical effectiveness between epoetin alfa and darbepoetin alfa for managing anemia due to cancer treatment. Darbepoetin is not labeled for the treatment of anemia in patients with human immunodeficiency virus (HIV) infection who are receiving zidovudine therapy or for the reduction of allogeneic blood transfusions in surgery patients. There are no comparative data for these two indications.

Anemia Associated With Chronic Kidney Disease (CKD)

Anemia is one of the most common complications of CKD. The primary cause of anemia in these patients is lack of sufficient quantities of endogenous erythropoietin. Anemia develops relatively early in the course of CKD. Significant anemia can appear when the glomerular filtration rate falls below 40 mL/minute. Anemia develops consistently when the glomerular filtration rate is less than 60 mL/minute (stage 3 CKD) and is present in most patients with end stage renal disease and in patients requiring dialysis. Patients with CKD should be evaluated for anemia if their serum creatinine is 2 mg/dL or greater. Hemoglobin testing is recommended for all patients with CKD, regardless of stage or cause, and should be evaluated at least annually in patients not receiving erythropoietic therapy and at least monthly in those receiving erythropoiesis-stimulating agents. Anemia is defined by the National Kidney Foundation as Hgb < 13.5 g/dL in adult males and Hgb < 12.0 g/dL in adult females.

Anemia due to erythropoietin is usually normocytic and normochromic. Patients with microcytic or macrocytic anemia require further evaluation, as these anemias are not due to erythropoietin deficiency. Treatment of anemia in patients with kidney disease using recombinant erythropoietin reduces symptoms and complications of anemia, including improved survival, decreased morbidity, and improved quality of life (QOL).

To date, no differences in efficacy have been demonstrated between darbepoetin alfa and epoetin alfa for the treatment of anemia associated with CKD. There are four published trials comparing epoetin alfa and darbepoetin alfa. Two trials demonstrated noninferiority (comparable efficacy) between the agents. However, the other two trials were not able to determine comparative efficacy; one of these trials was not powered to detect a difference between the two treatment groups, and one study is available in abstract form only.

CHOIR study, or Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), evaluated the potential benefit and harm from treatment with Procrit in patients with chronic kidney disease who are not on dialysis. In the study, harm was defined as a group of effects that included death, heart attack, hospitalizations for heart failure and stroke. The research found that more patients in the study who were treated with Procrit to raise their blood hemoglobin concentration to the higher 13.5 g/dL level experienced death and life-threatening harm than those who were treated to raise their blood hemoglobin concentration to the lower 11.3 g/dL level. Similar results were noted in the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial.

Anemia Associated With Cancer Chemotherapy

Anemia in patients with cancer may be related to the cancer chemotherapy, infiltration of the bone marrow by cancer cells, or nonspecific processes like iron deficiency, low endogenous erythropoietin levels, or the inhibitory effect of tumor necrosis factor. Prior to the development of epoetin alfa, the management of anemia in cancer patients primarily consisted of blood transfusions.

Both epoetin alfa and darbepoetin alfa reduce the need for blood transfusions in patients with chemotherapy-induced anemia compared to patients managed with transfusion alone. One agent is not superior to the other for reducing the risk of blood transfusions.

Three large meta-analyses evaluated the outcomes of managing anemia with epoetin alfa compared to transfusion alone. Seidenfeld et al. found the combined odds ratio of transfusion for patients treated with epoetin alfa was 0.38 (95% CI 0.28 to 0.5) relative to the odds of transfusion for the control group, which was managed by transfusion alone. This meta-analysis was unable to detect whether there was a difference in transfusion rates or patient outcomes based on baseline Hgb values (eg, Hgb levels < or > 10 g/dL). Clark et al. found the combined odds ratio of transfusion to be 0.41 (95% CI 0.33 to 0.5) and the relative risk to be 0.61 (95% CI 0.54 to 0.68), $p < 0.00001$ vs. control group. Bohlius et al. reported a relative risk 0.67 (95% CI 0.62 to 0.73) to receive a blood transfusion in epoetin alfa-treated patients. These meta-analyses indicate that epoetin alfa reduces the need for blood transfusions in patients with chemotherapy-induced anemia compared to patients managed with transfusion alone.

Anemia Associated with Zidovudine Therapy in Patients Infected with HIV

Anemia is the most common hematologic abnormality in patients with HIV infection, with frequency and severity increasing as the disease progresses to acquired immunodeficiency syndrome (AIDS). Anemia has been independently associated with disease progression and increased risk of mortality in patients with HIV infection. Some causes of anemia include decreased red blood cell production as a direct effect of HIV, nutritional causes, bone marrow infiltration, and toxicity of drug therapy. Zidovudine is a well-known cause of bone marrow suppression and anemia in this population. The introduction of highly active antiretroviral therapy (HAART) in 1996 has decreased HIV disease severity and decreased the incidence of severe anemia, but many patients still have mild to moderate anemia. Treatment options for anemia in patients with HIV include iron and vitamin B₁₂ supplementation if deficient, erythropoietin, blood transfusions, and androgens. The Anemia in HIV Working Group recently published their recommendations for managing anemia in HIV-infected patients. These recommendations include the initiation of epoetin alfa 40,000 units once weekly if correctable causes of anemia have been ruled out and Hgb is < 13 g/dL in men and < 12 g/dL in women.

Hematopoietic Growth Factors to Reduce Allogeneic Blood Transfusion Requirements

Patients undergoing elective or scheduled surgery may choose to have their own blood processed and stored prior to the surgery. Preoperative autologous donation (PAD) reduces the need for allogeneic blood transfusions. Henry et al. conducted a Cochrane systematic review to examine the efficacy of PAD in reducing the need for perioperative allogeneic blood transfusions. The results showed that PAD reduced the risk of receiving an allogeneic transfusion by 63% (RR=0.37; 95% CI 0.26 to 0.54). However, PAD has not been shown to be cost-effective. It is more expensive to produce an autologous unit, and more than 50% of PAD units are

discarded or become outdated before the scheduled surgeries. Additionally, many patients are not candidates for PAD, such as those with heart disease or who are already anemic. Keating et al. found that about one-third of patients are anemic before they undergo joint arthroplasty, with Hgb levels between 10–13 g/dL. The incidence of anemia increases with increasing age; elderly patients make up a substantial proportion of patients requiring major orthopedic surgeries. Anemia is also prevalent in patients with malignancy who need surgery as part of their treatment plan.

Multiple studies have demonstrated that epoetin alfa is effective for reducing transfusion requirements in anemic patients undergoing elective orthopedic surgery. Faris et al. summarized the results from four large randomized controlled trials involving 869 patients who were not candidates for PAD. Six hundred- nineteen patients received epoetin alfa (doses of 100–300 units/kg/day for 14–15 days or 600 units/kg/week for 4 doses), and 250 patients received placebo. Patients were undergoing elective hip or knee arthroplasty. The primary outcome in these trials was the incidence of allogeneic blood transfusions. In looking at the results of the four studies, between 11%–25% of patients treated with epoetin alfa received a blood transfusion, and 23%–54% of patients treated with placebo required a transfusion.

Recent data further support the efficacy of preoperative epoetin alfa for reducing blood transfusions in patients undergoing elective orthopedic surgery and supports the use of a two-dose epoetin alfa regimen. Epoetin alfa was administered 14 days and 7 days prior to surgery in these trials.

Epoetin alfa is FDA-labeled to reduce transfusion requirements in anemic patients (Hgb > 10 g/dL but \leq 13 g/dL) undergoing elective surgery that is noncardiac or nonvascular. Epoetin alfa is not indicated for anemic patients who are willing to donate autologous blood. Patients with initial Hct levels between 33% and 39% and who stand to lose up to three liters of blood during surgery are among those who can benefit the most from epoetin alfa therapy. Less benefit is expected in patients with normal preoperative Hgb levels. The reason epoetin alfa is not labeled for patients undergoing cardiac or vascular surgery may be for safety reasons. A randomized controlled trial by D'Ambra et al. in patients undergoing cardiac surgery showed that seven patients in epoetin alfa group (n=126) and no patients in the placebo group (n=56; p=0.06) died. Five of the seven deaths were thought to be drug-related, and four of these deaths resulted from thrombosis or vascular events. Although these findings were not statistically significant, the study was not adequately powered to detect differences in adverse effects. This was the first study that found a difference in mortality. It is not clear from the literature if there is an increase in thrombotic events because many studies have not screened for thrombotic events. Study sample sizes were small and unable to detect clinically important increases in adverse events.

No comparative trials have been conducted between darbepoetin alfa and epoetin alfa for the reduction of allogeneic blood transfusion requirements in patients undergoing surgery. Darbepoetin alfa has not been studied for this indication.

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.

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.

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.

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.

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.

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.

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.

Anemia Associated with Prematurity

There have been no comparative trials between darbepoetin alfa and epoetin alfa for the treatment of anemia associated with prematurity. Darbepoetin alfa has not been studied in this patient population. Overall, there was a trend that epoetin alfa therapy started during the first week of life would reduce the necessity for transfusion

during the first three weeks of life and significantly reduce the need for a transfusion during weeks 4–6 of life. The optimal duration of therapy is not known.

No differences in the safety or adverse effect profiles were observed in any of the comparative clinical trials between darbepoetin alfa and epoetin alfa. The most common adverse reactions associated with darbepoetin alfa and epoetin alfa therapy include infection, hypertension, hypotension, myalgia, headache, and diarrhea.

Higher hemoglobin concentrations and higher rates of rise of hemoglobin are associated with an increase in cardiovascular and other serious adverse events. Target hemoglobin concentrations should be ≤ 12 g/dL for both of these agents. An increase in adverse effects was also associated with an increase in hemoglobin of > 1 g/dL during a two-week period. Darbepoetin alfa and epoetin alfa dosage reductions are recommended if this rate is exceeded.

Several safety alerts released by the U.S. Food and Administration (FDA) including the alert posted on March 9, 2007 regarding the erythropoiesis-stimulating agents led to the inclusion of a black box warning in the package inserts for all of the erythropoietic agents. The update on safety information was based on the results from four new studies of patients with cancer and on the results from another study in patients scheduled for orthopedic surgery, in addition to the results from the CHOIR and CREATE trials. The FDA warned healthcare professionals about the increased risk for serious and life-threatening cardiovascular complications with target Hgb concentrations above 12 g/dL in an alert posted on November 16, 2006. This warning was based on the results of the published CHOIR and CREATE studies. On January 26, 2007, Amgen warned practitioners about the increased risk of death when darbepoetin alfa was used in cancer patients with anemia who were not receiving concurrent chemotherapy in a phase 3, double-blind, randomized, placebo-controlled trial. The FDA posted an alert regarding this information on February 16, 2007.

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 ≥ 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 (Epoen[®]/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 (≥ 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 ≥ 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).

Coding/Billing Information

Note: This section is not in use.

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Policy History

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

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.