Clinical Policy Bulletin: Erythropoiesis Stimulating Agents

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Policy

I. Aetna considers erythropoietin therapy (e.g., EPO, Epogen [epoetin alfa], epoetin beta, Procrit, r-HuEPO) and darbepoietin alfa therapy (Aranesp) medically necessary when any of the following selection criteria is met (see Appendix for specific criteria):

A. Anemia from myelodysplastic syndrome; or
B. Anemia of prematurity; or
C. Special circumstance members who will not or cannot receive whole blood or components as replacement for traumatic or surgical loss; or
D. Treatment of anemic members scheduled to undergo high-risk surgery who are at increased risk of or intolerant to transfusions; or
E. Treatment of anemia associated with chronic renal failure, whether or not on dialysis; or
F. Treatment of anemia in members receiving chemotherapy for hepatitis C; or
G. Treatment of anemia of chronic disease other than cancer when an underlying chronic disease associated with anemia has been identified (see Appendix); or
H. Treatment of anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphomas and lymphocytic leukemia; or
I. Treatment of anemia due to zidovudine in HIV-infected members.

II. Adults who are on dialysis due to chronic kidney disease (see appendix for specific criteria).

III. Aetna considers sodium ferric gluconate complex in sucrose injection (Ferrlecit) medically necessary when used as a first line treatment of iron deficiency anemia in members undergoing chronic hemodialysis who are receiving supplemental erythropoietin or darbepoietin therapy.

IV.
Aetna considers erythropoiesis stimulating agents experimental and investigational for all other indications, including the following conditions, because its use in these situations is not supported by the peer-reviewed medical literature (not an all-inclusive list):

- Acute renal injury
- Anemia associated only with radiotherapy
- Anemia associated with the treatment of acute and chronic myelogenous leukemia (AML, CML) or erythroid cancers
- Anemia due to bleeding (other than indications I.D. (high-risk surgery [e.g., colectomy, hip replacement, and knee replacement]) and I.C. (special circumstance members) above)
- Anemia due to cancer treatment in persons with uncontrolled hypertension
- Anemia due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, or bone marrow fibrosis
- Anemia in Castleman's disease
- Anemia in Gaucher's disease
- Anemia in paroxysmal nocturnal hemoglobinuria (PNH)
- Anemia in persons with erythropoietin-type resistance due to neutralizing antibodies
- Anemia of cancer not due to cancer treatment
- Aplastic anemia
- Autonomic dysfunction
- Cardiogenic shock-associated anemia
- Cerebral hypoxia/ischemia
- Cognitive decline in persons with schizophrenia
- Congestive heart failure
- Ehlers Danlos syndrome
- Guillain-Barre syndrome
- Heart failure
- Hemolytic anemia
- Immediate correction of severe anemia
- Ischemic heart disease
- Multiple sclerosis
- Myelofibrosis
- Myocardial infarction
- Physiologic anemia of pregnancy
- Postural tachycardia syndrome
- Prophylactic use to prevent anticancer chemotherapy-induced anemia
- Prophylactic use to prevent tumor hypoxia
- Scoliosis surgery
- Sepsis-associated anemia
- Sickle cell anemia
- Stroke/subarachnoid hemorrhage (except for I.G above)
- Thrombocytopenia
- Traumatic brain injury.
Background

Erythropoiesis Stimulating Agents

Erythropoietin therapy (e.g., EPO, Epogen [epoetin alfa], epoetin beta, Omontys (peginesatide), Procrit, r-HuEPO) is used to stimulate red blood cell (RBC) production in the bone marrow, thereby correcting anemia, minimizing the need for transfusion requirements, and improving the quality of life for patients.

Prior to initiation of therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. According to the literature, transferrin saturation should be at least 20% and ferritin at least 100 ng/ml. In addition, since ferritin is an acute phase reactant, it may be falsely elevated (to the normal range) in iron deficient dialysis patients. Therefore, the best guide for iron supplementation in this group of patients is an iron saturation greater than 20%.

In addition, the patient should have adequate serum folate levels (3.6 to 20 ng/dl) and normal Vitamin B12 levels (reference range varies and must be provided).

According to the United States Food and Drug Administration (FDA)-approved labeling of Procrit, the initial recommended dose of erythropoietin for anemia due to cancer chemotherapy in adults is 150 units/kg 3 times per week, or 40,000 units weekly. For pediatric patients, a starting dose of 600 Units/kg (maximum 40,000 units) is recommended. The labeling recommends reducing the dose by 25% when the hemoglobin approaches 12g/dL, or the hemoglobin increases by more than 1 g/dL in any 2-week period. The labeling recommends that the dose be withheld if the patient's hemoglobin exceeds 12 g/dL, until the hemoglobin falls below 11 g/dL, at which point the dose should then be restarted at 25% below the previous dose. For persons receiving erythropoietin 3 times per week, the labeling recommends that the dose of erythropoietin be increased to 300 units/kg 3 times per week if the response is not satisfactory (i.e., there is no reduction in transfusion requirements or a rise in hemoglobin) after 8 weeks to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for transfusions and not to exceed 12 g/dL. For persons receiving erythropoietin on a weekly dosing schedule, the dose should be increased to 60,000 units weekly in adults (900 units/kg in children) if response is not satisfactory (i.e., if hemoglobin fails to increase by 1 g/dL after 4 weeks of therapy) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for transfusions not to exceed 12 g/dL.

According to the FDA-approved labeling of Procrit, the recommended range for the starting dose of erythropoietin alpha for chronic renal failure is 50 to 100 units/kg 3 times weekly for adult patients. The recommended starting dose for pediatric patients on dialysis is 50 units/kg 3 times a week. A Cochrane review by Cody et al (2005) found that there is no significant difference between once-weekly versus thrice-weekly subcutaneous administration of rHuEPO for patients with chronic renal failure on dialysis. According to the literature, dosing should be discontinued if the hematocrit has not increased within 16 weeks, indicating a non-responder. Accepted guidelines state that dosage should be decreased if the hematocrit increases by more than 4 g/dL in any 2-week period. Dosing is adjusted after 8 weeks and at monthly intervals thereafter as necessary to maintain a hematocrit of 30 to 36%. The FDA-approved labeling for Procrit states that the dose of erythropoietin should be reduced as the hemoglobin approaches 11 g/dL or increases by more than 1 g/dL in any 2-week period. The dose should be adjusted for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion and not to exceed 11 g/dL. The labeling states that the dose of erythropoietin should be increased if the hemoglobin does not increase by 2 g/dL after 8 weeks of therapy, and the hemoglobin remains at a level not sufficient to avoid the need for a transfusion. The labeling states that the maintenance
dose of erythropoietin should be individually titrated to achieve and maintain the lowest hemoglobin sufficient to avoid the need for transfusions and not to exceed 11 g/dL.

The FDA-approved labeling for Procrit states that increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 11 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%. The labeling states that, if the increase in hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate, the dose of erythropoietin may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

There is a lack of reliable evidence that one brand of erythropoietin alpha (Procrit or Epogen) is more effective than another brand. In addition, there is a lack of reliable evidence that darbepoetin (Aranesp) is more or less effective than erythropoietin alpha for darbepoetin's established indications.

Recent data indicate that about half of patients undergoing dialysis in the United States have their hemoglobin levels maintained at values above the maximum target (12 g/dL that was specified in the product labeling for erythropoietin analogs at the time the study was performed (Steinbrook, 2007). Some investigators have posited that maintaining higher hemoglobin levels may benefit patients' quality of life. However, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study found that maintaining higher hemoglobin levels increases patients' risk of serious and life-threatening cardiovascular complications, including death (Singh et al, 2006). The CHOIR study found that targeting a hemoglobin level of 13.5 g/dL (as compared with 11.3 g/dL) in patients with chronic kidney disease who did not yet need dialysis was associated with a significantly increased risk of a composite end point of death, myocardial infarction, hospitalization for congestive heart failure without renal-replacement therapy, and stroke. On November 16, 2006, the day the CHOIR study was published, the FDA issued a public health advisory to "underscore the importance of following the currently approved prescribing information" by raising hemoglobin levels no higher than 12 g/dL (FDA, 2006; Steinbrook, 2006).

More recently, the FDA (2011) announced that, for patients on dialysis, erythropoiesis-stimulating agent (ESA) therapy can start when the hemoglobin level is less than 10 g/dL. But, if the hemoglobin level approaches or goes over 11 g/dL, the dose of the drug should be lowered or therapy stopped. FDA's announcement applies to patients with early-stage kidney failure as well as those on dialysis, the treatment for late-stage kidney failure. The previous labeling of ESAs recommended keeping patients' hemoglobin levels between 10 g/dL and 12 g/dL. The new label does away with that specific target range, stating only that physicians should initiate ESAs if patients' hemoglobins fall below 10 g/dL. This labeling change was prompted by studies that have found that hemoglobin levels greater than 11 g/dL of blood increase the risk of stroke, heart attack, heart failure and thromboembolism and haven't been proven to provide any additional benefit to patients. The revised labeling of ESAs states that for patients with chronic kidney disease not on dialysis, ESA therapy can be started when the hemoglobin level is less than 10 g/dL. However, the goal of treatment should not be to increase hemoglobin levels to 10 or more g/dL. The FDA recommends that, if the hemoglobin level exceeds 10 g/dL, the dose of ESA should be reduced or interrupted. For patients on dialysis, ESA therapy can start when the hemoglobin level is less than 10 g/dL. But, if the
hemoglobin level approaches or goes over 11 g/dL, the dose of the drug should be lowered or therapy stopped, the FDA said.

The FDA was notified in February 2007 of the preliminary results of a 681-patient, multi-center, randomized, open-label, non-inferiority study of erythropoietin alpha compared with the standard of care in adult patients undergoing elective spinal surgery. Erythropoietin alpha was administered according to the dosage and administration section of the label for pretreatment hemoglobin values greater than 10 and less than 13 g/dL. The frequency of deep venous thrombosis in patients treated with erythropoietin alpha was 4.7% (16 patients), more than twice that of patients who received usual blood conservation care (frequency of 2.1%, 7 patients).

The FDA-approved labeling for erythropoietin analogs has revised product labeling that includes updated warnings, a new boxed warning, and modifications to the dosing instructions (FDA, 2007). The new boxed warning advises physicians to monitor hemoglobin and to adjust the erythropoietin analogs dose to maintain the lowest hemoglobin level needed to avoid the need for blood transfusions. The labeling states that physicians and patients should carefully weigh the risks of erythropoietin analogs against transfusion risks.

In 2007, the FDA ordered changes to the labeling of ESAs, restricting their use. The FDA instructed manufacturers to change the labeling to reflect three major changes: the drugs are "not indicated for those receiving myelosuppressive therapy when the anticipated outcome is cure"; therapy should not be initiated at hemoglobin levels of 10 g/dL and above; and doses should be withheld if hemoglobin levels exceed a level needed to avoid transfusion. The black-box warnings for ESAs were updated with information on the increased risk for death and tumor progression in patients with early breast cancer and cervical cancer. The warnings note that ESAs pose higher risks when dosed to achieve hemoglobin levels of 12 g/dL or higher, and risks at lower hemoglobin targets have not been excluded. Accordingly, physicians are advised to use the lowest dose needed to avoid RBC transfusions. Previous warnings have highlighted the risks for patients with non-small-cell lung, head and neck, and lymphoid cancers.

Aranesp (darbepoetin alfa), also known as novel erythropoiesis stimulating protein (NESP), is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary cells by recombinant DNA technology. This FDA-approved drug stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. Erythropoietin interacts with progenitor stem cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure, and erythropoietin deficiency is the primary cause of their anemia. Aranesp is approved by the FDA for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis. In addition, the U.S. Pharmacopoeial Convention concluded that chemotherapy-induced anemia is an accepted indication for darbepoetin alfa. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp. Aranesp has an approximately 3-fold longer terminal half-life than Epoetin alfa when administered by either the IV or SC route as a single weekly injection. The dose should be started and slowly adjusted based on hemoglobin levels. The dose should be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dL.

Erythropoiesis stimulating agents have not been proven to be effective for the treatment of aplastic anemia. Erythropoietin levels are markedly elevated in most patients with aplastic
anemia. Guidelines from the British Society of Haematology (2002) state that the routine use of erythropoietin for aplastic anemia is "not recommended." The guidelines note the limitations of evidence for erythropoietin in aplastic anemia. In addition, the guidelines note that erythropoietin has the potential for inducing severe and sudden worsening of anemia due to red cell aplasia from anti-erythropoietin antibodies. The guidelines also note that there is a potential for toxicity when erythropoietin is used in combination with other drugs used routinely to treat aplastic anemia, such as cyclosporin.

Several randomized controlled trials (RCTs) have examined the effectiveness of erythropoietin in aplastic anemia. The most recent (Zeng et al, 2006) found that the addition of growth factors (erythropoietin plus G-CSF) to immunosuppressive therapy did not improve outcomes over immunosuppressive therapy alone. An earlier RCT by Bessho et al (1997) compared G-CSF plus erythropoietin to erythropoietin alone, but did not include an appropriate comparison to immunosuppressive therapy, which is the current standard of care for aplastic anemia. Another earlier RCT by Shao et al (1998) compared immunosuppressive therapy to G-CSF plus erythropoietin. Limitations of the study by Shao et al (1998) compared to the most recent study by Zeng et al (2006) include its smaller size and its measurement of only intermediate outcomes (response rates) rather than survival. Both studies are limited by the use of G-CSF with erythropoietin, which does not allow us to isolate the effect of erythropoietin.

The lack of proven effectiveness of erythropoietin in aplastic anemia, coupled with the potential noted by the British Society of Haematology for the sudden and severe worsening of anemia due to red cell aplasia due to the induction of erythropoietin antibodies, plus the synergistic toxic effects of erythropoietin when combined with cyclosporin and other drugs for aplastic anemia, counsel against the use of erythropoietin as a treatment for aplastic anemia.

Several studies have documented an increased risk of venous thromboembolism (VTE) in patients with cancer-associated anemia who are treated with the erythropoietin and darbepoetin. In an updated investigation of safety concerns related to erythropoiesis stimulating agents, Bennett and colleagues (2008) analyzed data from Phase III clinical trials published or presented between January 1993 and January 2007 to assess ESA-associated risks of VTE and mortality. The authors report that anemic patients with cancer who were treated with ESAs had a 1.55-fold increased risk of VTE and a 1.10-fold increased risk of mortality compared with patients who received placebo or standard care.

A number of clinical studies have examined the effect of erythropoietin analogs on cancer progression, apart from its effect on chemotherapy-induced anemia. Clinical observations in patients with multiple myeloma and animal studies have suggested that epoetin has an anti-myeloma effect, mediated via the immune system through activation of CD8+ T cells. Thus, the role of epoetin may go well beyond that of increasing hemoglobin levels in anemic patients, although additional studies are needed to confirm these promising results.

There are other studies, however, which raise suspicion about negative effects of erythropoietin on tumor size and survival in cancer patients (DACEHTA, 2004). In a multi-center, RCT, Leyland-Jones et al (2005) assessed the effect on survival and quality of life of maintaining hemoglobin (Hb) in the range of 12 to 14 g/dL with epoetin alfa versus placebo in women with metastatic breast cancer (MBC) receiving first-line chemotherapy. Eligible patients were randomly assigned to receive epoetin alfa 40,000 units once-weekly or placebo for 12 months. Study drug was initiated if baseline Hb was less than or equal to 13 g/dL or when Hb decreased to less than or equal to 13g/dL during the study. The primary end point was 12-month overall survival (OS). The study drug administration was stopped early in
accordance with a recommendation from the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa. Enrollment had been completed, with 939 patients enrolled (epoetin alfa, n = 469; placebo, n = 470). Most patients had Hb more than 12 g/dL at baseline (median Hb, 12.8 g/dL) or during the study. From the final analysis, 12-month OS was 70% for epoetin alfa recipients and 76% for placebo recipients (p = 0.01). Optimal tumor response and time to disease progression were similar between groups. The reason for the difference in mortality between groups could not be determined from additional subsequent analyses involving both study data and chart review. These researchers concluded that the use of epoetin alfa to maintain high Hb targets in women with MBC, most of whom did not have anemia at the start of treatment, was associated with decreased survival. Additional research is needed to clarify the potential impact of erythropoietic agents on survival when the Hb target range is 10 to 12 g/dL.

In a multicenter, randomized, double-blind, placebo-controlled trial, Wright et al (2007) found decreased OS in anemic patients with advanced non-small-cell carcinoma of the lung (NSCLC) treated with epoetin alpha. In this clinical study, the proposed sample size was 300 patients. Eligible patients were required to have NSCLC unsuitable for curative therapy and baseline hemoglobin (Hgb) levels less than 12 g/dL. Patients were assigned to 12 weekly injections of subcutaneous epoetin alpha or placebo, targeting Hgb levels between 12 and 14 g/dL. The study was intended to evaluate the effect of epoetin administration on quality of life. However, reports of thrombotic events in other trials of erythropoietin analogs prompted an unplanned safety analysis after 70 patients had been randomly assigned (33 to the active arm and 37 to the placebo arm). This revealed a significant difference in the median survival in favor of the patients on the placebo arm of the trial (63 versus 129 days; hazard ratio, 1.84; p = 0.04). Because of the poorer outcomes in the erythropoietin-treated patients, the Steering Committee closed the trial. The authors concluded that this unplanned safety analysis suggested decreased OS in patients with advanced NSCLC treated with epoetin alfa.

Randomized controlled clinical studies of the use of erythropoietin analogs in other types of cancer (head and neck cancer, lung cancer, lymphoproliferative disorders) have similarly found no improvements in progression-free survival or OS (Hedenus et al, 2005).

Interim results from the Danish Head and Neck Cancer Study Group trial (DAHANCA 10), an open-label, randomized trial that compared radiation therapy alone to radiation plus darbepoetin in treatment of advanced head and neck cancer found that 3-year loco-regional control was significantly worse for patients in the darbepoetin arm (p = 0.01) and OS favored those not treated with Aranesp, but the difference was not statistically significant (FDA, 2007). The trial was terminated December 2006. Results similar to the DAHANCA 10 study -- increased tumor progression and decreased survival -- were reported by Henke et al at the May 4, 2004, meeting of the FDA's Oncologic Drugs Advisory Committee.

In January 2007 the FDA was notified of the results of a 989-patient, multi-center, double-blind, randomized, placebo-controlled study of darbepoetin in anemic cancer patients who are not receiving chemotherapy (FDA, 2007). The target hemoglobin in the darbepoetin treatment group was 12 g/dL. The study results provided to the FDA show darbepoetin did not reduce the need for RBC transfusions and showed an increase in mortality in patients receiving Aranesp compared to those receiving placebo (hazard ratio 1.25; 95% confidence interval [CI]: 1.04 to 1.51).

The FDA was notified in February 2007 of the final results of a double-blind, placebo controlled study to evaluate whether use of epoetin alpha in anemic NSCLC patients not on chemotherapy improved their quality of life (FDA, 2007). The epoetin alfa dose was titrated to
maintain a hemoglobin level of 12 to 14 g/dL; epoetin alfa was dosed at 40,000 IU every week. The study was terminated early when the data safety monitoring committee determined that the median time to death was 68 days in the epoetin alfa arm versus 131 days in the placebo arm ($p = 0.040$) and the majority of deaths were due to disease progression. Also treatment with epoetin alfa did not significantly reduce the need for transfusion or improve the quality of life.

In February 2007, the FDA was notified by Roche that it was suspending a study of a new ESA because of safety concerns (FDA, 2007). The study was a multi-center, randomized, dose-finding assessment of a pegylated epoetin beta product in anemic patients with Stage IIIB or IV NSCLC who were receiving first line chemotherapy. Three dosing regimens of the investigational drug were being compared with Aranesp (given according to an FDA-approved dosing regimen). The dose of pegylated epoetin beta was titrated to maintain the hemoglobin level between 11 and 13 g/dL. An interim analysis, after randomization of 153 patients, demonstrated a numerical imbalance in the number of deaths across the 4 arms of the study.

Based on the results of a recent clinical trial of darbepoetin in cancer-related anemia, National Comprehensive Cancer Network (NCCN) updated its guidelines to recommend against the administration of erythropoetin to patients with cancer related anemia similar to the darbepoetin trial conducted by Amgen (NCCN, 2007). The NCCN panel added a statement to the “Adverse Effects of Erythropoietic Therapy” section of the guidelines, stating that, until new research evidence changes current benefit/risk estimates, physicians should be advised not to administer erythropoetin to patients similar to those in the Amgen trial.

Regarding use of erythropoietin analogs as a treatment for cancer, a technology assessment by the Danish Centre for Evaluation and Health Technology Assessment (DACEHTA, 2004) concluded: “At present there is not sufficient evidence that EPO [erythropoietin] treatment has an effect on the cancer disease itself. Therefore, EPO treatment should not be regarded as a treatment of cancer as such, but rather as a treatment of the side effects of the chemotherapy.”

An assessment by the National Institute for Health and Clinical Excellence (NICE, 2008) of erythropoietin analog therapy for cancer chemotherapy induced anemia recommended that erythropoietin only be used as part of clinical trials that are constructed to generate robust and relevant data in order to address the gaps in the currently available evidence. The assessment reported that some studies had shown benefits with erythropoietin in terms of improved survival, but that the results of other studies were consistent with a detrimental effect. The assessment also noted that there are biologically plausible reasons to suggest possible growth-enhancing effects of erythropoietin on some tumors. The assessment therefore concluded that the true effect of erythropoietin on survival remains unknown. The assessment noted that clinical trials examining the effects of erythropoietin on various measures of health-related quality of life had significant methodological weaknesses. Although most studies suggested that erythropoietin improved health-related quality of life, the additional benefits over standard care (i.e., blood transfusions and iron therapy where indicated) were small. The assessment found that the benefits of erythropoietin in reducing the need for blood transfusions were modest: in trials comparing erythropoietin therapy to standard care involving blood transfusions, erythropoietin therapy reduced the requirement for blood transfusions by approximately 1 unit per patient overall. The assessment also reported that fatigue in patients with cancer has a number of potential contributory factors, and that it is difficult in individual cases to determine the exact contribution of anemia to this symptom.
Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted the CMS to review its coverage of erythropoietin analog therapy. CMS (2007) determined that erythropoietin analog therapy is not reasonable and necessary for the following clinical conditions, either because of a deleterious effect of erythropoietin analogs on the underlying disease or because the underlying disease increases their risk of adverse effects related to erythropoietin analog use. These conditions include:

- Anemia due to cancer treatment if patients have uncontrolled hypertension;
- Any anemia associated only with radiotherapy;
- Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
- Patients with erythropoietin-type resistance due to neutralizing antibodies;
- Prophylactic use to prevent chemotherapy-induced anemia;
- Prophylactic use to reduce tumor hypoxia;
- The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers; and
- The anemia of cancer not related to cancer treatment;

In a phase III, multi-center, randomized, double-blind, placebo-controlled study, Smith and colleagues (2008) examined the effects of darbepoetin alpha (DA) for the treatment of anemia in patients with active cancer not receiving or planning to receive chemotherapy or radiotherapy. Patients were administered placebo or DA 6.75 microg/kg every 4 weeks (Q4W) for up to 16 weeks with a 2-year follow-up for survival. Patients who completed 16 weeks of treatment could receive the same treatment as randomized Q4W for an additional 16 weeks. The primary end point was all occurrences of transfusions from weeks 5 through 17; safety end points included incidence of adverse events and survival. The incidence of transfusions between weeks 5 and 17 was lower in the DA group but was not statistically significantly different from that of placebo. Darbepoetin alpha was associated with an increased incidence of cardiovascular and thromboembolic events and more deaths during the initial 16-week treatment period. Long-term survival data demonstrated statistically significantly poorer survival in patients treated with DA versus placebo (p = 0.022). This effect varied by baseline co-variates including, sex, tumor type, and geographic region; statistical significance diminished (p = 0.12) when the analysis was adjusted for baseline imbalances or known prognostic factors. The authors concluded that DA was not associated with a statistically significant reduction in transfusions. Shorter survival was observed in the DA arm; thus, this study does not support the use of ESA in this subset of patients with anemia of cancer.

The Centers for Medicare and Medicaid Services (CMS, 2007) has developed evidence based guidelines for dosing of erythropoietin analog therapy in persons with end-stage renal disease. CMS issued a final policy, effective April 2006, that, for claims for erythropoietin analog therapy in persons with hematocrit readings above a threshold of 39.0 % (or hemoglobin above 13.0 g/dL), the dose should be reduced by 25 % over the preceding month. Since that time, there have been several publications and an FDA “black box” warning that emphasize the risks facing end-stage renal disease patients who receive large doses of erythropoietin analogues and have higher hematocrits. In response to those concerns, CMS modified its erythropoietin analog therapy monitoring policy to provide greater restrictions on the amount of erythropoietin analogs for which payment is made at higher levels of hemoglobin. Effective for dates of service on or after January 1, 2008, for requests
for payments or claims for erythropoietin analog therapy for end-stage renal disease patients receiving dialysis in renal dialysis facilities and reporting a hematocrit level exceeding 39.0 % (or hemoglobin exceeding 13.0 g/dL) for 3 or more consecutive billing cycles immediately prior to and including the current billing cycle, the erythropoietin analog dose for which payment may be made shall be reduced by 50 % of the reported dose.

The discovery that erythropoietin and its receptor are located in regions outside the erythropoietic system has led to interest in the potential role of epoetin in other tissues, such as the central nervous system (Boogaerts et al, 2005). Bath and Sprigg (2005) report that erythropoietin was neuroprotective in experimental stroke and increased functional recovery, effects possibly mediated by inhibiting apoptosis in the penumbra. They note that, in a small clinical trial, erythropoietin was well-tolerated in stroke patients. Erythropoietin for stroke is currently being assessed in Phase II clinical trials. Bath and Sprigg (2005) reported that derivatives of erythropoietin which do not alter red cell kinetics but retain their neuroprotective activity have been developed, but clinical studies of these have yet to be reported.

However, more recent evidence suggests that erythropoiesis stimulating agents may increase stroke risk. The FDA (2008) stated that erythropoietin may carry heightened mortality risk when used to improve functional outcomes in stroke patients. In a clinical trial conducted in Germany, patients with acute ischemic stroke who received intravenous Eprex brand of erythropoietin (40,000 units daily for 3 days) were more likely to die within 90 days than were those on placebo (16 % versus 9 %). In particular, death from intracranial hemorrhage occurred in 4 % of Eprex recipients and 1 % of placebo recipients. The FDA noted, however, that the dose used was "considerably higher" than the erythropoietin doses approved for the treatment of anemia.

Erythropoiesis stimulating agents have not been proven to improve outcomes in persons with heart failure and anemia. In the randomized, double-blind, placebo-controlled Study of Anemia and Heart Failure Trial (STAMINA-HeFT), investigators evaluated the effects of treating anemia in patients with heart failure (Ghali et al, 2008). A total of 319 patients with symptomatic heart failure were randomized to placebo or darbepoetin for 52 weeks. The median hemoglobin level in the darbepoetin group increased by 1.5 g/dL from baseline to 12 to 14 weeks of treatment; target hemoglobin concentrations were maintained in the darbepoetin group for the remainder of the study period. At week 27, however, the groups did not differ significantly in mean change from baseline in either exercise duration or New York Heart Association functional class.

The American College of Obstetricians and Gynecologists' (ACOG, 2008) practice bulletin on anemia in pregnancy makes no recommendation for use of erythropoietin in pregnancy (2008). The bulletin states: "Few studies have examined the role of erythropoietin in pregnant patients with anemia." The ACOG practice bulletin cited two randomized controlled clinical studies of erythropoietin plus iron versus iron alone in anemia of pregnancy and postpartum anemia, with contrasting results (citing Breymann et al, 2001; Wagstrom et al, 2007).

Pfeffer and colleagues (2009) stated that anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease (CKD). Although darbepoetin alfa can effectively increase Hb levels, its effect on clinical outcomes in these patients has not been adequately tested. In this study involving 4,038 patients with diabetes, CKD, and anemia, these investigators randomly assigned 2,012 patients to darbepoetin alfa to achieve a Hb level of about 13 g/dL and 2,026 patients to placebo, with rescue darbepoetin alfa when the Hb level was less than 9.0 g/dL. The primary end points were the composite outcomes of death or a cardiovascular event (non-fatal
myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease. Death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo (hazard ratio for darbepoetin alfa versus placebo, 1.05; 95% CI: 0.94 to 1.17; p = 0.41). Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo (hazard ratio, 1.06; 95% CI: 0.95 to 1.19; p = 0.29). Fatal or non-fatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo (hazard ratio, 1.92; 95% CI: 1.38 to 2.68; p < 0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 patients assigned to placebo (p < 0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group. The authors concluded that the use of darbepoetin alfa in patients with diabetes, CKD, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the 2 primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will out-weigh the potential benefits.

The findings by Pfeffer et al (2009) are in agreement with those of the CHOIR study (Singh et al, 2006) as well as the CREATE study (Drüeke et al, 2006). Singh and colleagues reported that targeting a Hb level of 13.5 g/dL (as compared with 11.3 g/dL) in patients with CKD who did not yet need dialysis was associated with a significantly increased risk of a composite end point of death, myocardial infarction, hospitalization for congestive heart failure (without renal-replacement therapy), and stroke. Furthermore, Drüeke and associates found that in patients with stage 3 or stage 4 CKD, early complete correction of anemia (Hb levels of 13.0 to 15.0 g/dL) does not reduce the risk of cardiovascular events.

Ehrenreich et al (2009) stated that many pre-clinical findings and a clinical pilot study suggested that recombinant human EPO provides neuroprotection that may be beneficial for the treatment of patients with ischemic stroke. Although EPO has been considered to be a safe and well-tolerated drug over 20 years, recent studies have identified increased thromboembolic complications and/or mortality risks on EPO administration to patients with cancer or CKD. Accordingly, the double-blind, placebo-controlled, randomized German Multicenter EPO Stroke Trial was designed to evaluate safety and effectiveness of EPO in stroke. This clinical trial enrolled 522 patients with acute ischemic stroke in the middle cerebral artery territory (intent-to-treat population) with 460 patients treated as planned (per-protocol population). Within 6 hours of symptom onset, at 24 and 48 hours, EPO was infused intravenously (40,000 IU each). Systemic thrombolysis with recombinant tissue plasminogen activator was allowed and stratified for. Unexpectedly, a very high number of patients received recombinant tissue plasminogen activator (63.4%). On analysis of total intent-to-treat and per-protocol populations, neither primary outcome Barthel Index on Day 90 (p = 0.45) nor any of the other outcome parameters showed favorable effects of EPO. There was an overall death rate of 16.4% (n = 42 of 256) in the EPO and 9.0% (n = 24 of 266) in the placebo group (OR, 1.98; 95% CI: 1.16 to 3.38; p = 0.01) without any particular mechanism of death unexpected after stroke. The authors concluded that based on analysis of total intent-to-treat and per-protocol populations only, this is a negative trial that also raises safety concerns, particularly in patients receiving systemic thrombolysis.

In a matched case control study, Talving and co-workers (2010) examined if administration of ESA would improve survival following severe traumatic brain injury (sTBI). Patients with sTBI [head Abbreviated Injury Scale (AIS), greater than or equal to 3] receiving ESA while in the surgical intensive care unit (n = 89) were matched 1 to 2 (n = 178) by age, gender,
mechanism of injury, Glasgow Coma Scale, presence of hypotension on admission, Injury Severity Score, AIS for all body regions, and presence of anemia with patients who did not receive the agent. Each case's controls were chosen to have surgical intensive care unit length of stay more than or equal to the time from admission to first dose of ESA. The primary outcome measure in this study was mortality. Cases and controls had similar age, gender, mechanisms of injury, incidence of hypotension, Glasgow Coma Scale on admission, Injury Severity Score, and AIS for all body regions. Although the ESA-treated patients experienced protracted hospital length of stay and comparable surgical intensive care unit free days, they demonstrated a significantly lower in-hospital mortality in comparison to controls at 7.9% versus 24.2%, respectively (OR: 0.27; 95% CI: 0.12 to 0.62; p = 0.001). The authors concluded that administration of ESA in sTBI is associated with a significant in-hospital survival advantage without increase in morbidity. They stated that prospective, large, randomized controlled trials are needed to validate these findings.

In an editorial that accompanied the afore-mentioned study, Velmahos (2010) stated that the results serve more to provoke questions than provide answers. One of the questions is that "ESA was administered subcutaneously, a method with notorious unreliable absorption among critically ill patients. How do the authors assure us about adequate levels of the drug? If drug levels are inadequate in the blood stream and organ tissues, how can we accept causation between ESA and the purported outcome improvement?". Velmahos also noted that "[n]o information is provided about the timing of ESA administration, except that it was administered "within the first 2 weeks". However, according to Figure 2 most deaths also occurred within the first 2 weeks in the no-ESA group. This means that ESA saved patients from relatively early deaths. One should assume that a single injection prevented a patient from dying the next day. What exactly is this powerful quality of ESA that can reverse death so drastically? If the effects act through an amelioration of a rampant post-traumatic cascade, how is it that ESA patients suffered more complications?"

Ehrenreich and colleagues (2007) stated that the neurodegenerative aspects of chronic progressive multiple sclerosis (MS) have received increasing attention in recent years, since anti-inflammatory and immunosuppressive treatment strategies have largely failed. However, successful neuroprotection and/or neuroregeneration in MS have not been demonstrated yet. Encouraged by the multi-faceted neuroprotective effects of rHuEPO in experimental models, these researchers performed an investigator-driven, pilot open-label study (phase I/IIa) in patients with chronic progressive MS. Main study objectives were (i) evaluating safety of long-term high-dose intravenous rHuEPO treatment in MS, and (ii) collecting first evidence of potential efficacy on clinical outcome parameters. A total of 8 MS patients -- 5 randomly assigned to high-dose (48,000 IU), 3 to low-dose (8000 IU) rHuEPO treatment; and, as disease controls, 2 drug-naïve Parkinson patients (receiving 48,000 IU) were followed over up to 48 weeks: A 6-week lead-in phase, a 12-week treatment phase with weekly EPO, another 12-week treatment phase with bi-weekly EPO, and a 24-week post-treatment phase. Clinical and electrophysiological improvement of motor function, reflected by a reduction in expanded disability status scale (EDSS), and of cognitive performance was found upon high-dose EPO treatment in MS patients, persisting for 3 to 6 months after cessation of EPO application. In contrast, low-dose EPO MS patients and drug-naïve Parkinson patients did not improve in any of the parameters tested. There were no adverse events, no safety concerns and a surprisingly low need of blood-lettings. The authors concluded that the findings of this pilot study demonstrated the necessity and feasibility of RCTs using high-dose rHuEPO in chronic progressive MS.
Endre and colleagues (2010) performed a double-blind, placebo-controlled trial to study whether early treatment with erythropoietin could prevent the development of acute kidney injury in patients in 2 general intensive care units. As a guide for choosing the patients for treatment, these researchers measured urinary levels of 2 biomarkers: (i) the proximal tubular brush border enzymes gamma-glutamyl transpeptidase, and (ii) alkaline phosphatase. Randomization to either placebo or 2 doses of erythropoietin was triggered by an increase in the biomarker concentration product to levels above 46.3, with a primary outcome of relative average plasma creatinine increase from baseline over 4 to 7 days. Of 529 patients, 162 were randomized within an average of 3.5 h of a positive sample. There was no difference in the incidence of erythropoietin-specific adverse events or in the primary outcome between the placebo and treatment groups. The triggering biomarker concentration product selected patients with more severe illness and at greater risk of acute kidney injury, dialysis, or death; however, the marker elevations were transient. Early intervention with high-dose erythropoietin was safe but did not alter the outcome. Although these 2 urine biomarkers facilitated early intervention, their transient increase compromised effective triaging. Furthermore, this study showed that a composite of these 2 biomarkers was insufficient for risk stratification in a patient population with a heterogeneous onset of injury.

In a review on the potential of cytokines and growth factors in the treatment of ischemic heart disease, Behar et al (2010) stated that cytokine therapy promises to provide a non-invasive treatment option for ischemic heart disease. Several cytokines mobilize progenitor cells from the bone marrow or are involved in the homing of mobilized cells to ischemic tissue. The recruited cells contribute to myocardial regeneration both as a structural component of the regenerating tissue and by secreting angiogenic or anti-apoptotic factors, including cytokines. To date, RCTs have not reproduced the efficacy observed in pre-clinical and small-scale clinical investigations. Nevertheless, the list of promising cytokines continues to grow, and combinations of cytokines, with or without concurrent progenitor cell therapy, warrant further investigation. In particular, the authors noted that a long-acting EPO analog, darbepoetin alpha, was safely administered to patients with acute myocardial infarction (MI), but provided no functional benefit. The administration of EPO to patients with acute MI continues to be investigated in the ongoing HEBE III and REVEAL clinical trials.

The American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer (Rizzo et al, 2010) stated that for patients undergoing myelosuppressive chemotherapy who have a Hgb level less than 10 g/dL, the Update Committee recommends that clinicians discuss potential harms (e.g., thromboembolism, shorter survival) and benefits (e.g., decreased transfusions) of ESAs and compare these with potential harms (e.g., serious infections, immune-mediated adverse reactions) and benefits (e.g., rapid Hgb improvement) of RBC transfusions. Individual preferences for assumed risk should contribute to shared decisions on managing chemotherapy-induced anemia. The Committee cautions against ESA use under other circumstances. If used, ESAs should be administered at the lowest dose possible and should increase Hgb to the lowest concentration possible to avoid transfusions. Available evidence does not identify Hgb levels greater than or equal to 10 g/dL either as thresholds for initiating treatment or as targets for ESA therapy. Starting doses and dose modifications after response or non-response should follow FDA-approved labeling. Erythropoiesis-stimulating agents should be discontinued after 6 to 8 weeks in non-responders; they should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk myelodysplastic syndromes. Caution should be exercised when using ESAs with
chemotherapeutic agents in diseases associated with increased risk of thromboembolic complications.

Endre et al (2010) performed a double-blind placebo-controlled trial to study whether early treatment with EPO could prevent the development of AKI in patients in 2 general intensive care units. As a guide for choosing the patients for treatment, these researchers measured urinary levels of 2 biomarkers, the proximal tubular brush border enzymes gamma-glutamyl transpeptidase and alkaline phosphatase. Randomization to either placebo or 2 doses of erythropoietin was triggered by an increase in the biomarker concentration product to levels above 46.3, with a primary outcome of relative average plasma creatinine increase from baseline over 4 to 7 days. Of 529 patients, 162 were randomized within an average of 3.5 hrs of a positive sample. There was no difference in the incidence of EPO-specific adverse events or in the primary outcome between the placebo and treatment groups. The triggering biomarker concentration product selected patients with more severe illness and at greater risk of AKI, dialysis, or death; however, the marker elevations were transient. Early intervention with high-dose EPO was safe but did not alter the outcome. Although these 2 urine biomarkers facilitated early intervention, their transient increase compromised effective triaging. Further, this study showed that a composite of these 2 biomarkers was insufficient for risk stratification in a patient population with a heterogeneous onset of injury.

In a systematic review of randomized trials on erythropoietin as a treatment of anemia in heart failure, Kotecha et al (2011) reviewed the effects of ESAs in chronic heart failure. An extensive search strategy identified 11 RCTs with 794 participants comparing any ESA with control over 2 to 12 months of follow-up. Published and additionally requested data were incorporated into a Cochrane systematic review (CD007613). A total of 9 studies were placebo controlled, and 5 were double blinded. Erythropoiesis-stimulating agent treatment significantly improved exercise duration by 96.8 seconds (95% CI: 5.2 to 188.4, p = 0.04) and 6-min walk distance by 69.3 m (95% CI: 17.0 to 121.7, p = 0.009) compared with control. Benefit was also noted for peak oxygen consumption (+2.29 ml/kg/min, p = 0.007), New York Heart Association class (-0.73, p < 0.001), ejection fraction (+5.8%, p < 0.001), B-type natriuretic peptide (-226.9 pg/ml, p < 0.001), and quality-of-life indicators with a mean increase in hemoglobin level of 2 g/dL. There was a significantly lower rate of heart failure-related hospitalizations with ESA therapy (odds ratio 0.56, 95% CI: 0.37 to 0.84, p = 0.005). No associated increase in adverse events or mortality (odds ratio 0.58, 95% CI: 0.34 to 0.99, p = 0.047) was observed, although the number of events was limited. The authors concluded that meta-analysis of small RCTs suggested that ESA treatment can improve exercise tolerance, reduce symptoms, and have benefits on clinical outcomes in anemic patients with heart failure. Moreover, they stated that confirmation requires larger, well-designed studies with careful attention to dose, attained Hb level, and long-term outcomes. This is in agreement with the observations of Lipsic et al (2011) as well as Santilli et al (2011). Lipsic and colleagues (2011) stated that large-scale trials with ESAs are needed to examine the safety and effectiveness of anemia treatment in patients with heart failure. Santilli and associates (2011) stated that further studies are needed to define the magnitude of the problem and establish appropriate therapeutic strategies. It is likely that more reliable data will be derived from an ongoing randomized, double-blind, multi-center study, the RED-HF (Reduction Event with Darbepoetin alfa in Heart Failure), which aims at evaluating morbidity and mortality in a cohort of 2,600 heart failure patients with anemia treated with darbepoetin alfa.

In a prospective, randomized, double-blind, placebo-controlled trial with a dose-escalation safety phase and a single dose (60,000 U of epoetin alfa) efficacy phase, Najjar et al (2011)
evaluated the safety and effectiveness of a single intravenous bolus of epoetin alfa in patients with acute ST-segment elevation myocardial infarction (STEMI). The Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction (REVEAL) trial was conducted at 28 U.S. sites between October 2006 and February 2010, and included 222 patients with STEMI who underwent successful percutaneous coronary intervention (PCI) as a primary or rescue reperfusion strategy. Participants were randomly assigned to treatment with intravenous epoetin alfa or matching saline placebo administered within 4 hours of re-perfusion. Main outcome measure was infarct size, expressed as percentage of left ventricle (LV) mass, assessed by cardiac magnetic resonance (CMR) imaging performed 2 to 6 days after study medication administration (first CMR) and again 12 +/- 2 weeks later (second CMR). In the efficacy cohort, the infarct size did not differ between groups on either the first CMR scan (n = 136; 15.8 % LV mass [95 % CI: 13.3 to 18.2 % LV mass] for the epoetin alfa group versus 15.0 % LV mass [95 % CI: 12.6 to 17.3 % LV mass] for the placebo group; p = 0.67) or on the second CMR scan (n = 124; 10.6 % LV mass [95 % CI: 8.4 to 12.8 % LV mass] versus 10.4 % LV mass [95 % CI: 8.5 to 12.3 % LV mass], respectively; p = 0.89). In a pre-specified analysis of patients aged 70 years or older (n = 21), the mean infarct size within the first week (first CMR) was larger in the epoetin alfa group (19.9 % LV mass; 95 % CI: 14.0 to 25.7 % LV mass) than in the placebo group (11.7 % LV mass; 95 % CI: 7.2 to 16.1 % LV mass) (p = 0.03). In the safety cohort, of the 125 patients who received epoetin alfa, the composite outcome of death, MI, stroke, or stent thrombosis occurred in 5 (4.0 %; 95 % CI: 1.31 % to 9.09 %) but in none of the 97 who received placebo (p = 0.04). The authors concluded that in patients with STEMI who had successful re-perfusion with primary or rescue PCI, a single intravenous bolus of epoetin alfa within 4 hours of PCI did not reduce infarct size and was associated with higher rates of adverse cardiovascular events. Subgroup analyses raised concerns about an increase in infarct size among older patients.

In an editorial that accompanied the afore-mentioned study, Bhatt (20110 stated that `[b]ecause these findings appeared in a blinded trial, they raise further questions about the safety of epoetin alfa in the context of acute MI .... Until compelling data become available to support routine use of these agents in patients with anemia, it would be prudent to minimize their use, especially in patients at high risk for cardiovascular disease or with an acute ischemic syndrome`.

Peginesatide is a new synthetic, pegylated, peptide-based ESA that aids in the formation of RBCs. It works by stimulating the bone marrow to produce more RBCs to reduce the need for transfusions in patients with CKD. Doss and Schiller (2010) stated that peginesatide is a peptide-based ESA for increasing and maintaining Hb. In phase 2 studies, peginesatide increases and maintains target Hb levels in patients with CKD, both those on hemodialysis and those not on hemodialysis; phase 3 trials have recently been completed. The authors discussed unmet needs in the management of anemia of CKD, presented peginesatide attributes, reviewed the results of select peginesatide clinical studies, and discussed the potential value of peginesatide as an alternative anemia management option.

Macdougall et al (2011) examined the safety and effectiveness of peginesatide in correcting renal anemia in a population of 139 non-dialysis CKD patients. Chronic kidney disease patients who were not on dialysis and not receiving treatment with ESAs in the 12 weeks before study drug administration were sequentially assigned to 1 of 10 cohorts; cohorts differed in starting peginesatide dose (different body weight-based or absolute doses), route of administration (intravenous or subcutaneous), and frequency of administration (every 2 or 4 weeks). Across all cohorts, 96 % of patients achieved a Hb response. A dose-response
A relationship was evident for Hb increase. Comparable subcutaneous and intravenous peginesatide doses produced similar Hb responses. Rapid rates of Hb rise and Hb excursions greater than 13 g/dL tended to occur more frequently with every 2-weeks dosing than they did with every 4-weeks dosing. The range of final median doses in the every 4-weeks dosing groups was 0.019 to 0.043 mg/kg. Across all cohorts, 20% of patients reported serious adverse events (1 patient had a possibly drug-related serious event) and 81% reported adverse events (11.5% reported possibly drug-related events); these events were consistent with those routinely observed in this patient population. The authors concluded that the findings of this study suggested that peginesatide administered every 4 weeks can increase and maintain Hb in non-dialysis CKD patients. They stated that additional long-term data in larger groups of patients are required to further elucidate the safety and effectiveness of this peptide-based ESA.

On March 27, 2012, the FDA approved peginesatide (Omontys) to treat anemia in adult dialysis patients who have CKD. Omontys represents the first new FDA-approved and marketed ESA for this condition since 2001. The approval of Omontys was based on 2 randomized, active-controlled, open-label, multi-center clinical trials, which showed the safety and effectiveness of Omontys in patients with CKD who were on dialysis. The trials randomly selected a total of 1,608 patients with Hb levels initially stabilized by ESA to receive either Omontys once-monthly or to continue their current ESA (epoetin) treatment. Results showed that Omontys was as safe and effective as epoetin in maintaining Hb levels within the studies’ pre-specified range of 10 to 12 g/dL. The most common side effects observed in 10% or more of dialysis patients treated with Omontys were arthralgia, diarrhea, hypertension and vomiting.

According to the FDA-approved labeling, Omontys should not be used in patients with CKD who are not receiving dialysis or in patients with cancer-related anemia. Furthermore, it should not be used as a substitute for RBC transfusions in patients who require immediate correction of anemia. Omontys is administered as a once-monthly injection.

On February 24, 2013, the FDA alerted health care providers and patients of a voluntary nationwide recall of all lots of Omontys injection by Affymax, Inc. (Palo Alto, CA) and Takeda Pharmaceuticals Company Limited (Deerfield, IL). The recall is due to reports of anaphylaxis. The FDA stated that until further notice, health care providers should stop using Omontys and return the product to Takeda Pharmaceuticals. According to the companies, serious and fatal hypersensitivity reactions have been reported in some patients receiving their first dose of Omontys, given by intravenous injection. The reactions have occurred within 30 minutes following the dose. There have been no reports of reactions following subsequent dosing, or in patients who have completed their dialysis session. The FDA was notified by Affymax of 19 reports of anaphylaxis from dialysis centers in the United States; 3 of the anaphylaxis cases resulted in death. Other patients required prompt medical intervention and in some cases hospitalization. Some of the reports included patients who were able to be resuscitated by doctors.

MacDougall et al (2013) evaluated the safety and efficacy of peginesatide, as compared with darbepoetin, in 983 such patients who were not undergoing dialysis. In 2 randomized, controlled, open-label studies (PEARL 1 and 2), patients received peginesatide once a month, at a starting dose of 0.025 mg or 0.04 mg/kg of body weight, or darbepoetin once every 2 weeks, at a starting dose of 0.75 μg/kg. Doses of both drugs were adjusted to achieve and maintain Hb levels between 11.0 and 12.0 g per deciliter for 52 weeks or more. The primary efficacy end point was the mean change from the baseline Hb level to the mean level during
the evaluation period; non-inferiority was established if the lower limit of the 2-sided 97.5 % CI was -1.0 g/dL or higher. Cardiovascular safety was evaluated on the basis of an adjudicated composite end point. In both studies and at both starting doses, peginesatide was non-inferior to darbepoetin in increasing and maintaining Hb levels. The mean differences in the Hb level with peginesatide as compared with darbepoetin in PEARL 1 were 0.03 g/dL (97.5 % [CI]: -0.19 to 0.26) for the lower starting dose of peginesatide and 0.26 g/dL (97.5 % CI: 0.04 to 0.48) for the higher starting dose, and in PEARL 2 they were 0.14 g/dL (97.5 % CI: -0.09 to 0.36) and 0.31 g/dL (97.5 % CI: 0.08 to 0.54), respectively. The hazard ratio for the cardiovascular safety end point was 1.32 (95 % CI: 0.97 to 1.81) for peginesatide relative to darbepoetin, with higher incidences of death, unstable angina, and arrhythmia with peginesatide. The authors concluded that the efficacy of peginesatide (administered monthly) was similar to that of darbepoetin (administered every 2 weeks) in increasing and maintaining hemoglobin levels. However, cardiovascular events and mortality were increased with peginesatide in patients with chronic kidney disease who were not undergoing dialysis. They stated that there is a need for additional data to clarify the benefit-risk profile of peginesatide in this patient population.

In an editorial that accompanied the afore-mentioned study, Drueke (2013) stated that "Peginesatide has been recently approved in the United States for patients undergoing hemodialysis, but not for patients who are not receiving hemodialysis. Is there any advantage of using peginesatide rather than the existing ESAs? Less frequent dosing may be an advantage under certain circumstances. Peginesatide does not induce pure red-cell aplasia, but antibody development against this compound, although infrequent, may reduce its efficacy. As with any new class of drugs, prolonged experience and monitoring are necessary. Another important issue is cost. At a time when the prescription of much cheaper, biologically similar ESAs is steadily growing outside the United States, expensive new drugs will be competitive only if proven to result in better patient outcomes. Such outcomes remain to be demonstrated for peginesatide and other new types of ESAs that are in development".

In a review on "Guillain-Barre syndrome", Yuki and Hartung (2012) states that "eculizumab, erythropoietin, and fasudil, which have been used in the treatment of other, unrelated medical conditions, have shown promise in animal models of the Guillain-Barre syndrome, but clinical studies are lacking".

In a review on "Mechanisms and management of retinopathy of prematurity", Hartnett and Penn (2012) stated that "very-low-birth-weight infants are at high risk not only for retinopathy of prematurity but also for subsequent neurodevelopmental impairment. Interest in erythropoietin as a neuroprotective agent is increasing. When administered in preterm infants, erythropoietin was associated with improved cognition in childhood. Laboratory studies have shown that early administration of erythropoietin reduced phase 1 avascularization in both mouse and rat models of oxygen-induced retinopathy. However, retrospective studies have shown an association between erythropoietin and severe oxygen-induced retinopathy in preterm infants. Erythropoietin was also found to promote intravitreal angiogenesis in a transgenic mouse model of oxygen-induced retinopathy. Some investigators have proposed administering erythropoietin early in preterm infants to promote physiologic retinal vascular development and attempt to reduce the risk of development of stage 3 retinopathy of prematurity, but additional studies are needed to determine the window of time for relatively safe administration". The authors concluded that current therapies for severe retinopathy of prematurity focuses on laser therapy as well as visual rehabilitation, and
potential new treatment strategies include targets within oxidative pathways, erythropoietin, and anti-vascular endothelial growth factor agents.

Moebus et al (2013) noted that the AGO-ETC trial compared 5-year relapse-free survival of intense dose-dense (IDD) sequential chemotherapy with epirubicin (E), paclitaxel (T), and cyclophosphamide (C) (IDD-ETC) every 2 weeks versus conventional scheduled epirubicin/cyclophosphamide followed by paclitaxel (EC→T) (every 3 weeks) as adjuvant treatment in high-risk breast cancer patients. These researchers evaluated the safety and effectiveness of epoetin alfa in a second randomization of the IDD arm. A total of 1,284 patients were enrolled; 658 patients were randomly assigned to the IDD-ETC treatment group. Within the IDD-ETC group, 324 patients were further randomly assigned to the epoetin alfa group, and 319 were randomly assigned to the non-ESA control group. Primary efficacy end-points included change in Hb level from baseline to Cycle 9 and the percentage of subjects requiring red blood cell transfusion. Relapse-free survival, overall survival, and intra-mammary relapse were secondary end-points estimated with Kaplan-Meier and Cox regression methods. Except for the primary hypothesis, all statistical tests were 2-sided. Epoetin alfa avoided the decrease in Hb level (no decrease in the epoetin alfa group versus -2.20 g/dL change for the control group; p < 0.001) and statistically significantly reduced the percentage of subjects requiring red blood cell transfusion (12.8 % versus 28.1 %; p < 0.0001). The incidence of thrombotic events was 7 % in the epoetin alfa arm versus 3 % in the control arm. After a median follow-up of 62 months, epoetin alfa treatment did not affect overall survival, relapse-free survival, or intra-mammary relapse. The authors concluded that epoetin alfa resulted in improved Hb levels and decreased transfusions without an impact on relapse-free or overall survival. However, epoetin alfa had an adverse effect, resulting in increased thrombosis.

Kansagara et al (2013) evaluated the benefits and harms of treatments for anemia in adults with heart disease. Data sources included MEDLINE, EMBASE, and Cochrane databases; clinical trial registries; reference lists; and technical advisors. English-language trials of blood transfusions, iron, or ESAs in adults with anemia and congestive heart failure or coronary heart disease and observational studies of transfusion were selected for analysis. Data on study design, population characteristics, Hb levels, and health outcomes were extracted. Trials were assessed for quality. Low-strength evidence from 6 trials and 26 observational studies suggested that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols (combined relative risk among trials, 0.94 [95 % CI: 0.61 to 1.42]; I2 = 16.8 %), although decreased mortality rates occurred in a small trial of patients with the acute coronary syndrome (1.8 % versus 13.0 %; p = 0.032). Moderate-strength evidence from 3 trials of intravenous iron found improved short-term exercise tolerance and quality of life in patients with heart failure. Moderate- to high-strength evidence from 17 trials of ESA therapy found they offered no consistent benefits, but their use may be associated with harms, such as VTE. The authors concluded that higher transfusion thresholds do not consistently improve mortality rates, but large trials are needed. Intravenous iron may help to alleviate symptoms in patients with heart failure and iron deficiency and also warrants further study. Moreover, they stated that ESAs do not seem to benefit patients with mild-to-moderate anemia and heart disease and may be associated with serious harms.

In a Cochrane review, Marti-Carvajal et al (2013) evaluated the clinical benefits and harms of ESAs for anemia in rheumatoid arthritis. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (issue 7 2012), Ovid MEDLINE and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1948 to August
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7, 2012), OVID EMBASE (1980 to August 7, 2012), LILACS (1982 to August 7, 2012), the Clinical Trials Search Portal of the World Health Organization, reference lists of the retrieved publications and review articles. They did not apply any language restrictions. These researchers included RCTs in patients aged 16 years or over, with a diagnosis of rheumatoid arthritis affected by anemia. They considered health-related quality of life, fatigue and safety as the primary outcomes. Two authors independently performed trial selection, risk of bias assessment, and data extraction. They estimated difference in means with 95% CIs for continuous outcomes. They estimated risk ratios with 95% CIs for binary outcomes. These investigators included 3 RCTs with a total of 133 participants. All trials compared human recombinant erythropoietin (EPO), for different durations (8, 12 and 52 weeks), versus placebo. All RCTs assessed health-related quality of life. All trials had high or unclear risk of bias for most domains, and were sponsored by the pharmaceutical industry. Two trials administered EPO by a subcutaneous route while the other used an intravenous route. These researchers decided not to pool results from trials, due to inconsistencies in the reporting of results. Health-related quality of life: subcutaneous EPO -- 1 trial with 70 patients at 52 weeks showed a statistically significant difference in improvement of patient global assessment (median and interquartile range 3.5 (1.0 to 6.0) compared with placebo 4.5 (2.0 to 7.5) (p = 0.027) on a VAS scale (0 to 10)). The other shorter-term trials (12 weeks with subcutaneous EPO and 8 weeks with intravenous administration) did not find statistically significant differences between treatment and control groups in health-related quality of life outcomes. Change in Hb: both trials of subcutaneous EPO showed a statistically significant difference in increasing Hb levels; (i) at 52 weeks (1 trial, 70 patients), intervention Hb level (median of 134, interquartile range 110 to 158 g/L) compared with the placebo group level (median of 112, interquartile range; 86 to 128 g/L) (p = 0.0001); (ii) at 12 weeks (1 trial, 24 patients) compared with placebo (difference in means of 8.00, 95% CI: 7.43 to 8.57). Intravenous EPO at 8 weeks showed no statistically significant difference in increasing hematocrit level for EPO versus placebo (difference in means of 4.69, 95% CI: -0.17 to 9.55; p = 0.06). Information on withdrawals due to adverse events was not reported in 2 trials, and 1 trial found no serious adverse events leading to withdrawals. None of the trials reported withdrawals due to high blood pressure, or to lack of efficacy or to fatigue. The authors concluded that there are conflicting data for ESAs to increase quality of life and Hb level by treating anemia in patients with rheumatoid arthritis. However, this conclusion was based on RCTs with a high-risk of bias, and relies on trials assessing EPO. They stated that the safety profile of EPO is unclear; and future trials assessing ESAs for anemia in rheumatoid arthritis should be conducted by independent researchers and reported according to the CONSORT statements.

Tran et al (2014) noted that ESAs are widely used in treating anemia associated with renal failure. They are also now used peri-operatively to reduce the use of allogeneic blood transfusions (ABTs) in patients undergoing surgery with anticipated high blood loss. Although they can reduce the risks associated with ABT and improve quality of life, the use of ESAs is still associated with adverse effects. These investigators performed a systematic review to examine the current evidence for the safety and effectiveness of peri-operative ESAs use. A search of PubMed and Medline databases has been performed using a combination of search terms including erythropoietin, peri-operative, surgical, safety and efficacy. The authors concluded that current evidence supported the use of peri-operative ESAs to reduce the need for ABT. However, large studies assessing safety in anemic patients with chronic renal disease have found adverse effects including cardiovascular, stroke and thromboembolic events. However, whether these concerns can be conferred onto the surgical population remains to be seen as the peri-operative dosing strategies have been more variable in timing,
dose and duration in comparison with those used for chronic diseases. Moreover, they stated that future research needs to address the questions of optimal dosing strategies in order to maximize the positive effects and minimize adverse events.

Appendix

Specific Criteria for Erythropoietin and Darbepoietin Therapy:

I. Criteria for Initiation of Therapy:

A. For treatment of anemia associated with myelosuppressive anticancer chemotherapy:

1. Erythropoiesis stimulating agents (ESAs) are considered medically necessary where hemoglobin (Hgb) has fallen below 10g/dL and the following criteria are met:

   a. Anemia is secondary to myelosuppressive anticancer chemotherapy for solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia; and
   b. Adequate iron stores have been demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum transferrin saturation (TSAT greater than 20%) within the prior 12 months (Note: For persons with iron deficiency, ESAs may be initiated simultaneously with iron replacement), and
   c. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
   d. ESAs intended to decrease the need for transfusions in persons who will receive chemotherapy for a minimum of 2 months.

2. Providers must confirm compliance and participation in the REMS program that has been implemented for ESA being used in cancer; and

3. The starting dose of ESAs are equal to the following, based upon FDA labeling, or comparable fixed dosing schedules:

   a. Erythropoietin: 150 units/kg 3 times per week, or 40,000 units weekly in adults; 600 units/kg (maximum 40,000 units) weekly for children.
   b. Darbepoetin: 2.25 mcg/kg per week, or 500 mcg every 3 weeks.

B. For treatment of anemia associated with myelodysplastic syndrome, ESAs are considered medically necessary where hemoglobin (Hgb) has fallen below 10g/dL, and the following criteria are met:

1. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin
saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency, ESAs may be initiated simultaneously with iron replacement), and
2. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
3. Bone marrow has less than 15% blasts, and
4. Member has required transfusion of 2 or fewer units of blood per month, and
5. Endogenous serum erythropoietin (EPO) levels are less than or equal to 500 IU/L.

A. For treatment of anemia associated chronic renal failure on dialysis:

1. ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:
   a. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
   b. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
2. The starting dose is equal to the following, based upon FDA labeling, or comparable fixed dose schedules:

   a. Erythropoietin: 50 to 100 units/kg body weight 3 times per week for adults; 50 units/kg body weight for children.

   b. Darbepoetin: 0.45 mcg/kg body weight once-weekly or 0.75 mcg/kg body weight every 2 weeks.

B. For treatment of anemia associated chronic renal failure not on dialysis:

1. ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:
   a. Member has chronic kidney failure (defined as creatinine clearance less than 60 ml/min, or glomerular filtration rate (GFR) less than 60 ml/min/1.73 m2); and
   b. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%)
within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and

c. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
d. The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell (RBC) transfusion; and

e. Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

2. The starting dose is equal to the following, based upon FDA labeling, or comparable fixed dose schedules:

   a. Erythropoietin: 50 to 100 units/kg body weight 3 times per week for adults; 50 units/kg body weight for children.

   b. Darbepoetin: 0.45 mcg/kg body weight once-weekly or 0.75 mcg/kg body weight every 2 weeks.

C. For treatment of anemia related to zidovudine in HIV-infected persons, ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:

   1. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum iron saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and

   2. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and

   3. Endogenous EPO level is less than or equal to 500 IU/L; and

   4. Dose of zidovudine is less than or equal to 4200 mg/week.

D. For treatment of anemia due to chemotherapy (e.g., ribavirin) in persons with hepatitis C, ESAs are considered medically necessary where the Hgb is less than 10 g/dL and the following criteria are met:

   1. Member is receiving interferon or pegylated interferon plus ribavirin; and

   2. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and

   3. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform
activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and

4. Hgb remains below 10 g/dl despite reduction of dose or ribavirin (dose of ribavirin can be decreased by 80 percent of target dose; daily ribavirin dose should not be less than 800 mg).

E. For treatment of anemia of chronic disease other than cancer, ESAs are considered medically necessary where Hgb is less than 10 g/dL and the following criteria are met:

1. An underlying chronic disease has been identified; and
2. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
3. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia.

F. For treatment of anemic members scheduled to undergo high-risk surgery at increased risk of or intolerant to transfusions, ESAs are considered medically necessary in persons with a Hgb less than 13 g/dL.

G. For treatment of anemia of prematurity, ESAs are considered medically necessary when the member has either a birth weight of less than 1,500 grams or a gestational age of less than 33 weeks (medically necessary duration of therapy limited to 6 weeks).

H. For special circumstance members who will not or can not receive whole blood or components as replacement for traumatic or surgical loss, ESAs are considered medically necessary in persons with a Hgb less than 12 g/dL.

II. Criteria for continuation of chronic ESAs in persons with anemia due to myelosuppressive anticancer chemotherapy:

A. The maintenance dose of ESAs are equal to the starting dose if: (i) the hemoglobin remains below 10 g/dL 4 weeks after initiation of therapy; and (ii) the rise in hemoglobin is greater than or equal to 1 g/dL;

B. Continued administration of ESAs are considered not medically necessary if there is a rapid rise in hemoglobin greater than 1 g/dl over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to less than 10 g/dL. Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.

C. For persons whose hemoglobin rises less than 1 g/dl compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains less than 10 g/dL after the 4 weeks of treatment, the recommended FDA label starting dose of ESAs may be increased once by 25%. Continued use of ESAs are considered not medically necessary if the hemoglobin rises less than 1 g/dl compared to pretreatment baseline by 8 weeks of treatment.
III. Criteria for continuation of chronic ESAs for chronic renal failure on dialysis:

A. ESAs should be administered with a Hgb range of 10 g/dL to 11 g/dL (Note: maintenance at a higher Hgb level may be necessary for persons with acute myocardial infarction, angina, orthostatic hypotension, living at an elevation of greater than 6000 feet, or anemia with Hgb below 11 g/dL has significantly interfered with activities of daily living).

B. For hemoglobin less than 10 g/dL, dose may be increased by up to 50 % over the previously administered dose, until the hemoglobin is between 10 g/dL and less than or equal to 11 g/dL. Dosage adjustments may be made as frequently as twice monthly. Exception: If, after increasing the ESA dose, the hemoglobin has risen more than 0.5 g/dL in the past 2 weeks or more than 1 g/dL in the past 4 weeks, decrease dose by 25 % over the previously administered dose.

C. For hemoglobin greater than 11 g/dL and less than or equal to 14 g/dL, the dose should be decreased by 10 % over the previously administered dose. Dose decreases should be made twice-monthly until the hemoglobin is less than or equal to 11 g/dL.

D. For hemoglobin greater than 14 g/dL and less than or equal to 15 g/dL, the dose should be decreased by 25 % over the previously administered dose. Dose decreases can be made twice-monthly or monthly until the hemoglobin falls to less than 11 g/dL.

E. For hemoglobin greater than 15 g/dL, the dose of ESAs should be held and should be restarted at 50 % of the previously administered dose when the hemoglobin is less than or equal to 11 g/dL.

IV. Criteria for continuation of chronic ESAs for chronic renal failure not on dialysis:

A. If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESAs, and use the lowest dose of ESAs sufficient to reduce the need for RBC transfusions.

V. Criteria for continuation of chronic ESAs for other indications:

For persons who meet medical necessity criteria for ESAs, continued ESAs are considered medically necessary for persons with a Hgb less than 11g/dL. (For anemic members scheduled to undergo high-risk surgery, continued ESAs are considered medically necessary where Hgb is less than 13 g/dL).

VI. Discontinuation criteria for ESAs:

A. For indications other than end-stage renal disease, continued ESAs are considered not medically necessary if the member's Hgb has failed to rise by 1 g/dL compared to pre-treatment baseline within 8 weeks of therapy despite appropriate dose escalation.

B. Continued ESAs are considered not medically necessary for myelodysplastic syndrome if transfusion requirements have been reduced by less than 50% after 6 months of therapy.

C. ESAs for each course of chemotherapy for anemic persons with cancer or hepatitis C includes the 8 weeks following the final dose of chemotherapy in a
chemotherapy regimen.

VII. Underlying Causes of Anemia of Chronic Disease: The following conditions have been associated with anemia of chronic disease (Weiss and Goodnough, 2005):

A. Infections (acute and chronic)
   1. Bacterial
   2. Fungal
   3. Parasitic
   4. Viral infections, including human immunodeficiency virus infection

B. Autoimmune
   1. Inflammatory bowel disease
   2. Rheumatoid arthritis
   3. Sarcoidosis
   4. Systemic lupus erythematosus and connective tissue diseases
   5. Vasculitis

C. Cancer
   1. Hematologic
   2. Solid tumor

D. Chronic rejection after solid-organ transplantation

VIII. FDA-Approved Indications and Brands of Erythropoiesis-Stimulating Agents

Note: There is a lack of evidence that one brand of erythropoietin alpha (i.e., Procrit, Epogen) is more effective than another brand. In addition, there is a lack of reliable evidence that darbepoetin is more effective than erythropoietin alpha for darbepoetin’s labeled indications.

<table>
<thead>
<tr>
<th>FDA-Approved Indications</th>
<th>Brands of ESAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of anemia of chronic renal failure</td>
<td>Epogen, Omontys, Procrit, Aranesp</td>
</tr>
<tr>
<td>Treatment of anemia in zidovudine-treated HIV-infected patients</td>
<td>Epogen, Procrit</td>
</tr>
<tr>
<td>Treatment of anemia in cancer patients on chemotherapy</td>
<td>Epogen, Procrit, Aranesp</td>
</tr>
<tr>
<td>Reduction of allogeneic blood transfusion in surgery patients</td>
<td>Epogen, Procrit</td>
</tr>
</tbody>
</table>
IX. Normal Reference Range of Serum Iron and Serum Ferritin:

A. Serum Iron:

Children: 50 to 120 µg/dL  
Men: 65 to 176 µg/dL  
Newborns: 100 to 250 µg/dL  
Women: 50 to 170 µg/dL


B. Serum Ferritin:

Female: 12 to 150 ng/mL  
Male: 12 to 300 ng/mL

Source: Gersten, 2009.

CPT Codes / HCPCS Codes / ICD-9 Codes

_Erythropoietin or darbepoetin therapy:_

Other CPT codes related to the CPB:

96401 - 96417

99601 - 99602

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0881</td>
<td>Injection, darbepoetin alfa, 1 mcg (non-ESRD use)</td>
</tr>
<tr>
<td>J0882</td>
<td>Injection, darbepoetin alfa, 1 mcg (for ESRD on dialysis)</td>
</tr>
<tr>
<td>J0885</td>
<td>Injection, epoetin alfa, (for non-ESRD use), 1,000 units</td>
</tr>
<tr>
<td>J0886</td>
<td>Injection, epoetin alfa, 1000 units (for ESRD on dialysis)</td>
</tr>
<tr>
<td>Q4081</td>
<td>Injection, epoetin alfa, 100 units (for ESRD on dialysis)</td>
</tr>
<tr>
<td>S9537</td>
<td>Home therapy; hematopoietic hormone injection therapy (e.g., erythropoietin,</td>
</tr>
<tr>
<td></td>
<td>G-CSF, GM-CSF); administrative services, professional pharmacy services,</td>
</tr>
<tr>
<td></td>
<td>care coordination, and all necessary supplies and equipment (drugs and</td>
</tr>
<tr>
<td></td>
<td>nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

Modifier EB  Erythropoietic stimulating agent (ESA) administered to treat anemia due to anticancer radiotherapy

Other HCPC codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9213</td>
<td>Injection, interferon, alfa-2a, recombinant, 3 million units</td>
</tr>
</tbody>
</table>
J9214  Injection, interferon, alfa-2b, recombinant, 1 million units
S0145  Injection, pegylated interferon alfa-2a, 180 mcg per ml
S0148  Injection, pegylated interferon alfa-2B, 10 mcg

**ICD-9 codes covered if selection criteria are met:**

042  Human immunodeficiency virus [HIV] disease
079.53  Human immunodeficiency virus, type 2 [HIV-2]
140.0 - 204.92  Malignant neoplasm
238.72 - 238.75  Myelodysplastic syndrome
285.3  Antineoplastic chemotherapy induced anemia
285.21 - 285.29  Anemia of chronic disease [not covered for breast cancer]
585.1 - 585.9  Chronic kidney disease (CKD)
776.6  Anemia of prematurity

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

205.00 - 208.92  Myeloid leukemia, monocytic leukemia, and other specified leukemia
238.71  Essential thrombocytemia
238.76  Myelofibrosis with myeloid metaplasia
272.7  Lipidoses [Gaucher's disease]
280.0 - 280.9  Iron deficiency anemias
281.1 - 281.2  Other vitamin B12 deficiency anemia
282.0 - 282.9  Hereditary hemolytic anemias
283.0 - 283.9  Acquired hemolytic anemias
284.0 - 284.9  Aplastic anemia and other bone marrow failure syndromes
285.1  Acute posthemorrhagic anemia
286.6  Defibrination syndrome
289.83  Myelofibrosis
295.00 - 295.95  Schizophrenic disorders
310.2  Postconcussion syndrome
337.00 - 337.9  Disorders of the autonomic nervous system
340  Multiple sclerosis
348.1  Anoxic brain damage
357.0  Acute infective polyneuritis [Guillain-Barre syndrome]
362.20 - 362.29  Retinopathy of prematurity
410.00 - 414.9  Ischemic heart disease
427.89  Other specified cardiac dysrhythmias
428.0 - 428.9  Heart failure
433.00 - 434.91, 436 - 438.9  Occlusion and stenosis of precerebral arteries, cerebral arteries, acute, but ill-defined, cerebrovascular disease, other and ill-defined, cerebrovascular disease, and late effects of cerebrovascular disease [except transient ischemic attacks]
584.5 - 584.9  Acute kidney failure
648.20 - 648.24  Anemia complicating pregnancy, childbirth, or the puerperium
737.30 - 737.39  Kyphoscoliosis and scoliosis
737.43  Scoliosis associated with other conditions
756.83  Ehlers-Danlos syndrome
772.4  Fetal and neonatal gastrointestinal hemorrhage
785.51  Cardiogenic shock
785.6  Enlargement of lymph nodes [Castleman's disease]
850.0 - 854.19  Intracranial injury
905.0  Late effect of fracture of skull and face bones
907.0  Late effect of intracranial injury without mention of skull fracture
990  Effects of radiation, unspecified

Other ICD-9 codes related to the CPB:
001.0 - 139.8  Infectious and parasitic diseases [acute and chronic viral, bacterial, parasitic, and fungal]
230.0 - 234.9  Carcinoma in situ
401.0 - 405.99  Hypertensive disease
411.1  Intermediate coronary syndrome [unstable angina]
413.9  Other and unspecified angina pectoris
447.6  Arteritis, unspecified
447.7  Other specified disorders of arteries and arterioles
458.0  Orthostatic hypotension
555.0 - 556.9  Regional enteritis and ulcerative colitis
564.1  Irritable bowel syndrome
585.1 - 585.9  Chronic kidney disease
710.0  Systemic lupus erythematosus
714.0 - 714.33  Rheumatoid arthritis
780.2  Syncope and collapse
780.4  Dizziness and giddiness [light-headedness]
780.79  Other malaise and fatigue
785.0  Tachycardia, unspecified
786.05  Shortness of breath
993.2  Other and unspecified effects of high altitude [living at an elevation of greater than 6000 feet]
996.80 - 996.89  Complications of transplanted organ
E930.7  Adverse effects of antineoplastic antibiotics
E933.1  Adverse effects of antineoplastic and immunosuppressive drugs
V45.11  Renal dialysis status
V56.0  Encounter for extracorporeal dialysis
V56.8  Encounter for other dialysis
V58.11 - V58.12  Encounter for antineoplastic chemotherapy and immunotherapy
V62.6  Refusal of treatment for reasons of religion or conscience

_Peginesatide (Omontys):_

**HCPCS codes covered if selection criteria are met:**

J0890  Injection, Peginesatide 0.1 MG (for ESRD on dialysis)

**ICD-9 codes covered if selection criteria are met:**

285.21  Anemia in chronic kidney disease

_Sodium Ferric Gluconate:_

**HCPCS codes covered if selection criteria are met:**

J2916  Injection, sodium ferric gluconate complex in sucrose injection, 12.5 mg
ICD-9 codes covered if selection criteria are met:

280.0 - 280.9  Iron deficiency anemias

Other ICD-9 codes related to the CPB:

V45.11  Renal dialysis status

The above policy is based on the following references:


80. Aher S, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2006; (3):CD004868.


http://qawww.aetna.com/cpb/medical/data/100_199/0195_draft.html 11/03/2014