**INSTRUCTIONS FOR USE**

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage.

**Claim Processing Instructions**

ESA claims submitted on a 1500 form and/or 837P electronic claim form require the Hct level be submitted with the claim. The Hct should be from within 30 days of the injection.
This policy 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.

1. Anemia Due to Chronic Kidney Disease:
   a. Patients receiving dialysis
      Aranesp, Epogen, Mircera and Procrit are **proven** for the treatment of anemia of chronic kidney disease (CKD) when all of the following criteria are met:1,4,5,42,46
      (1) Patient is on dialysis
      AND
      (2) Hematocrit is less than 30% at initiation of therapy.1, 4, 5, 42, 46
      ESAs are **unproven** to treat anemia of CKD in patients on dialysis for a hematocrit greater than or equal to 33%.1,4,5,42
   b. Patients not receiving dialysis
      Aranesp, Epogen, Mircera and Procrit are **proven** for the treatment of anemia of chronic kidney disease (CKD) when all of the following criteria are met:1,4,5,42,46
      (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 **unproven** to treat anemia of CKD in patients not on dialysis for a hematocrit greater than 30%.1,4,5,42

2. Anemia Due to Cancer Chemotherapy:
   a. Aranesp, Epogen, and Procrit are **proven** when used to treat anemia in cancer chemotherapy when both of the following criteria are met:1,4,5
      (1) Hematocrit less than 30% at initiation of therapy
      AND
      (2) There is a minimum of two additional months of planned chemotherapy.
   b. Mircera is **unproven** for the treatment of anemia due to cancer chemotherapy.42

   ESAs are **unproven** to treat anemia in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.1, 4, 5

3. Anemia Associated with Myelodysplastic Disease:
   a. Aranesp, Epogen, and Procrit are **proven** to treat anemia associated with myelodysplastic disease (MDS) when both of the following criteria are met:2,3,8,9,32,46
      (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 **proven** to treat anemia in HIV-infected patients when both of the following criteria are met:4,5,46
      (1) Patient is receiving zidovudine administered at ≤ 4200 mg/week
      AND
(2) Endogenous serum erythropoietin level ≤ 500 mUnits/mL.\textsuperscript{4,5} 
\textbf{AND} 
(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 proven to treat anemia associated with hepatitis C virus infection when all of the following criteria are met: \textsuperscript{22, 23, 33-36, 46}
   (1) Patient is receiving ribavirin and interferon therapy
   \textbf{AND} 
   (2) Hematocrit is less than or equal to 30% at initiation of therapy 
   \textbf{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 proven perioperatively to reduce the need for allogeneic blood transfusions when all of the following criteria are met: \textsuperscript{4, 5, 46}
   (1) Perioperative Hct is greater than 30% and less than or equal to 39%
   \textbf{AND} 
   (2) Patient is at high risk for blood loss during surgery
   \textbf{AND} 
   (3) Patient is unable or unwilling to donate autologous blood
   \textbf{AND} 
   (4) Surgery procedure is elective, noncardiac, and nonvascular

   Epogen and Procrit are unproven for patients who are willing to donate autologous blood pre-operatively or in patient undergoing cardiac or vascular surgery.\textsuperscript{4,5}

\textbf{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 unproven for:\textsuperscript{1,4,5,6, 42}
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.

**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.\textsuperscript{4,5}

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.\textsuperscript{1}

Mircera is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.\textsuperscript{42}

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...
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:
   - 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.
   - 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:
   - Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.
   - 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.
9. Adverse events involving ESAs should be reported to the FDA MedWatch program at www.fda.gov/medwatch.

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.1,4,5, 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.38

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.1,4,5,42

- 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.1,4,5,42
- 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 from myelosuppressive chemotherapy when there is a minimum of two additional months of planned chemotherapy1,4,5
- Due to increased risk of deep venous thrombosis (DVT) with epoetin alfa, DVT prophylaxis is recommended for perisurgery patients receiving ESAs.4,5
- Safety and labeling information is available at the FDA website:

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.1,4,5,42
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^{52} or Lys^{56}, 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.

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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<td>J0882</td>
<td>Injection, darbepoetin alfa, 1 mcg (for ESRD on dialysis)</td>
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CLINICAL EVIDENCE

Proven 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) -0.78, 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.

Anemia Drugs: Darbepoetin Alfa, Epoetin Alfa, and Methoxy Polyethylene Glycol-Epoetin Beta
UnitedHealthcare Commercial Drug Policy

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Effective 10/01/2016
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 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**

Surgical 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 transfusion 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%

**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-naive 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. 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.
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).\textsuperscript{43} 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).\textsuperscript{44} 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.\textsuperscript{45} 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.\textsuperscript{41} Inclusion into the report required enrollment of more than 50 patients per arm in order to avoid potential differential endpoints associated with smaller studies.

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.\textsuperscript{6} 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.\textsuperscript{32} Refer to 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,\textsuperscript{6} and also for myelodysplastic syndromes.\textsuperscript{32} For anemia associated with myeloid malignancies or acute lymphoblastic leukemia (ALL), refer to NCCN’s guidelines for the condition or appropriate therapy for ALL.

Reference:

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-mediated 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.6,32

- 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.32

**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-KDQI 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):
  o The patient suffers an ESA-related adverse event
  o 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):
  o Decline in Hb concentration
  o Continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required
  o 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 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)\(^\text{10}\), Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)\(^\text{11}\), and other studies\(^\text{13,15,19,20}\) 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.\(^\text{1,4,5,11}\) 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.\(^\text{10}\)

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**


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) for ESA exist. See the LCDs for Erythropoiesis Stimulating Agents and Drugs and Biologicals: Erythropoietin Analogues. (Accessed May 5, 2016)

**REFERENCES**


31. U.S. Food and Drug Administration. October 18, 2010: Cardiovascular and Renal Drugs Advisory Committee Meeting Announcement.


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>11/1/2012</td>
<td>Policy updated per annual review. Added peginesatide to proven use for anemia of CKD for those patients on dialysis with an HCT ≤ 30% at initiation of therapy. Added...</td>
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<tr>
<td>Date</td>
<td>Action/Description</td>
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<tr>
<td></td>
<td>Q2047 HCPCS code for peginesatide. Updated Instructions for Use, CMS, Background, Clinical Evidence, U.S. FDA section, and References. Approved by the National Pharmacy &amp; Therapeutics Committee 8/21/2012. Policy 2011D0028F archived.</td>
</tr>
<tr>
<td>11/1/2011</td>
<td>Policy updated per annual review. Specified ESAs are proven for HCT &lt; 30% for CKD. Added additional criteria to CKD not on dialysis, anemia of cancer and hepatitis C. Removed Hct level from zidovudine-treated HIV indication and added proven for serum erythropoietin levels ≤ 500 mUnits/mL. Added Hct &gt; 30% to allogenic blood transfusions. Removed unproven Hct levels of &gt; 39% for CKD and unproven &gt; 36% for cancer. Added ESAs unproven for pre-operative blood donations, immediate correction of RBC volume, for cancer in patient not on concomitant myelosuppressive therapy, and in Hct &gt; 33% in CKD. Hepatitis C clinical trial summaries added to Clinical Evidence. U.S. FDA section revised per current labeling and REMS program. Added 6/24/2011 FDA Advisory Committee Safety Announcement. Approved by the National Pharmacy &amp; Therapeutics Committee 9/13/2011. Policy 2011D0028E archived.</td>
</tr>
<tr>
<td>N/A</td>
<td>Added &quot;Additional Information&quot; to Coverage Rationale. Anemia associated with myelodysplastic disease added as proven use for darbepoetin. Policy updated to include TREAT study and meta-analysis of trials of cancer patients. Revised NCCN guideline information. U.S. FDA section revised per current labeling and REMS program. Approved by National Pharmacy &amp; Therapeutics Committee 9/14/2010.</td>
</tr>
<tr>
<td>N/A</td>
<td>Policy revised, all sections. Approved by National Pharmacy &amp; Therapeutics Committee 12/8/2009.</td>
</tr>
<tr>
<td>12/19/2007</td>
<td>Added HCPC code Q4081 to policy as recommended by the Manager of Coding and Integrity.</td>
</tr>
<tr>
<td>8/17/2006</td>
<td>Expired HCPCS codes J0880, Q0137 and Q4054 deleted; HCPCS codes J0880 and J0881 added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.</td>
</tr>
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</table>

Anemia Drugs: Darbepoetin Alfa, Epoetin Alfa, and Methoxy Polyethylene Glycol-Epoetin Beta

UnitedHealthcare Commercial Drug Policy

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Effective 10/01/2016