Erythropoiesis-Stimulating Agents (ESA's): epoetin alfa (Epogen® and Procrit®), darbepoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®)

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

epoetin alfa (Epogen® or Procrit®)‡ Selection Criteria-Labeled Usage
Patient Selection Criteria
Coverage eligibility will be considered for the use of epoetin alfa (Epogen or Procrit) when the following lab criteria are met (unless otherwise specified) and at least one of the clinical criteria listed below is met:

Lab Criteria:

- Hematocrit (Hct)/hemoglobin (Hgb) levels are less than 30%/10g/dL prior to initiation of therapy (not applicable to elective, noncardiac, nonvascular surgery patients); and
- Adequate iron stores with a transferrin saturation of at least 20% and ferritin at least 100ng/ml.

Clinical Criteria:

- Treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (treatment should be discontinued if hemoglobin [Hgb] level exceeds 12g/dl); (*Note:* epoetin alfa (Epogen or Procrit) is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure); or
- Treatment of anemia related to therapy with zidovudine (AZT) in human immunodeficiency virus (HIV) infected adults and children (treatment should be discontinued if hemoglobin [Hgb] level exceeds 12g/dl); or
- Treatment of anemia associated with chronic kidney disease (CKD) including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusions (treatment should be discontinued if Hematocrit [Hct]/hemoglobin [Hgb] levels exceed 33%/11g/dL); or
- Treatment for surgery patients (hemoglobin [Hgb] >10 to ≤13g/dL) who are scheduled to undergo elective, noncardiac, nonvascular surgery, to reduce the need for allogeneic blood transfusions.

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epoetin alfa (Epogen or Procrit) Selection Criteria- Off Label Usage

Patient Selection Criteria
Coverage eligibility for the off-label use of epoetin alfa (Epogen or Procrit) will be considered when the following lab criteria are met (unless otherwise specified) and at least one of the clinical criteria listed below is met:

Lab Criteria:
- Hematocrit (Hct)/hemoglobin (Hgb) levels are less than 30%/10g/dL prior to initiation of therapy (not applicable to anemia patients who donate blood prior to elective surgery); and
- Adequate iron stores with a transferrin saturation of at least 20% and ferritin at least 100ng/ml.

Clinical Criteria:
- To prevent anemia in patients who donate blood and to increase the capacity for donation (for future autologous transfusion) prior to elective surgery ; or
- Treatment of anemia associated with myelodysplastic syndromes in selected patients (treatment should be discontinued if hemoglobin [Hgb] level exceeds 12g/dl); or
- Treatment of anemia in patients with hepatitis C virus infection related to ribavirin treatment (treatment should be discontinued if hemoglobin [Hgb] level exceeds 12g/dl); or
- Treatment of anemia in critically ill patients in hospital intensive care units (treatment should be discontinued if hemoglobin [Hgb] level exceeds 12g/dl).

Note: *epoetin alfa is not a substitute for blood transfusions, which may be required for the emergency treatment of severe anemia. Chronic use of epoetin alfa reduces the need for repeated maintenance blood transfusions.*

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of epoetin alfa (Epogen or Procrit) † for usage not indicated in the patient selection criteria to be **investigational.***

Based on review of available data, the Company considers the use of epoetin alfa (Epogen or Procrit) for non-FDA approved indications (except those mentioned in the patient selection criteria) to be **investigational.***

Erythropoiesis Stimulating Agents (ESA's): epoetin alfa (Epogen® and Procrit®), darbepoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®)

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darbepoetin alfa (Aranesp®)‡ Selection Criteria

Patient Selection Criteria
Coverage eligibility will be considered for the use of darbepoetin alfa (Aranesp) † when there is documented failure of epoetin alfa (defined as failure to achieve a rise in hemoglobin [Hgb] of 2g/dL or a target hemoglobin [Hgb] of 12g/dL after eight weeks of therapy or significant side effects) for the treatment of anemia in cancer patients and all of the following lab criteria are met and at least one of the clinical criteria listed below is met:

Note: Documented failure of epoetin alfa is exempt in the treatment of anemia associated with chronic renal failure.

Lab Criteria:
- Hematocrit (Hct)/hemoglobin (Hgb) levels are less than 30%/10g/dL prior to initiation of therapy; and
- Adequate iron stores with a transferrin saturation of at least 20% and ferritin at least 100ng/ml.

Clinical Criteria:
- Treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy (treatment should be discontinued if Hgb level exceeds 12g/dl); (*Note:* Darbepoetin Alfa [Aranesp] is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure); or
- Treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis (treatment should be discontinued if hematocrit (Hct)/hemoglobin (Hgb) levels exceed 33%/11g/dL).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of darbepoetin alfa (Aranesp) when patient selection criteria are not met [except for the lack of a documented failure of epoetin alfa (Epogen or Procrit) when treating anemia in cancer patients which is considered **not medically necessary****] to be **investigational.***

Based on review of available data, the Company considers the use of darbepoetin alfa (Aranesp) for non-FDA approved indications to be **investigational.***

Erythropoiesis Stimulating Agents (ESA's): epoetin alfa (Epogen® and Procrit®), darbepoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®)

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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of darbepoetin alfa (Aranesp) when there is no documented failure of epoetin alfa (Epogen or Procrit) when treating anemia in cancer patients to be **not medically necessary.****

pegylated epoetin beta (Mircera®)‡ Selection Criteria

Patient Selection Criteria
Coverage eligibility will be considered for the use of pegylated epoetin beta (Mircera) when the following lab criteria are met and the clinical criterion listed below is met:

Lab Criteria:
- Hematocrit (Hct)/hemoglobin (Hgb) levels are less than 30%/10g/dL prior to initiation of therapy; and
- Adequate iron stores with a transferrin saturation of at least 20% and ferritin at least 100ng/ml.

Clinical Criterion:
- Treatment of anemia due to chronic kidney disease (CKD), in adult patients on dialysis and adult patients not on dialysis (treatment should be discontinued if hematocrit (Hct)/hemoglobin (Hgb) levels exceed 33%/11g/dL).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of pegylated epoetin beta (Mircera)† for usage not indicated in the patient selection criteria or for non-FDA approved indications to be **investigational.***

Background/Overview
EPO (erythropoietin) is a glycoprotein hematopoietic growth factor synthesized by cells near the renal tubules in response to changes in the blood oxygen concentration. When a patient is anemic, the ability of the blood to carry oxygen is decreased. An oxygen-sensing protein in the kidney detects the decrease in blood oxygen concentration and induces the production of erythropoietin, which then acts on the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood Hgb concentrations. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin results in anemia in several disease processes, including CKD, many types of cancer treatment, other chronic diseases, and use of certain drugs.

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Erythropoiesis-stimulating agent (ESA)s are produced using recombinant DNA technologies. They were initially developed as replacement therapy to treat anemia due to endogenous erythropoietin deficiency that commonly occurs in patients with chronic renal failure secondary to chronic kidney disease. Patients with chronic renal failure will become severely anemic and experience severe fatigue and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia by ESA treatment of patients with chronic renal failure reduces the need for red blood cell (RBC) transfusions and enhances physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms: Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B12) essential for RBC production. Antibodies and/or immunoregulatory abnormalities associated with certain tumor types (most commonly, B cell malignancies) may cause increased erythrocyte destruction (hemolysis). Tumors may cause blood loss via tissue invasion, for example gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. However, marrow dysfunction can occur even in the absence of frank invasion. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization, as well as a direct suppression of RBC production. Cancer treatments also may cause anemia: radical cancer surgery can result in acute blood loss; and radiotherapy and many cytotoxic chemotherapeutic agents suppress marrow to varying degrees. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage; antimetabolites damage DNA indirectly; and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

Red blood cell transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, this approach carries risk for several potential adverse events. The highest adverse event risk (1 per 432 whole blood units transfused) is for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (eg, type mismatch) are estimated to occur at a rate of 1 per 5000 to 10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), HIV (<1 in 1,000,000), and bacterial contaminants (1 per 10,000 to 100,000) have fallen dramatically since the early 1990s. Therefore, although the initial impetus to commercialize erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those risks. Nonetheless, blood shortages, transfusion errors, and risks of alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Four ESA products have been licensed in the United States: Epoetin alfa is manufactured, distributed, and marketed by Amgen, Inc. under the proprietary name, Epogen. The same epoetin alfa product manufactured by Amgen Inc. is also marketed and distributed by Janssen Products, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit. Under a contractual agreement with Amgen, Janssen Products LP has rights to develop and market Procrit for any indication other than for treatment of anemia associated with chronic renal failure (CRF) in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all FDA-approved indications. A second ESA, darbepoetin alfa, is marketed solely by Amgen, under the proprietary name, Aranesp. The third ESA product, peginesatide, was codeveloped and commercialized by Affymax Inc. and Takeda Pharmaceuticals, who market it under the proprietary name, Omontys. In February 2013, Affymax, Takeda, and FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. FDA currently lists peginesatide (Omontys) as discontinued. Pegylated-epoetin beta was FDA-approved in 2007 and is marketed outside the U.S. by Hoffmann-LaRoche under the proprietary name Mircera. Due to a copyright infringement lawsuit brought by Amgen in 2009, U.S. sales have been prohibited until mid-2014.

Epoetin alfa and epoetin beta have the same amino acid sequence as endogenous erythropoietin but differ from each other in glycosylation; clinical effects are considered interchangeable. Darbepoetin alfa is similar to endogenous erythropoietin but has 2 additional oligosaccharide chains. In contrast, peginesatide lacks any amino acid sequence homology to erythropoietin. It is a synthetic dimer of identical 21-amino acid peptides bound to a linker and to polyethylene glycol, with a total molecular weight of approximately 45,000 Da. (The molecular weight of endogenous erythropoietin is approximately 34,000 Da.) However, the epoetins, darbepoetin, and peginesatide all have pharmacologic actions similar to those of the endogenous hormone. Each binds to and activates the human erythropoietin receptor and thus increases the number of RBCs and the blood concentration of hemoglobin, when given to individuals with functioning erythropoiesis. Both epoetin alfas, pegylated-epoetin beta, and darbepoetin are FDA-approved to treat anemia in patients with CKD who are on dialysis or not on dialysis. Epoetin alfa and darbepoetin also are approved for other indications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The major regulatory timelines for approval actions pertaining to new indications are summarized next:
Epoetin alfa (Epogen/Procrit):

- 1989: Approved for use in patients with anemia due to chronic renal failure
- 1991: Approved for use in zidovudine-treated, HIV-infected patients
- 1993: Approved for chemotherapy-induced anemia in patients with nonmyeloid malignancies
- 1996: Approved for presurgical use in certain patients undergoing surgery

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Darbepoetin alfa (Aranesp):
- 2001: Approved for use in patients with anemia due to chronic renal failure
- 2002: Approved for chemotherapy-induced anemia in patients with nonmyeloid malignancies

Peginesatide (Omontys):
- 2012: Approved for use in adults with anemia due to chronic kidney disease who are on dialysis
- 2013: Voluntary recall of all lots due to postmarketing reports of serious hypersensitivity

Pegylated epoetin-beta (Mircera)
- 2007: Approved for use in patients with anemia due to chronic renal failure who are on dialysis or not on dialysis
- 2009: Injunction prohibiting U.S. sales until mid- 2014 due to copyright infringement
- 2014: Resumption of U.S. sales anticipated

Centers for Medicare and Medicaid Services (CMS) Postapproval Decision Memorandum
In July 2007, CMS released a Decision Memorandum on the use of ESAs for non-renal disease indications (CAG-00383N). Safety concerns such as thrombosis, cardiovascular events, tumor progression, and reduced survival, derived from clinical trials in several cancer and non-cancer populations, prompted CMS to review its coverage of ESAs. The CMS reviewed a large volume of scientific literature, including basic science research, to see if safety findings observed in RCTs could be reasonably explained in whole or in part by the actions of ESAs on normal or cancerous cells. Based on this review, CMS proposed conditions of coverage based on expression of EPO receptors. However, the scientific understanding of this mechanism is controversial and requires additional study.

The CMS also reviewed comments on ESAs treatment of myelodysplastic syndrome (MDS), a precursor of acute myeloid leukemia (AML) in many patients. The CMS retains interest in these specific issues but does not differentiate ESA coverage by the EPO receptor status of the underlying disease and has decided to make no national coverage determination (NCD) at this time on ESAs in MDS.

The CMS has determined that evidence is sufficient to conclude that ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:
- Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
- Any anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers
- Anemia of cancer not related to cancer treatment
- Any anemia associated only with radiotherapy

- Prophylactic use to prevent chemotherapy-induced anemia
- Prophylactic use to reduce tumor hypoxia
- Patients with EPO-type resistance due to neutralizing antibodies
- Anemia due to cancer treatment if patients have uncontrolled hypertension.

The CMS also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

- The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).
- The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150U/kg/3 times weekly for epoetin and 2.25mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.
- Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is > 1g/dL (hematocrit > 3%).
- For patients whose hemoglobin rises < 1g/dL (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10g/dL after the 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1g/dL (hematocrit rise < 3%) compared to pretreatment baseline by 8 weeks of treatment.
- Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1g/dL (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
- ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Pegylated epoetin beta is not addressed in the Decision Memorandum or NCD.

This decision by CMS also allows local Medicare contractors to continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield

Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Two 1995 TEC Assessments (Myelodysplastic Syndrome and Chronic Anemia of Cancer; Allogeneic Bone Marrow Transplantation or High-Dose Chemotherapy with Autologous Stem-Cell Support) provided the basis for the original policy statements regarding these 2 settings. The most recent literature review was performed for the period through August 5, 2014. Primary data sources for oncology included a 2006 comparative meta-analysis on the outcomes of epoetin or darbepoetin for managing anemia in patients undergoing cancer treatment prepared for the Agency for Healthcare Research and Quality (AHRQ) and the 2005 AHRQ report, updated in 2013; a meta-analysis using individual patient data for outcomes of ESA therapy in patients with cancer, with additional outcomes reported in 2012; American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) 2010 clinical practice guidelines on the use of epoetin and darbepoetin to treat chemotherapy-associated anemia; 2007 briefing documents available from the U.S. FDA Oncologic Drugs Advisory Committee (ODAC); and a 2007 Decision Memorandum from the Centers for Medicare and Medicaid Services on the use of ESAs for nonrenal disease indications.

Information on the use of ESAs in CRF was obtained from several sources including 2007 briefing documents from a joint meeting of FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) and Drug Safety and Risk Management Advisory Committee (DSRMAC) to reassess ESA risks; and, a meta-analysis of blood Hgb targets for patients with CRF associated anemia. FDA-approved labels for ESAs available (or soon to be available) in the United States comprised additional data sources for this Policy, in particular, recommended dosing information for the different clinical settings covered.

The 2010 ASCO/ASH clinical practice guideline for the use of ESAs considers epoetin and darbepoetin, used at dosages recommended in current FDA-approved package inserts, to be equivalent with respect to effectiveness and safety. Epoetin and darbepoetin are identical with respect to: (1) indications for use in chemotherapy-induced anemia, (2) Hgb limits for adjusting doses, initiating or discontinuing treatment, (3) warnings and cautions to consider, and (4) increased rates of thromboembolic events in the experimental arms of separate trials on each product versus controls/placebo.

Chronic Kidney Disease

<u>epoetin and darbopoetin</u>

At initial approval of epoetin in 1989, the primary objective of treatment was to raise Hgb concentration sufficiently to avoid transfusion, with a target range of 9 to 10 g/dL in anemic patients with chronic kidney disease (CKD). The first National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKFKDOQI) guidelines in 1997 recommended an Hgb concentration of 11 g/dL, a level that was increased by subsequent NKF-KDOQI anemia guidelines, to 11 to 13 g/dL in 2007. With increased experience in the use of ESAs, it became unclear whether higher Hgb target concentrations, including normalization, would yield additional benefits, in particular in physical function and improved cardiovascular outcomes. Clinical doubts increased with publication of the first large randomized controlled trial (RCT) of Hgb normalization

using epoetin alfa in hemodialysis patients (Normal Hematocrit Cardiac Trial [NHCT]). NHCT showed a trend toward increased mortality risk and significantly increased risk for vascular access thrombosis with ESA treatment to a hematocrit (Hct) target of 42%. Subsequently, 4 published RCTs in hemodialysis patients with end-stage renal disease (ESRD) and 8 in nondialysis patients with CKD found improved physical function at higher Hgb targets, but none demonstrated significant improvements in cardiovascular end points or mortality.

The Epogen/Procrit label was modified in 1996 to include results of the NHCT study that showed a higher mortality rate for anemic dialysis patients randomized to an Hct of 42%, compared with an Hct of 30%. Ten years later, the CHOIR study reported worse cardiovascular outcomes for anemic CRF patients who were not undergoing dialysis and who were randomized to a target Hgb of 13.5 g/dL, compared with an Hgb of 11.3 g/dL. Subsequent analyses of outcomes in CHOIR showed shorter times to progression of kidney disease and higher rates of renal replacement therapy and death among patients randomized to the higher Hgb target. The CREATE study, also reported in 2006, was similar to CHOIR but enrolled fewer patients. CREATE did not demonstrate statistically significant differences in adverse cardiovascular outcomes for the higher Hgb group, but the general trend of major cardiovascular outcomes was similar to the CHOIR findings. The 2009 TREAT study randomized 4038 patients with type 2 diabetes mellitus, Hgb of 11 g/dL or less, and CKD not on dialysis. Patients in 1 arm were treated with darbepoetin to a target Hgb of 13 g/dL, and those in the other arm received darbepoetin only if Hgb fell below 9 g/dL. Risks for 2 end points were not significantly different between arms: death or a cardiovascular event (hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.94 to 1.17; p=0.41) and death or ESRD (HR=1.06; 95% CI, 0.95 to 1.19; p=0.29). However, fatal or nonfatal stroke was significantly increased among patients randomized to the higher Hgb target (HR=1.92; 95% CI, 1.38 to 2.68; p<0.001). Multivariate analysis found no statistically significant relationship of increased stroke risk to any baseline characteristic; to effects on blood pressure, Hgb, or platelet count; or to darbepoetin dose. A 2012 meta-analysis by Vinhas et al included only large RCTs (N >500) with a minimum duration of 1 year. Outcomes of interest were vascular access thrombosis, stroke, progression to ESRD, and all-cause mortality. Five trials (7902 patients), including the CHOIR, CREATE, NHCT, and TREAT trials, were identified. Mean or median follow-up duration ranged from 14 to 36 months. These trials demonstrated that higher Hgb targets were associated with increased risks of vascular access thrombosis and stroke but not with progression to ESRD or all-cause mortality.

In 2012, the American Society of Nephrology released its evidence-based recommendations for the "Choosing Wisely" campaign to improve patient care and resource use. Citing the evidence reviewed here, the society included the following among its top 5 recommendations: "Do not administer erythropoiesis-stimulating agents to CKD patients with hemoglobin levels ≥10 g/dL without symptoms of anemia."

A 2014 Cochrane review included 8 trials (total N=2051) that compared darbepoetin with epoetin (alfa or beta) in adults with anemia due to CKD. No statistically significant differences were observed in random effects meta-analyses of final Hgb or mean change in Hgb level, overall mortality, cardiovascular events or cardiovascular mortality, blood transfusions, or adverse events due to hypertension or vascular access

thrombosis. Risk of bias was rated as moderate to high, and statistical heterogeneity was minimal (I^2=0%) for all outcomes.

pegylated epoetin beta

FDA's 2007 approval of pegylated epoetin beta (Mircera) was based on 6 phase 3, international, open-label, RCTs in patients with anemia due to CKD. In 2 trials (total N=505), patients were not receiving ESA therapy (correction trials), and in 6 trials (total N=1894), Hgb was stable on maintenance ESA therapy (maintenance trials). All but 1 trial (ARCTOS) enrolled dialysis-dependent patients. The primary efficacy outcome in all trials was maintenance of Hgb levels over 24 to 52 weeks, adjusted for baseline Hgb and center, in the intent-to-treat and per protocol patient samples. For this outcome, the trials demonstrated noninferiority of pegylated epoetin beta once or twice monthly to epoetin (alfa or beta) 1 to 3 times weekly (AMICUS, MAXIMA, PROTOS, RUBRA) and to darbepoetin weekly or twice monthly (ARCTOS and STRIATA). In the correction trials (ARCTOS and AMICUS), median time to response was longer in the pegylated epoetin beta groups (43 days and 57 days, respectively) compared with the darbepoetin (29 days) and epoetin (31 days) groups.

Although target Hgb ranges in these trials included levels that have since been associated with increased mortality in CKD (ie, >11 g/dL), FDA's summary review of safety (based on 1789 pegylated epoetin betatreated patients [64% for >1 year] and 948 ESA-treated patients) reported that mortality was similar between the 2 groups (10% vs 11%, respectively). Incidence of serious adverse events also was similar between groups (37% vs 40%, respectively), although serious bleeding events (5.2% vs 4%), serious gastrointestinal bleeding events (1.2% vs 0.2%), and thrombocytopenia less than $100x10^9$ platelets/L (7.5% vs 4.4%) occurred more commonly in pegylated epoetin beta-treated patients. FDA reviewers attributed these imbalances to the greater proportion of patients on hemodialysis in the pegylated epoetin beta group (84% vs 80%), and considered the risks of hemorrhage and thrombocytopenia similar to or slightly increased above that for other ESAs. Trials excluded patients with poorly controlled hypertension; 27% of enrolled patients required increases in antihypertensive therapy.

A 2014 Cochrane review included random effects meta-analyses of the 5 trials in dialysis patients reported no statistical between-group differences in final Hgb level (compared with epoetin), overall mortality, blood transfusions, or adverse events due to hypertension or vascular access thrombosis. In the STRIATA trial, final Hgb level was statistically higher in the pegylated epoetin group compared with the darbepoetin group (mean difference, 0.30 g/dL [95% CI, 0.05 to 0.55]). Risk of bias was rated as low to moderate, and statistical heterogeneity was low to moderate (I^2 range, 0%-34%).

Since FDA approval, subsequent short-term trials (24-40 weeks; total N=841) have replicated the findings of the pivotal correction trials in patients on hemodialysis and not on hemodialysis, and of the pivotal maintenance trials in patients on hemodialysis. Of 324 non-dialysis patients in the ARCTOS correction trial, 296 (96%) entered a 24-week extension study. Patients who responded to pegylated epoetin beta biweekly (n=145) were re-randomized 1:1 to biweekly or monthly dosing to maintain Hgb between 11 to 13g/dL.

Mean (SD) Hgb levels were 11.9 (0.9) g/dL, 11.7 (0.9) g/dL, and 11.9 (1.0) g/dL in the pegylated epoetin biweekly, pegylated epoetin monthly, and darbepoetin (weekly or biweekly) groups (n=151), respectively. Within-patient variation in Hgb levels was similar across groups.

Section Summary
Three ESAs are FDA-approved for use in patients with CRF: epoetin alfa, pegylated epoetin beta (pegylated epoetin beta), and darbepoetin alfa. Placebo-controlled clinical trials have established that epoetin alfa and darbepoetin alfa effectively increase Hgb concentrations and decrease the need for blood transfusions. Evidence does not support an improvement in other clinical outcomes such as mortality, morbidity, functional status, or quality of life (QOL). Some trials and a meta-analysis published in 2012 have reported increased cardiovascular events and/or increased mortality in patients treated with ESAs. These trials generally have treated to a Hgb of 12g/dL or higher. The optimal target Hgb is unclear, and it is uncertain whether treating to lower Hgb levels avoid the increase in adverse events. Both peginesatide and pegylated epoetin beta have been compared with other ESAs in randomized trials. Peginesatide has shown noninferiority to epoetin for adult patients with CRF on dialysis. There are no trials reporting benefit for peginesatide for other indications or in pediatric patients with kidney disease. Currently, peginesatide is unavailable and should not be used. Pegylated epoetin beta has shown noninferiority to epoetin and darbepoetin for correcting or maintaining Hgb levels in RCTs of patients on dialysis or not on dialysis. In meta-analyses of trials in dialysis patients, no statistical differences were reported in overall mortality, blood transfusions, or adverse events due to hypertension or venous access thrombosis.

Oncology
epoetin and darbopoetin
In 1993, FDA approved Procrit/Epogen (epoetin alfa) to treat anemia in patients receiving cancer chemotherapy based on data from 2 multicenter randomized placebo-controlled, double-blind clinical trials; 1 enrolled 344 adult patients and the second enrolled 222 pediatric patients, and an additional pooled analysis of 6 smaller double-blind RCTs enrolled a total of 131 patients. Patients in all 3 studies received at least 12 weeks of concurrent chemotherapy and were randomized (1:1) to receive Procrit/Epogen or placebo subcutaneously for 12 weeks. Overall, the data showed a reduction in the proportion of patients requiring blood transfusion during the second and third months of epoetin treatment.

The approval of Aranesp (darbepoetin alfa) in 2002 for the treatment of anemia associated with cancer chemotherapy was based on demonstration of a significant reduction in the proportion of patients transfused during chemotherapy from week 5 through the end of treatment. Study 980297, a phase 3, double-blind, placebo-controlled randomized (1:1) multicenter, multinational trial of darbepoetin alfa enrolled 314 anemic patients with previously untreated non-small cell or small cell lung cancer receiving at least 12 weeks of platinum-containing chemotherapy.

After the first approval of an ESA for treatment of chemotherapy-associated anemia in 1993, additional data became available regarding increased risks of mortality and possible tumor promotion from the use of

ESAs. Increased mortality has been observed in patients with cancer (BEST, ENHANCE, 20000161, EPO-CAN-20 studies) when ESA treatment strategies were designed to achieve and maintain Hgb levels above 12 g/dL. In addition, ESA treatment strategies intended to achieve and maintain Hgb levels above 12 g/dL have demonstrated poorer tumor outcomes (BEST, ENHANCE, DAHANCA studies). More recently, a 2009 meta-analysis using individual patient data on 13,933 subjects from 53 RCTs reported significantly greater on-study mortality (HR=1.17; 95% CI, 1.06 to 1.30) and poorer survival to end of follow-up (HR=1.06; 95% CI, 1.00 to 1.12), with little heterogeneity between trials. Results were qualitatively similar when the analysis was limited to 10,441 patients receiving concurrent chemotherapy in 38 trials, and there was little evidence for a difference between trials of patients receiving different chemotherapy regimens.

Data from multiple trials, consistent with data presented to ODAC in May 2004, led to revised product labeling with broader and more detailed warnings against ESA treatment strategies targeting Hgb levels above 12 g/dL. More recent data, including the individual patient data meta-analysis summarized earlier, suggested that factors such as the planned Hgb ceiling for stopping ESA therapy had little influence on increased mortality resulting from ESA treatment. Although risks of Hgb targets greater than needed to avoid transfusions are now well-established, data from adequate, well-controlled studies employing recommended ESA doses and Hgb targets are as yet insufficient to assess effects on survival or tumor promotion. The only data provided to FDA which used the recommended dose and Hgb target was from Amgen Study 20010103, which demonstrated significantly shorter survival in cancer patients receiving ESAs compared with those supported by transfusion alone. However, this study was not adequately designed to assess effects on tumor promotion or on thrombotic risks.

Despite these caveats, data from available studies were sufficient for FDA to reassess the safety of ESAs in patients with cancer and to re-evaluate the net clinical benefit of ESAs in this setting.

Results of the updated AHRQ comparative effectiveness review (2013) were consistent with those reported in 2006. Among patients receiving chemotherapy and/or radiotherapy for malignancy, use of ESAs to treat anemia reduced the risk of transfusion and increased the risk of thromboembolic events and on-study mortality. Both thromboembolic events and on-study mortality were reduced (but not eliminated) when ESA treatment was initiated at Hgb less than 10 g/dL. Although the reviewed evidence incorporated higher baseline and target Hgb levels than those currently recommended, sensitivity analyses suggested that these findings were robust. QOL, as assessed by the Functional Assessment of Cancer Therapy (FACT) fatigue scale, was improved in patients receiving ESAs, but the magnitude of improvement was less than the minimal clinically important difference of 3 points. Fifteen included trials did not support an association between ESA use and tumor response or progression; meta-analysis was not possible due to varying outcome definitions.

The AHRQ update incorporated the individual patient data meta-analysis previously described. Despite differing inclusion criteria and methodologies, additional analyses of these data by Tonia et al (2012) supported results of the updated AHRQ review.

A 2014 meta-analysis examined the incidence of thromboembolic events in patients with solid and hematologic cancers who received ESAs, and found a similar result. Gao et al pooled 51 RCTs (12,115 patients) and reported a 75% increased odds of thromboembolic events among patients receiving ESAs (pooled odds ratio, 1.75; 95% CI, 1.50 to 2.05; I^2=0%).

pegylated epoetin beta

Pegylated epoetin beta is not FDA-approved for anemia due to cancer chemotherapy, and Hoffmann-LaRoche, manufacturer of pegylated epoetin beta, has not sought this indication. A 2010 phase 2, open-label RCT by Gascon et al compared 3 doses of subcutaneous pegylated epoetin beta with subcutaneous darbepoetin in 153 patients who were receiving first-line chemotherapy for stage 3B or 4 non-small-cell lung cancer. Baseline Hgb at screening was 11 g/dL or less. Pegylated epoetin beta was administered every 3 weeks, and darbepoetin was administered weekly or every 3 weeks. The primary efficacy outcome, mean change from baseline Hgb during weeks 5 to 13, did not differ between groups and indicated inadequate treatment responses in all groups (0.17 g/dL and 0.26 g/dL in the pegylated epoetin beta and darbepoetin groups, respectively). At week 12, the trial was terminated due to more deaths in the 3 pegylated epoetin beta groups compared with the darbepoetin group (29 [25%] of 114 patients vs 4 [10%] of 39 patients, respectively). Post hoc analyses did not convincingly demonstrate that baseline imbalances accounted for the mortality difference.

Section Summary

Epoetin alfa and darbepoetin alfa are approved for patients with anemia associated with concurrent cancer chemotherapy. These ESAs effectively increase Hgb concentrations and decrease the need for blood transfusions in patients with anemia caused by cancer chemotherapy. The evidence does not support an improvement in other clinical outcomes such as mortality, morbidity, functional status, or QOL. Some trials have reported higher thromboembolic events and/or mortality in cancer patients treated with ESAs, and 2 meta-analyses published in 2012 and 2013 also reported increases in mortality and thromboembolic events. Trials that reported increased adverse events have generally treated to a Hgb of 12 g/dL or higher, and adverse events appear to be correlated with higher treatment targets. However, it is unclear whether treating to a lower Hgb reduces or eliminates these adverse events. These concerns over potential harm from ESAs have led FDA to reassess the risk/benefit ratio and to modify the labeled indications. Current FDA labeling recommends against starting ESA therapy in a cancer patient whose Hgb exceeds 10 g/dL.

Pegylated epoetin beta is not FDA-approved for patients with anemia due to cancer chemotherapy. A phase 2 RCT demonstrated increased mortality among patients with advanced non-small cell lung cancer who received pegylated epoetin beta compared with those who received darbepoetin.

Hepatitis C Related Anemia

Standard treatment for hepatitis C infection includes ribavirin, however treatment regimens for hepatitis C are constantly evolving. Anemia related to ribavirin use often is the limiting step in treatment. Options for treatment of ribavirin-related anemia are reduction in the dose of ribavirin and use of ESAs and/or blood

transfusions as needed. However, a reduction in ribavirin dose has been associated with less favorable response rates, and some experts therefore prefer using ESAs to maintain full-dose ribavirin. Evidence on the benefit of using ESAs for this purpose comprises several RCTs, some of which are reviewed next.

At least 2 RCTs randomized patients with hepatitis C and ribavirin-related anemia to epoetin alfa or usual care. The larger of these was conducted by Afdhal et al (2004). This trial included 185 patients with a Hgb level of 12 g/dL or less who received 8 weeks of epoetin alfa at a dose of 40,000 units weekly. Outcomes included the proportion of patients who were able to maintain full-dose treatment with ribavirin, mean Hgb level, and QOL as measured by 36-Tiem Short-Form Health Survey. More patients in the epo group (88%) than in the usual care group (60%, $p<0.001$) were able to maintain full-dose ribavirin. Increase in mean Hgb level also was higher in the epo group (2.2 g/dL) than in the usual care group (0.1g/dL, $p<0.001$). Improvement in QOL was significantly greater for the epo group on 7 of 8 domains, with incremental improvement ranging from 1.3 to 10.0 for patients on epoetin.

A second RCT by Dieterich et al (2003) was similar to the Afdhal trial. Dieterich et al enrolled 64 patients with hepatitis C and ribavirin-related anemia, as defined by Hgb less than 12 g/dL. Patients were followed for 16 weeks and treated with epoetin alfa 40,000 units weekly. Primary end points were ribavirin dose and Hgb level. Mean ribavirin dose decreased less in the epoetin group (-34 mg/d) than in the usual care group (-146 mg/d), but this difference was not statistically significant ($p=0.06$). More patients in the epo group (83%) than in the usual care group (54%, $p=0.02$) were able to maintain full-dose ribavirin. Mean Hgb level was higher in the epo group (13.8 g/dL) than in the usual care group (11.4 g/dL, $p<0.001$).

A third RCT by Shiffman et al (2007) evaluated ESAs for anemia in patients with hepatitis C who were treated with ribavirin. This trial randomized 150 patients to 3 groups at the onset of treatment: (1) ribavirin at standard dose; (2) ribavirin at standard dose plus epoetin alfa; and (3) ribavirin at higher dose plus epoetin alfa. Primary end points were reduction in ribavirin dose and the proportion of patients with a sustained virologic response (SVR). Fewer patients treated with epoetin required dose reduction (10%) compared with patients not treated with epo (40%, $p<0.05$), but the proportion of patients with SVR did not differ between groups.

Section Summary

RCTs of ESAs versus placebo for patients with hepatitis C and ribavirin-related anemia have demonstrated that use of ESAs can improve Hgb levels and allow more patients to maintain treatment at full ribavirin doses. One RCT also reported improvement in QOL for patients treated with ESAs. Improvements in these parameters may lead to health outcome benefits, although no study has reported an improvement in clinical outcomes such as SVR or survival.

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Policy History

Original Effective Date: 08/01/2006
Current Effective Date: 03/21/2018

07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee approval
07/10/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. FDA box warning, lab criteria and the use of Epoetin alpha and Darbepoetin alfa when hgb exceeds 12g/dL is considered not medically necessary was added.
09/03/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. Clinical criteria changed to reflect coverage is only when a cure is not the anticipated outcome in patients with non-myeloid malignancies with anemia. New FDA black box warning update added to rationale.
12/04/2009	Medical Policy Committee approval.

Erythropoiesis Stimulating Agents (ESA's): epoetin alfa (Epogen® and Procrit®), darbepoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®)

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Current Effective Date: 03/21/2018

12/16/2009	Medical Policy Implementation Committee approval. Changed title from Recombinant Human Erythropoietin: Epoetin (Epogen and Procrit) and Darbepoetin (Aranesp) to Erythropoiesis-Stimulating Agents (ESA's): Epoetin (Epogen and Procrit) and Darbepoetin (Aranesp)**.** When Services Are Considered Not Medically Necessary and/or Excluded from Coverage verbiage deleted from the policy. Added an investigational statement for Epoetin Alfa usage for non-FDA approved indications and for off-label usage not indicated in the patient selection criteria. Added investigational statements for Darbepoetin Alfa usage when patient selection criteria are not met and for usage for non-FDA approved indications. Added a third bullet for Epoetin Alfa lab criteria that a target hemoglobin of ≤12g/dL is indicated for all labeled and off-labeled usage.
12/01/2010	Medical Policy Committee approval.
12/15/2010	Medical Policy Implementation Committee approval. No change to coverage.
07/07/2011	Medical Policy Committee approval.
07/20/2011	Medical Policy Implementation Committee approval. Lab values for chronic renal failure was changed to Hct/Hgb levels are less than 30%/10 g/dl prior to initiation of therapy. Added, "or ribavirin and peginterferon alfa with boceprevir or telaprevir" to the third criteria bullet for Epoetin Alfa Selection Criteria- Off Label Usage.
08/19/2011	"Discontinue treatment if (Hct/Hgb levels exceeds ≥ 33%/11g/dL" was added to chronic renal failure patients criteria. "For all labeled usage, a target hemoglobin of ≤ 12g/dL is indicated and should not be exceeded for maintenance or recurrent use" was removed from policy.
05/03/2012	Medical Policy Committee approval.
05/16/2012	Medical Policy Implementation Committee approval. New FDA approved drug Omontys added to the policy. Hgb level as to when to stop therapy has been changed to >11 to match ESI call tree.
02/04/2013	Coding update
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Clarified that the lack of use of Epogen/Procrit prior to Aranesp in cancer patients is Not Medically Necessary. Aesthetic changes throughout. Language clarified to match Pharmacy call tree. No coverage changes.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Removed Omontys from policy.
03/05/2015	Medical Policy Committee review
03/20/2015	Medical Policy Implementation Committee approval. Updated background information, FDA section, and Rationale/Source with the latest scientific information from the association. Changed the title to include Mircera (pegylated epoetin beta). Added patient selection criteria for Mircera.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2019

Erythropoiesis Stimulating Agents (ESA's): epoetin alfa (Epogen® and Procrit®), darbepoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®)

Policy # 00210
Original Effective Date: 08/01/2006
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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0881, J0882, J0885, J0887, J0888, J0890, Q4081
ICD-10 Diagnosis	B18.2 B20 D46.0 D46.1 D46.20 D46.21 D46.22 D46.4 D46.9 D46.A D46.B D46.C D46.Z D47.3 D64.9 N18.1 N18.2 N18.3 N18.4 N18.5 N18.6 N18.9 Z48.290 Z94.81 Z94.84

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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