ANEMIA DRUGS: DARBEPOETIN ALFA, EPOETIN ALFA, AND METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA

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INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

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COMMERCIAL AND MEDICAID COVERAGE RATIONALE

This protocol addresses the following erythropoiesis stimulating agents (ESAs):

- Aranesp® (darbepoetin alfa)
- Epogen® (epoetin alfa)
- Mircera® (methoxy polyethylene glycol-epoetin beta [MPG-epoetin beta])
- Procrit® (epoetin alfa)

For the purposes of the coverage rationale, all hematocrit (Hct) values are either pretreatment (for the first 4-6 weeks of therapy) or obtained during treatment to assess ongoing titration and safety. Iron
studies must have been completed within the last three (3) months** and must meet the following requirements for coverage consideration:

- Serum Ferritin ≥100 mcg/L and TSAT% ≥20%
  or
- Serum Ferritin ≥500 mcg/L and TSAT% <20%

**in chemotherapy-induced anemia, initial ESA treatment may be approved for one month in the absence of an iron panel. Subsequent treatment will require criteria to be met.

1. Anemia Due to Chronic Kidney Disease:
   a. Patients receiving dialysis
      Aranesp, Epogen, Mircera and Procrit are **medically necessary** for the treatment of anemia of chronic kidney disease (CKD) when all of the following criteria are met:
      1. Patient is on dialysis
         AND
      2. Hematocrit is less than 30% at initiation of therapy.

      ESAs are **not medically necessary** to treat anemia of CKD in patients on dialysis for a hematocrit greater than or equal to 33%.

   b. Patients **not** receiving dialysis
      Aranesp, Epogen, Mircera and Procrit are **medically necessary** for the treatment of anemia of chronic kidney disease (CKD) when all of the following criteria are met:
      1. Patient is **not** on dialysis
         AND
      2. Hematocrit less than 30% at initiation of therapy.
         AND
      3. The rate of hematocrit decline indicates the likelihood of requiring a red blood cell (RBC) transfusion.
         AND
      4. Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

      ESAs are **not medically necessary** to treat anemia of CKD in patients **not** on dialysis for a hematocrit greater than 30%.

2. Anemia Due to Cancer Chemotherapy
   a. Aranesp, Epogen, and Procrit are **medically necessary** when used to treat anemia in cancer chemotherapy when both of the following criteria are met:
      1. Hematocrit less than 30% at initiation of therapy
         AND
      2. There is a minimum of two additional months of planned chemotherapy.

      Mircera is **not medically necessary** for the treatment of anemia due to cancer chemotherapy.
Anemia Drugs

ESAs are **not medically necessary** to treat anemia in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

3. Anemia Associated with Myelodysplastic Disease:
   a. Aranesp, Epogen, and Procrit are **medically necessary** to treat anemia associated with myelodysplastic disease (MDS) when both of the following criteria are met:
      (1) **One** of the following:
          (a) Serum erythropoietin level ≤ 500 mUnits/mL  
          OR  
          (b) Hematocrit is less than or equal to 30% at the initiation of therapy  
          AND
      (2) For continuation of therapy: the hematocrit remains less than 36%

4. Anemia Associated with Zidovudine Treatment in HIV-Infected Patients:
   a. Epogen and Procrit are **medically necessary** to treat anemia in HIV-infected patients when both of the following criteria are met:
      (1) Patient is receiving zidovudine administered at ≤4200 mg/week  
      AND
      (2) Endogenous serum erythropoietin level ≤ 500 mUnits/mL.  
      (3) Hematocrit is less than 30% at initiation of therapy

5. Anemia in Patients with Hepatitis C with Ribavirin and Interferon Therapy:
   a. Epogen and Procrit are **medically necessary** to treat anemia associated with hepatitis C virus infection when all of the following criteria are met:
      (1) Patient is receiving ribavirin and interferon therapy  
      AND
      (2) Hematocrit is less than or equal to 30% at initiation of therapy  
      AND
      (3) For continuation of therapy: the hematocrit remains less than 36%

6. Preoperative Use for Reduction of Allogeneic Blood Transfusions in Surgery Patients:
   a. Epogen and Procrit are **medically necessary** perioperatively to reduce the need for allogeneic blood transfusions when all of the following criteria are met:
      (1) Perioperative Hct greater than 30% and less than or equal to 39%  
      AND
      (2) Patient is at high risk for blood loss during surgery  
      AND
      (3) Patient is unable or unwilling to donate autologous blood  
      AND
      (4) Surgery procedure is elective, noncardiac, and nonvascular

Epogen and Procrit are **not medically necessary** for patients who are willing to donate autologous blood pre-operatively or in patient undergoing cardiac or vascular surgery.

**Note:** For the purposes of this policy, a conversion factor of 3 should be used to estimate hematocrit when only the hemoglobin is measured, e.g., hemoglobin of 10 g/dL is approximately equal to a
hematocrit of 30%, a hemoglobin of 11 g/dL is approximately equal to a hematocrit of 33%, and a hemoglobin of 12 g/dL is approximately equal to a hematocrit of 36%.

ESAs are not medically necessary for:
1. Patients undergoing curative chemotherapy. For information regarding use of ESAs in patients receiving cancer chemotherapy, please refer to information in the National Comprehensive Cancer Network (NCCN) Practice Guideline, Cancer- and Chemotherapy-Induced Anemia, as referenced in the Professional Societies section of this policy.
2. Patients with cancer receiving hormonal agents, biologic products or radiotherapy (unless also receiving concomitant myelosuppressive chemotherapy).
3. Patients who require an immediate correction of anemia as a substitute for RBC transfusions.
4. Patients undergoing cardiac or vascular surgery.
5. Patients scheduled for surgery who will donate autologous blood.

**MEDICARE COVERAGE RATIONALE**


Medicare covers ESA treatment for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia when criteria is met. See the National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). Local Coverage Determinations (LCDs) do exist for Nevada for ESAs, refer to Erythropoietin Stimulating Agents (L34167). (Accessed October 2016)

**Erythropoiesis Stimulating Agents (ESAs ) in Cancer and Related Neoplastic Conditions (110.21)**

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service

**Item/Service Description**

Erythropoiesis stimulating agents (ESAs) stimulate the bone marrow to make more red blood cells and are United States Food and Drug Administration (FDA) approved for use in reducing the need for blood transfusion in patients with specific clinical indications. The FDA has issued alerts and warnings for ESAs administered for a number of clinical conditions, including cancer. Published studies report a higher risk of serious and life-threatening events associated with oncologic uses of ESAs.

**Indications and Limitations of Coverage**

ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:
The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).

The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/3 times weekly for epoetin and 2.25 mcg/kg/1 time weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.

Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is ≥ 1g/dL (hematocrit ≥ 3%);

For patients whose hemoglobin rises < 1g/dl (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10g/dL after the 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1g/dl (hematocrit rise < 3%) compared to pretreatment baseline by 8 weeks of treatment.

Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.

ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Nationally Non-Covered Indications
ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

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

Other
Local Medicare Administrative Contractors may continue to make reasonable and necessary determinations on all other uses of ESAs not specified in this National Coverage Determination.
Erythropoietin Stimulating Agents (L34167)
Coverage Indications, Limitations, and/or Medical Necessity

An erythropoietin stimulating agent (ESA) is an analog of erythropoietin. ESAs are biologically engineered hormones produced by recombinant DNA technology. Erythropoietin analogs contain the identical amino acid sequence as naturally occurring erythropoietin, and have the same biological effect. Primarily, the kidneys produce erythropoietin in response to hypoxia. Both erythropoietin and ESAs stimulate the bone marrow to form new red blood cells. They are used to treat anemia by elevating or maintaining the red blood cell level (as demonstrated by the hematocrit and/or hemoglobin levels), therefore decreasing anemia and the need for transfusions. Darbepoetin alfa (brand name Aranesp ®), an erythropoietin analog, differs from recombinant human erythropoietin alfa (brand name Epogen ® or Procrit ®) in having two additional N-glycosylation sites, which slows its clearance and makes its half-life two-three times longer, allowing less frequent injections. This policy will apply to new ESAs as they are approved.

Since darbepoetin alfa and epoetin alfa have a similar mode of action and their structures differ only by the number of N-linked oligosaccharides on the protein, this policy does not distinguish differences for on or off-label indications and contraindications, except for pre treatment of selective surgery where blood loss is anticipated. Several off-label uses are well-accepted clinically, as indicated by inclusion in various compendia. However, a contraindication for either ESA is binding on both. In March 2007, the FDA issued new warnings against target Hgb levels above 12 gm/dl (36% Hct) “for all patients.” The FDA also issued specific warnings against off-label use in cancer patients whose anemia is not directly linked to chemotherapy. The FDA also reminded physicians that the main endpoint in studies for on-label indications has been avoidance or reduction in transfusions. The LCD contains descriptions of specific coverage guidelines and documentation that supports medical necessity for individual patients.

CMS has issued a national coverage decision for both renal and non-renal uses of ESAs. The Decision Memo for ESAs for non-renal disease indications (CAG-00383N) is located at http://www.cms.gov/center/coverage.asp. This local decision elaborates on the NCD and covers some additional indications.

Erythropoietin analogs are covered for the following indications:
1. Treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis;
2. Treatment of significant anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy;
3. Treatment of anemia induced by AZT and/or other Nucleoside Reverse Transcriptase Inhibitors (NRTI) used in treatment of HIV/AIDS;
4. Treatment of selected patients with anemia related to myelodysplastic syndrome;
5. Preoperative adjuvant therapy (epoetin alfa only);

The following causes of anemia should be considered, documented, and corrected (when possible) before starting erythropoietin analog therapy for any of the covered indications:
1. Iron deficiency;
2. Underlying infection or inflammatory process;
3. Underlying hematological disease;
4. Hemolysis;
5. Vitamin deficiencies (e.g. folic acid or B12);
6. Blood loss
7. Aluminum intoxication

The ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

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

There are rare patients whose cardiac, pulmonary or other medical conditions warrant the use of ESAs to maintain a Hgb/Hct higher than the target level discussed in this LCD. Documentation to support this practice must be available upon request. This does not apply to ESA therapy for anemia related to cancer chemotherapy, which follows the rules mandated by the National Coverage Decision.

During therapy with an erythropoietin analog, many patients will eventually require supplemental iron. For these patients, stores of iron should be regularly monitored to ensure transferrin saturation greater than 20% and/or serum ferritin levels greater than 100 ng/ml, in order to guide appropriate supplementation.

For patients receiving chemotherapy for non-myeloid malignancies, the goal of therapy is to maintain the Hgb/Hct at 10/30%. ESA therapy will not be reimbursed when the Hgb/Hct is greater than 10/30%. For all other indications, the goal of therapy is to maintain a stable Hgb/Hct, with a target of 10-12 gm/dL / 30-36%. Doses must be titrated according to the patient’s response. Erythropoietin analog therapy need not be stopped completely simply due to the achievement of the target Hgb/Hct. However, judicious, appropriately timed dose adjustments are expected to prevent inappropriate increases in Hgb/Hct levels.

ESAs may be administered by intravenous or subcutaneous routes. The dosage may be dependent on several factors including the availability of iron stores, the baseline Hgb/Hct, and the presence of concurrent medical problems.

Although subcutaneous medications are generally considered to be self-administered and therefore not covered, erythropoietin analogs are covered regardless of route of administration when used within the ESRD benefit or for chronic kidney disease patients not yet on dialysis who meets the conditions below.
Coverage Criteria:

A. For End Stage Renal Disease (ESRD) patients on dialysis
   1. Diagnosis of end stage renal disease
   2. Anemia of ESRD should be treated to maintain a Hgb level of 10-12 gm/dl or a Hct 30%-36%.

B. For chronic kidney disease patients NOT on dialysis
   1. Anemia of chronic kidney disease should be treated to maintain the Hgb level of 10-12 gm/dl or a Hct of 30%-36%.
   2. Serum creatinine equal to or greater than 2.5, creatinine clearance less than 60 ml/min, or glomerular filtration rate (GFR) less than 60 ml/min/1.73 m2.

C. For patients with non-myeloid malignancies where anemia is due to the effect of chemotherapy
   1. Anemia with Hgb/Hct less than 10 / 30% at initiation of therapy.
   2. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/1 time weekly for darbopoetin alpha. Equivalent doses may be given over other approved time periods.
   3. Maintenance of ESA therapy is the same as the starting dose if the Hgb level remains below 10 gm/dl (or Hct is <30%) 4 weeks after initiation of therapy and the rise in Hgb ≥1 gm/dl (Hct 3%).
   4. For patients whose Hgb rises <1 gm/dl (Hct rise <3%) compared to pre-treatment baseline over 4 weeks of treatment and whose Hgb level remains < 10 gm/dl after the 4 weeks of treatment (or Hct is <30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the Hgb rises < 1 gm/dl (Hct rise <3%) compared to pretreatment baseline by 8 weeks of treatment.
   5. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in Hgb >1 gm/dl (Hct >3%) over 2 weeks of treatment unless the Hgb remains below or subsequently falls to < 10 gm/dl (or the Hct is <30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
   6. The FDA labeling states that ESAs are indicated for treatment of anemia of malignancy when receiving concomitant chemotherapy, which means during an established course of planned chemotherapy. It will also cover ESAs for eight weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

D. For patients with anemia related to AZT and/or other Nucleoside Reverse Transcriptase Inhibitors (NRTI) therapy for HIV/AIDS:
   1. The goal of therapy is to maintain a stable Hbg/Hct, with a Hgb target of 10-12 gm/dl or a Hct of 30%-36%.

E. For patients with myelodysplastic syndrome:
   1. Low risk myelodysplasia
   2. Pretreatment erythropoietin levels of 500 or less
   3. The goal of therapy is to avoid transfusions by maintaining a stable Hgb/Hct, with a target of 10-12gm/dl / 30%-36%. If after two months of treatment, there is no significant increase in Hgb/Hct and/or a significant decrease in transfusion requirements, erythropoietin analogs therapy should be stopped.
*For ESA therapy initiated on or after 12/1/2007, this A/B MAC requires an EPO level less than or equal to 500 IU/L.

F. Preoperative adjuvant therapy: (erpoetin alfa only) for patients who:
   1. Are undergoing hip or knee surgery
   2. Have an anemia with a Hgb between 10 and 13 g/dL
   3. Are not a candidate for autologous blood transfusion
   4. Are expected to lose more than two units of blood
   5. Have been evaluated to ensure that their anemia is due to chronic disease.

For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada.
http://www.cms.hhs.gov/mcd/search

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

BACKGROUND

Anemia is a condition in which the number of red blood cells is below normal. Anemia can be caused by a loss of red blood cells due to excessive bleeding, decreased production of red blood cells by the bone marrow, increased red blood cell destruction by the body, or a combination of these factors. There are many treatments available for anemia depending upon the severity of the condition and etiology of the condition, ranging from vitamin or mineral supplementation, to self-administered medications such as erythropoietin or similar agents, to transfusion of red blood cells.

Erythropoietin is an endogenous glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the diversion and differentiation of committed erythroid progenitors in the bone marrow. Epoetin alfa is a recombinant form of erythropoietin. Darbepoetin alfa is an erythropoiesis stimulating protein, closely related to erythropoietin, and is also produced by recombinant DNA technology. Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin, but it has two additional carbohydrate chains to give it a longer half-life. Methoxy polyethylene glycol-epoetin beta, an erythropoiesis stimulating protein, differs from erythropoietin through formation of a chemical bond between either Lys or Lys, and methoxy polyethylene glycol (MPG) butanoic acid. This conjugation allows for greater erythropoietin receptor activity as well as an increased half-life, in contrast to erythropoietin.

CLINICAL EVIDENCE

Medically Necessary
Oncology Related Anemia
Researchers in The Cochrane Collaboration conducted a review of the effect of epoetin and darbepoetin for people with cancer. After searching for all relevant studies, they found 91 studies with up to 20,102 people. Trials included in the review consisted of randomized controlled trials on managing anemia in cancer patients receiving or not receiving anti-cancer therapy that compared the use of recombinant human erythropoiesis stimulating agents (ESAs) plus transfusion if needed.
Outcomes showed that use of ESAs significantly reduced the relative risk of red blood cell transfusions (risk ratio (RR) 0.65; 95% confidence interval (CI) 0.62 to 0.68, 70 trials, n = 16,093). On average, patients in the ESAs group received one unit of blood less than the control group (mean difference (MD) -0.98; 95% CI -1.17 to -0.78, 19 trials, n = 4,715) and hematological response was observed more often in participants receiving ESAs (RR 3.93; 95% CI 3.10 to 3.71, 31 trials, n = 6,413). There was strong evidence that ESAs increased mortality during the active study period (hazard ratio (HR) 1.17; 95% CI 1.06 to 1.29, 70 trials, N = 15,935) and some evidence that ESAs decreased overall survival (HR 1.05; 95% CI 1.00 to 1.11, 78 trials, n = 19,003). Researchers found that RR for thromboembolic complications was increased in patients receiving ESAs compared to controls (RR 1.52, 95% CI 1.34 to 1.74; 57 trials, n = 15,498). Additionally, ESAs may have increased the risk for hypertension (fixed-effect model: RR 1.30; 95% CI 1.08 to 1.56; random-effects model: RR 1.12; 95% CI 0.94 to 1.33, 31 trials, n = 7,228) and thrombocytopenia/hemorrhage (RR 1.21; 95% CI 1.04 to 1.42; 21 trials, n = 4,507). Evidence did not support efficacy of ESA on tumor response (fixed-effect RR 1.02; 95% CI 0.98 to 1.06, 15 trials, n = 5,012). Authors concluded that treatment with ESAs reduced the need for red blood cell transfusions but increased the risk for thromboembolic events and deaths. Evidence suggested that quality of life may be improved with ESAs. Treating providers need to balance the increased risk of death and thromboembolic events against the potential benefits of ESA treatment taking into account each patient’s clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumor progression. Further research is warranted to assess cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumor growth.

A randomized-placebo-controlled study was conducted to explore the effect on survival and/or disease progression of erythropoietin dosed with higher hemoglobin targets ranges to prevent anemia. Women with metastatic breast cancer (n = 939) treated with chemotherapy and using an erythropoietin product received weekly dosing with attempted titration to maintain hemoglobin levels between 12 and 14 g/dL. At four months, death attributed to disease progression was higher (8.7% vs. 3.4%) in women receiving epoetin alfa. There was also a higher rate of fatal thrombotic events in the epoetin group (1.1% vs. 0.2%). Although the study was terminated at that time, Kaplan-Meier estimates of overall survival were significantly lower at 12 months in the epoetin alfa arm (70% vs. 76%).

Additionally, decreased locoregional control/progression-free survival, and/or overall survival with erythropoiesis-stimulating agents has been demonstrated in studies of patients with advanced head and neck cancer receiving radiation therapy, patients receiving chemotherapy for lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

The studies of patients with various non-myeloid malignancies not receiving chemotherapy or radiotherapy included a large, phase 3, multicenter, randomized, placebo-controlled trial of 989 patients with hemoglobin (Hgb) < 11 g/dl. The treatment period was 16 weeks. The target hemoglobin in the darbepoetin alfa treatment group was 12-13 g/dL. The final analysis of the initial 16-week treatment period did not show a statistically significant decrease in the proportion of patients receiving red blood cell transfusions. The mean survival was also shorter in the darbepoetin alfa group vs. placebo (8 vs. 10.8 months).
A systematic review of randomized, controlled trials of cancer patients showed an increased relative risk of thromboembolic events (RR 1.67, 95% CI 1.35-2.06) with erythropoiesis stimulating agents. This review also showed an overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18). Three recent meta-analyses support these findings of increased risk of mortality in patients with cancer receiving ESAs. The relative risks/hazard ratios of mortality in these trials were 1.10 (95% CI, 1.01-1.20), 1.17 (95% CI, 1.06-1.30), and 1.15 (95% CI, 1.03-1.29).

Additionally, two analyzed for the relative risks of thromboembolism and reported values of 1.57 (95% CI, 1.31-1.87) and 1.69 (95% CI, 1.27-2.24). However, two other recent meta-analyses did not find an association between ESAs and increased risk of death or disease progression but did confirm the increased relative risk of thromboembolism: 1.57 (95% CI, 1.10-2.26) and 1.48 (95% CI, 1.28-1.72).

**CKD-Related Anemia**

An increased risk of mortality was also observed in a randomized, prospective trial of 1265 hemodialysis patients. These patients had clinically evident cardiac disease (ischemic heart disease or congestive heart failure) and target Hct of 42 or 30%. The rate of mortality was 35% in the higher target group vs. 29%.

The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study randomized type II diabetes patients with chronic kidney disease (average glomerular filtration rate 34 and 33 mL per minute per 1.73 m2 of body surface area) to darbepoetin alfa (n=2012) or placebo (n=2026). Patients in the placebo group could receive rescue darbepoetin alfa if their hemoglobin fell to below 9 g/dL. The hemoglobin target was 13 g/dL for the darbepoetin alfa patients. The median follow-up was 29.1 months and the average hemoglobin achieved was 12.5 g/dL with darbepoetin alfa and 10.6 g/dL with placebo. There was a non-statistically significant higher rate of death or nonfatal cardiovascular events in the darbepoetin alfa group vs. the placebo group (31.4% vs. 29.7%, p=0.41). There was no difference in the rate of development of end stage renal disease between the two groups. However, fatal or nonfatal stroke occurred in a significantly greater percentage of darbepoetin alfa patients (5.0% vs. 2.6%, p<0.001). Significantly fewer red-cell transfusions were administered in the darbepoetin alfa group (297 patients, 14.8%) than in the placebo group (496 patients, 24.5%) (p<0.001). Patient-reported outcomes were measured at week 25 using the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue) instrument (higher scores indicating less fatigue) and the 36-Item Short-Form General Health Survey questionnaire (higher scores indicating a better quality of life). There was a greater degree of improvement in the FACT-Fatigue score in the darbepoetin alfa group than in the placebo group (P<0.001), summarized in the study abstract as a “modest improvement in patient-reported fatigue”. There was not a statistically significant difference in the domains of energy and physical functioning as measured with the 36-Item Short-Form General Health Survey.

**Surgery Patients**

Spinal surgery patients (n=681) were randomized to receive four doses of 600 U/kg epoetin alfa (days 7, 14, and 21 before and day of surgery) and standard of care or standard of care alone. Preliminary analysis showed a higher incidence of deep vein thrombosis (DVT) and other thrombotic vascular events in the epoetin alfa group. However, DVT prophylaxis was not used in this trial.

So-Osman et al. evaluated the use of erythropoietin in hip and knee surgery patients, and the ability to reduce the incidence of blood transfusions. This prospective, randomized, multicenter, controlled trial
enrolled 683 patients with a preoperative hemoglobin level between 10 and 13 g/dl undergoing primary or revision hip and/or knee arthroplasty. Patients were randomized to receive erythropoietin (n=339) or placebo (N=344), and subsequently for autologous reinfusion by cell saver or postoperative drain reinfusion devices or for no blood salvage device. A fixed weekly dose of 40,000 units (U) was given to patients randomized for erythropoietin with simultaneous prescription of ferrofumarate 200 mg three times per day (195 mg Fe2+ a day) for 3 weeks before surgery. A total of four erythropoietin doses were administered by subcutaneous injection on days 21, 14, 7, and on the day of surgery (day 0), respectively. If the hemoglobin level, determined before the fourth dose, exceeded the value of 15 g/dl, the final erythropoietin dose was withheld. Primary outcomes were mean allogeneic intra- and postoperative erythrocyte use and proportion of transfused patients (transfusion rate). Secondary outcome was cost-effectiveness. Patients who received erythropoietin, mean erythrocyte use was 0.50 U/patient and transfusion rate 16% while without, these were 0.71 U/patient and 26%, respectively. Consequently, erythropoietin resulted in a nonsignificant 29% mean erythrocyte reduction (ratio, 0.71; 95% CI, 0.42 to 1.13) and 50% reduction of transfused patients (odds ratio, 0.5; 95% CI, 0.35 to 0.75). Erythropoietin increased costs by €785 per patient (95% CI, 262 to 1,309), that is, €7,300 per avoided transfusion (95% CI, 1,900 to 24,000). With autologous reinfusion, mean erythrocyte use was 0.65 U/patient and transfusion rate was 19% with erythropoietin (n=214) and 0.76 U/patient and 29% without (n=206). Compared with controls, autologous blood reinfusion did not result in erythrocyte reduction and increased costs by €537 per patient (95% CI, 45 to 1,030). Erythropoietin was found to significantly reduce the number of patients requiring the use of erythrocyte transfusion, but not the amount of erythrocytes transfused. In hip- and knee-replacement patients (hemoglobin level, 10 to 13 g/dl), even with a restrictive transfusion trigger, erythropoietin significantly avoids transfusion, however, at unacceptably high costs. Autologous blood salvage devices were not effective.

HCV Infection
Sulkowski et al. evaluated the relationship among treatment outcomes, anemia, and their management with RBV dose reduction and/or erythropoiesis-stimulating agents (ESAs) in treatment-naïve hepatitis C (HCV) genotype 1-infected patients treated with pegylated interferon and ribavirin (PEG-IFN/RBV) in the Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study.36 Patients included in the analysis were treated up to 48 weeks with one of three PEG-IFN/RBV regimens. Treatment with ESAs were permitted for anemic patients (hemoglobin [Hb] <10 g/dL) after RBV dose reduction. Sustained virologic responses (SVR) were assessed based on decreases in hemoglobin (Hb), anemia, and ESA use. Randomized patients (n=3023) that received at least one treatment dose of medication treatment and underwent Hb measurement at baseline and at least once during the treatment phase were included. An SVR was associated with the magnitude of Hb decrease: >3 g/dL, 43.7%; ≤3 g/dL, 29.9% (p<0.001). Anemia occurred in 865 patients (28.6%); 449 of these (51.9%) were treated with ESAs. In patients with early-onset anemia (≤ 8 weeks of therapy), treatment with ESAs were associated with higher SVR rate (45.0% vs 25.9%; p<0.001) and reduced discontinuation of treatment because of adverse events (12.6% vs 30.1%, p<0.001). Researchers noted that ESA treatment did not affect SVR or discontinuation rates among patients with late-stage anemia. Among HCV genotype 1-infected patients treated with PEG-IFN/RBV, anemia was associated with higher rates of SVR. Additionally, the effect of ESAs varied by time to anemia. Patients with early-onset anemia had higher rates of SVR with ESA treatment, whereas no effect was observed in those with late-onset anemia.
Patients with chronic hepatitis C virus (HCV) infection receiving combination ribavirin (RBV) and interferon alfa therapy (n=64) with a hemoglobin level of 12 g/dL or less were randomized to treatment with epoetin alfa 40,000 units weekly or standard of care (RBV dose reduction or discontinuation, transfusions). The mean hemoglobin level at week 16 was 13.8 g/dL in the epoetin alfa group compared with 11.4 g/dL in the standard of care group. At the study end, 83% of epoetin alfa treated patients maintained RBV dosages of at least 800 mg/day, compared with 54% of patients receiving stand of care (p=0.022). The study concludes that in anemic HCV-infected patients currently being treated with RBV and interferon alfa therapy, epoetin alfa increases hemoglobin levels and maintains ribavirin dosing.

Afdhal et al conducted a study of HCV-infected patients (n=185) on combination therapy (RBV and interferon-alpha or pegylated interferon-alpha) who developed anemia (hemoglobin ≤ 12 g/dL) and were randomized to epoetin alfa 40,000 units weekly or placebo. The study design used an 8-week, double-blind phase (DBP) followed by an 8-week, open-label phase (OLP), in which placebo patients were crossed over to epoetin alfa. At the end of the DBP, RBV doses were maintained in 88% of patients receiving epoetin alfa vs. 60% of patients receiving placebo (P <0.001). For placebo patients initiating epoetin alfa in the OLP , the percentage of patients who were able to maintain their initial RBV dose increased (46% at the end of the DBP compared to 64% at the end of the OLP [P< 0.001]); the percentage of patients who were able to maintain their randomization RBV dose increased from 63% at the end of the DBP to 78% at the end of the OLP (P <0.001). Mean hemoglobin increased by 2.2 ±1.3 g/dL (epoetin alfa) and by 0.1±1.0 g/dL (placebo) in the DBP (P < 0.001). Similar results were demonstrated in patients who switched from placebo to epoetin alfa in the OLP. The study concludes epoetin alfa maintained RBV dose and improved hemoglobin in anemic HCV-infected patients receiving combination therapy.

Technology Assessment
A 2014 Cochrane review was published to assess the benefits and harms of darbepoetin alfa to treat anemia in adults and children with chronic kidney disease (CKD). Twenty-one studies with 8,328 participants were included in the meta-analysis. One study (4,038 participants) compared darbepoetin alfa to placebo, 16 studies (2,955 participants) compared darbepoetin alfa to epoetin alfa or beta, four studies (1,198 participants) compared darbepoetin alfa to methoxy polyethylene glycol-epoetin beta (MPG-epoetin beta), three studies (420 participants) compared more frequent with less frequent administration, and four studies (303 participants) compared intravenous (IV) with subcutaneous (SC) darbepoetin alfa. The authors concluded that darbepoetin alfa effectively reduces need for blood transfusions in adults with CKD stage 3 to 5, but has little or no effect on mortality or quality of life. The effects of darbepoetin alfa in adults with CKD stage 5D and kidney transplant recipients and children with CKD remain uncertain as do the relative benefits and harms of darbepoetin alfa compared with other ESAs.

A 2014 Cochrane review was published to compare the efficacy and safety of the different ESAs for treating anemia in adults with chronic kidney disease (CKD). Fifty-six eligible studies were included in the analysis, involving 15,596 adult patients with CKD. The authors concluded that in the CKD setting, there is currently insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data. Directly comparative data for the effectiveness of different ESA formulations based on patient-centered outcomes (such as quality of life, fatigue, and functional status) are sparse and poorly reported and current research studies are unable to inform care. All proprietary
ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta) prevent blood transfusions but information for biosimilar ESAs is less conclusive. Comparative treatment effects of different ESA formulations on other patient-important outcomes such as survival, MI, stroke, breathlessness and fatigue are very uncertain.

For consumers, clinicians and funders, considerations such as drug cost and availability and preferences for dosing frequency might be considered as the basis for individualizing anemia care due to lack of data for comparative differences in clinical benefits and harms.

A 2012 Cochrane review was published to assess the effects of erythropoietin or darbepoetin to either prevent or treat anemia in cancer patients. This review was an update of a Cochrane review first published in 2004. The update includes a total of 91 trials with 20,102 participants. The authors concluded that ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve quality of life. Whether and how ESAs affect tumor control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumor progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumor growth.

**Agency for Healthcare Research and Quality (US)**

In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted an updated systematic review of the comparative benefits and harms of erythropoiesis-stimulating agent (ESA) strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy and/or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia), including the impact of alternative thresholds for initiating treatment and optimal duration of therapy. Results of this update were consistent with the results of the 2006 review. Researchers found:

- ESAs reduced the need for transfusions and increased the risk of thromboembolism.
- Functional Assessment of Cancer Therapy (FACT)-Fatigue scores were better with ESA use but the magnitude was less than the minimal clinically important difference.
- An increase in mortality accompanied the use of ESAs.
- An important unanswered question is whether dosing practices and overall ESA exposure might influence harms.

**Professional Societies**

**Cancer- and Chemotherapy-Induced Anemia**

The NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia provide recommendations for the evaluation of Hgb ≤ 11 g/dL or ≥ 2 g/dL below baseline in patients with cancer. These guidelines reference the National Cancer Institute (NCI) anemia grading scale of the severity of anemia based on Hgb. Additionally, the NCCN Guidelines for Myelodysplastic Syndromes (MDS) provides recommendations for use of ESA in the management of symptomatic anemia in MDS patients. Refer to
Anemia Drugs

the NCCN’s guidelines for further information. The portions of the guidelines applicable to this policy are:

- ESAs are only recommended for anemia due to myelosuppressive chemotherapy for lymphoid malignancies and solid tumors, and also for myelodysplastic syndromes. For anemia associated with myeloid malignancies or acute lymphoblastic leukemia (ALL), refer to NCCN’s guidelines for the condition or appropriate therapy for ALL.
- ESAs are not indicated for patients with cancer with an identified, treatable cause of anemia.
- For patients with anemia from myelosuppressive chemotherapy, ESAs are not indicated for chemotherapy with curative intent. For anemia due to chemotherapy with a non-curative intent, ESAs may be considered according to FDA-approved indications/dosing/dosing adjustments, and under risk evaluation and mitigation strategy (REMS) guidelines, with informed consent of the patient.
  - Healthcare providers should counsel each patient on the risk and benefits of ESAs prior to each new course of ESA therapy.
- The risks and benefits of ESA therapy versus red blood cell transfusion should be considered.
- ESAs may be administered with or without iron supplementation depending on functional iron deficiency status.
- ESA therapy should be discontinued following the completion of a chemotherapy course or when a loss in response is identified. ESAs should be permanently discontinued in patients with antibody-mediate anemia.
- Initial dosing, monitoring and dosage adjustments based on Hgb levels are recommended according to the manufacturer’s product information or alternative regimens detailed in the guideline.
  - ESAs may be used in patients with del(5q) and symptomatic anemia where serum epo levels are ≤ 500 mU/mL.
- For cancer with chronic kidney disease, consider treatment with ESAs according to FDA indications and dosing for chronic kidney disease. Risk versus benefit evaluation is required. CKD patients not receiving active therapy for a malignancy should try to avoid ESAs, while those receiving palliative chemotherapy may favor ESAs over transfusion for severe anemia. A CKD patient with a curable solid tumor should not receive ESAs during chemotherapy, but they may be utilized with caution after chemotherapy is complete.
- Studies have reported possible decreased survival in cancer patients receiving ESAs. Analyses of eight studies in patients with cancer found decreased survival with ESAs when anemia was corrected to a target Hgb level of > 12 g/dL. However, the shortened survival and tumor progression risks have not been excluded when ESAs are dosed to a target Hgb < 12 g/dL. Also, three meta-analysis updates on survival indicate increased risk of mortality with use of ESAs. However, two meta-analyses did not show significant affect on mortality or disease progression with ESA use. ESA’s may be used in the management of symptomatic anemia in myelodysplastic syndromes with a treatment target hemoglobin ≤ 12 g/dL. Recent pharmacovigilance trials have reported no adverse effects on survival in cancer patients with chemotherapy-induced anemia receiving ESAs.

**Chronic Kidney Disease**

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) released a new Clinical Practice Guideline for Anemia in Chronic Kidney Disease guideline, updating the 2002 NKF-KDOQI
Anemia Drugs

guideline. Utilizing a Grading of Recommendations Assessment, Development and Evaluation (GRADE) System, KDIGO evaluated the quality of evidence for an outcome. Their recommendations are as follows:

Use of ESAs and Other Agents to Treat Anemia in CKD:

- In initiating and maintaining ESA therapy, the Work Group recommends balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)
- The Work Group recommends using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(1B), a history of stroke (1B), or a history of malignancy. (2C)
- For adult CKD ND (non-dialysis dependent) patients with Hb concentration ≥10.0 g/dl (≥100 g/l), the Work Group suggests that ESA therapy not be initiated. (2D)
- For adult CKD ND patients with Hb concentration <10.0 g/dl (<100 g/l), the Work Group suggests that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (2C)
- For adult CKD stage 5D patients, the Work Group suggests that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (2B)
- Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (Not Graded)
- For all pediatric CKD patients, the Work Group suggests that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D)

ESA Maintenance Therapy

- In general, the Work Group suggests that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (2C)
- Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (Not Graded)
- In all adult patients, the Work Group recommends that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (1A)
- In all pediatric CKD patients receiving ESA therapy, the Work Group suggests that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (2D)

ESA Dosing

- The Work Group recommends determining the initial ESA dose using the patient’s Hb concentration, body weight, and clinical circumstances. (1D)
- The Work Group recommends that ESA dose adjustments be made based on the patient’s Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (1B)
- The Work Group suggests decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (2C)
- Re-evaluate ESA dose if (Not Graded):
  - The patient suffers an ESA-related adverse event
  - The patient has an acute or progressive illness that may cause ESA hyporesponsiveness

**ESA Administration**
- For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, the Work Group suggests either intravenous or subcutaneous administration of ESA. (2C)
- For CKD ND and CKD 5PD patients, the Work Group suggests subcutaneous administration of ESA. (2C)

**Frequency of Administration**
- The Work Group suggests determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (2C)

**Type of ESA**
- The Work Group recommends choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (1D)
- The Work Group suggests using only ESAs that have been approved by an independent regulatory agency. Specifically for 'copy' versions of ESAs, true biosimilar products should be used. (2D)

**Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hemoglobin Concentration**

**Frequency of Monitoring**
- During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (Not Graded)
- For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (Not Graded)
- For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (Not Graded)

**Initial ESA Hyporesponsiveness**
- Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (Not Graded)
- In patients with ESA hyporesponsiveness, the Work Group suggests avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (2D)

**Subsequent ESA Hyporesponsiveness**
- Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (Not Graded)
- In patients with acquired ESA hyporesponsiveness, the Work Group suggests avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (2D)

**Management of Poor ESA Responsiveness**
- Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (Not Graded)
For patients who remain hyporesponsive despite correcting treatable causes, the Work Group suggests individualization of therapy, accounting for relative risks and benefits of (2D):
- Decline in Hb concentration
- Continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required
- Blood transfusions

**Adjuvant Therapies**
- The Work Group recommends not using androgens as an adjuvant to ESA treatment. (1B)
- The Work Group suggests not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (2D)

**Evaluation for Pure Red Cell Aplasia (PRCA)**
- The Work Group recommends investigating for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (Not Graded):
  - Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week OR requirement of transfusions at the rate of approximately 1 to 2 per week, AND
  - Normal platelet and white cell counts, AND
  - Absolute reticulocyte count less than 10,000/µl.
- The Work Group recommends that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (1A)
- The Work Group recommends that peginesatide to be used to treat patients with antibody-mediated PRCA. (1B)

A change in the 2006 Updates to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Guidelines for the Management of Anemia in CKD, was to change the target Hgb for patients receiving erythropoietic agents from the previous narrow and inflexible range of 11-12 g/dL to the recommendation for a lower limit of 11 g/dL with no specified upper ceiling. There is a qualifier that there is insufficient evidence to maintain Hgb > 13.0 g/dL However, their 2007 update, supported by the more recent Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), and other studies evaluating higher targeted Hgb levels with epoetin products in CKD, limits the Hgb target to not greater than 13 g/dL. CHOIR showed a higher risk (18% vs. 14%) of the combined end point of death, myocardial infarction, congestive heart failure hospitalization, and stroke and no quality of life benefit in patients receiving epoetin alfa to a target Hgb of 13.5 g/dL vs. 11.3 g/dL. CREATE showed a higher rate of progression to dialysis with epoetin beta (not available in the U.S.) targeted to a higher Hgb range but a better quality of life.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Epogen and Procrit are indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis; treatment of anemia in zidovudine treated HIV-infected patients; treatment of anemia in cancer patients on concomitant myelosuppressive chemotherapy and upon initiation, there is a minimum of two additional months of planned chemotherapy; and in reduction of the need for allogeneic blood transfusion in noncardiac, nonvascular, elective surgery patients.
Aranesp is indicated for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis; and for the treatment of anemia in cancer patients on concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Mircera is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.

On June 24, 2011, The U.S. Food and Drug Administration (FDA) released a safety announcement informing healthcare professionals of modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The FDA is further evaluating the use of ESAs in anemia associated with CKD.

In an August 2013 podcast (http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm260913.htm), the FDA recommended that healthcare professionals who treat patients with chronic kidney disease (CKD) be aware that:

1. Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular events and has not been shown to provide additional patient benefit.
2. No clinical trial to date has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
3. The ESA Medication Guide (Epogen/Procrit or Aranesp) should be provided to each patient or their representative when an ESA is dispensed.
4. The lowest ESA dose sufficient to reduce the need for red blood cell transfusions should be used.
5. For patients with CKD not on dialysis:
   o Consider initiating ESA treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
     ▪ The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion; and
     ▪ Reducing the risk of alloimmunization and/or other red blood cell transfusion-related risks is a goal.
   o If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.
6. For patients with CKD on dialysis:
   o Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.
   o If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.
7. When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly.
8. For patients who do not respond adequately over a 12-week escalation period, increasing the ESA dose further is unlikely to improve response and may increase risks.
Additional information can be found at:

A risk evaluation and mitigation strategy (REMS) program is required by the FDA for ESAs. The REMS includes provision of a Medication Guide explaining the risks and benefits of ESAs to all patients receiving them. Additional information about the ESA APPRISE (Assisting Providers and cancer Patients with Risk information for the Safe use of ESAs) Oncology Program may be found at https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp. Accessed October 2016.

The product labeling for these products includes the class warning that ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

- In clinical studies, patients with chronic kidney disease experienced greater risks for death, serious cardiovascular events, and stroke when administered ESAs to target hemoglobin levels of greater than 11 g/dL. The warning states that no trial has identified a hemoglobin target level, ESA dose or dosing strategy that does not increase these risks. Use the lowest ESA dose sufficient to reduce the need for red blood cell transfusions.
- Due to clinical studies showing that ESAs can shorten survival and/or increase the risk of tumor progression or recurrence in some patients with cancer, providers and hospitals must enroll in and comply with the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology to prescribe and/or dispense ESAs to patients with cancer in addition to the REMS program. ESAs should only be used for anemia for myelosuppressive chemotherapy when there is a minimum of two additional months of planned chemotherapy.
- Due to increased risk of deep venous thrombosis (DVT) with epoetin alfa, DVT prophylaxis is recommended for peri-surgery patients receiving ESAs.

The prescribing information for darbepoetin alfa, epoetin alfa, and MPG-epoetin beta contains a warning regarding reports of pure red cell aplasia (PRCA) and severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin. This warning states that any patient who develops a sudden loss of response, accompanied by severe anemia and low reticulocyte count should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody-associated anemia is suspected, ESAs should be withheld and the manufacturer contacted as directed in the prescribing information to perform assays for binding and neutralizing antibodies.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.
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erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology. 2014 Apr;120(4):839-51..


**PROTOCOL HISTORY/REVISION INFORMATION**

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Corporate Medical Affairs Committee
The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.