ERYTHROPOIESIS-STIMULATING AGENTS

Policy Number: CSLA2020D0028D **Effective Date**: TBD

Instructions for Use

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APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

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)
- Retacrit™ (epoetin alfa)

The epoetin alfa (i.e., Retacrit, Epogen, Procrit) preferred product criteria in this section applies to the following states: CA, HI, MD, MI, MS, NE, NJ, NY, OH, RI, TN. For all other states, coverage will be provided contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for Retacrit is contingent on criteria in the Diagnosis-Specific Criteria section.
- Prior authorization is not required.

Coverage for Epogen or Procrit is contingent on Medical Necessity Criteria and Diagnosis-Specific Criteria.
- In order to continue coverage, members already on these products will be required to change therapy to Retacrit unless they meet the criteria below.

~~Medical Necessit~~Preferred Product~~y~~ Criteria

Treatment with Epogen or Procrit is medically necessary for the indications specified in this policy when ONE of the criteria below are met:
- **Both** of the following:
  - History of a trial of adequate dose and duration of Retacrit, resulting in minimal clinical response; **and**
  - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior than experienced with Retacrit

  or
- **Both** of the following:
  - History of failure, contraindication, or intolerance to Retacrit; **and**

- Physician attests that, in their clinical opinion, the same failure, contraindication, or intolerance would not be expected to occur with Epogen or Procrit

Diagnosis-Specific Criteria

"ESAs" will be used to refer to all erythropoiesis stimulating agents, unless otherwise specified.

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.

Anemia Due to Chronic Kidney Disease

Patients Receiving Dialysis

- **ESAs 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]
  - Patient is on dialysis; **and**
  - 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]

Patients NOT Receiving Dialysis

- **ESAs 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]
  - Patient is **not** on dialysis; **and**
  - Hematocrit less than 30% at initiation of therapy; **and**
  - The rate of hematocrit decline indicates the likelihood of requiring a red blood cell (RBC) transfusion; **and**
  - 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]

Anemia Due to Cancer Chemotherapy

- **Aranesp, Epogen, Procrit, and Retacrit are proven when used to treat anemia in cancer chemotherapy when BOTH of the following criteria are met:**[1,4,5]
  - Hematocrit less than 30% at initiation of therapy; **and**
  - There is a minimum of two additional months of planned chemotherapy

- **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]

- **ESAs are unproven to treat anemia in patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.**

Anemia Associated with Myelodysplastic Disease

- **Aranesp, Epogen, Procrit, and Retacrit are proven to treat anemia associated with myelodysplastic disease (MDS) when BOTH of the following criteria are met:** [2,3,8,9,32,46]
  - **One** of the following:
    - Serum erythropoietin level ≤ 500 mUnits/mL; **or**
    - Hematocrit is less than or equal to 30% at the initiation of therapy;

    and
  - For continuation of therapy, the hematocrit remains less than 36%

Anemia Associated with Zidovudine Treatment in HIV-Infected Patients

- **Epogen, Procrit, and Retacrit are proven to treat anemia in HIV-infected patients when BOTH of the following criteria are met:**[4,5,46]
  - Patient is receiving zidovudine administered at ≤ 4200 mg/week; **and**
  - Endogenous serum erythropoietin level ≤ 500 mUnits/mL[4,5]; **and**

- Hematocrit is less than 30% at initiation of therapy

Anemia in Patients with Hepatitis C with Ribavirin and Interferon Therapy

- **Epogen, Procrit, and Retacrit are proven to treat anemia associated with hepatitis C virus infection when ALL of the following criteria are met:**[22,23,33-36,46]
  - Patient is receiving ribavirin and interferon therapy; **and**
  - Hematocrit is less than or equal to 30% at initiation of therapy; **and**
  - For continuation of therapy, the hematocrit remains less than 36%

Preoperative Use for Reduction of Allogeneic Blood Transfusions in Surgery Patients

- **Epogen, Procrit, and Retacrit are proven perioperatively to reduce the need for allogeneic blood transfusions when ALL of the following criteria are met:**[4,5,46]
  - Perioperative Hct is greater than 30% and less than or equal to 39%; **and**
  - Patient is at high risk for blood loss during surgery; **and**
  - Patient is unable or unwilling to donate autologous blood; **and**
  - Surgery procedure is elective, noncardiac, and nonvascular

- **ESAs are unproven for patients who are willing to donate autologous blood pre-operatively or in patient undergoing cardiac or vascular surgery.**[4,5]

Additional Information

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%.

Unproven

ESAs are unproven for:[1,4,5,6,42]

- 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.
- Patients with cancer receiving hormonal agents, biologic products or radiotherapy (unless also receiving concomitant myelosuppressive chemotherapy).
- Patients who require an immediate correction of anemia as a substitute for RBC transfusions.
- Patients undergoing cardiac or vascular surgery.
- Patients scheduled for surgery who will donate autologous blood.
- Patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
- Patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.

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 federal, state or contractual requirements 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.

HCPCS Code	Description
J0881	Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882	Injection, darbepoetin alfa, 1 mcg (for ESRD on dialysis)
J0885	Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887	Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888	Injection, epoetin beta, 1 microgram, (for non-ESRD use)

HCPCS Code	Description
Q4081	Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105	Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for ESRD on dialysis), 100 units
Q5106	Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for non-ESRD use), 1000 units

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.[4,5] Darbepoetin alfa is an erythropoiesis stimulating protein, closely related to erythropoietin, and is also produced by recombinant DNA technology.[1] 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^{45}, 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

Proven

Oncology Related Anemia

Researchers in The Cochrane Collaboration conducted a review of the effect of epoetin and darbepoetin for people with cancer.[39] 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.[1,4,5,16] 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[1,4,5,18], patients receiving chemotherapy for lymphoid malignancy[1,4,5], and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.[1,4,5]

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) $\leq$ 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).[1,4,5]

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).[1,4,5,17] 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)[26], 1.17 (95% CI, 1.06-1.30)[27], and 1.15 (95% CI, 1.03-1.29)[28]. Additionally, two analyzed for the relative risks of thromboembolism and reported values of 1.57 (95% CI, 1.31-1.87)[26] and 1.69 (95% CI, 1.27-2.24).[28] However, two other recent meta-analyses did not find an association between ESAs and increased risk of death or disease progression[29,30] but did confirm the increased relative risk of thromboembolism: 1.57 (95% CI, 1.10-2.26)[29] and 1.48 (95% CI, 1.28-1.72).[30]

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%.[1,4,5,21]

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 m^2 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.[25]

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.[4,5]

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.[37] This prospective, randomized, multicenter, controlled trial enrolled 683 patients with a 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 ribavririn (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.[33]

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.[34]

Technology Assessment

In 2017, several Cochrane reviews were published assessing the efficacy of erythropoietin products in various clinical scenarios:

An analysis was performed to assess the effectiveness and safety of ESAs (erythropoietin (EPO) and/or Darbe) initiated early (before eight days after birth) compared with placebo or no intervention in reducing red blood cell (RBC) transfusions, adverse neurological outcomes, and feeding intolerance including necrotising enterocolitis (NEC) in preterm and/or low birth weight infants.[45] This updated review includes 34 studies enrolling 3643 infants. All analyses compared ESAs versus a control consisting of placebo or no treatment. Early ESAs reduced the risk of 'use of one or more [red blood cell] RBC transfusions' (typical risk ratio (RR) 0.79, 95% confidence interval (CI) 0.74 to 0.85; typical risk difference (RD) -0.14, 95% CI -0.18 to -0.10; I2 = 69% for RR and 62% for RD (moderate heterogeneity); number needed to treat for an additional beneficial outcome (NNTB) 7, 95% CI 6 to 10; 19 studies, 1750 infants). The quality of the evidence was low.Necrotising enterocolitis was significantly reduced in the ESA group compared with the placebo group (typical RR 0.69, 95% CI 0.52 to 0.91; typical RD -0.03, 95% CI -0.05 to -0.01; I2 = 0% for RR and 22% for RD (low heterogeneity); NNTB 33, 95% CI 20 to 100; 15 studies, 2639 infants). The quality of the evidence was moderate.Data show a reduction in 'Any neurodevelopmental impairment at 18 to 22 months' corrected age in the ESA group (typical RR 0.62, 95% CI 0.48 to 0.80; typical RD -0.08, 95% CI -0.12 to -0.04; NNTB 13, 95% CI 8 to 25. I2 = 76% for RR (high heterogeneity) and 66% for RD (moderate); 4 studies, 1130 infants). The quality of the evidence was low.Results reveal increased scores on the Bayley-II Mental Development Index (MDI) at 18 to 24 months in the ESA group (weighted mean difference (WMD) 8.22, 95% CI 6.52 to 9.92; I2 = 97% (high heterogeneity); 3 studies, 981 children). The quality of the evidence was low.The total volume of RBCs transfused per infant was reduced by 7 mL/kg. The number of RBC transfusions per infant was minimally reduced, but the number of donors to whom infants who were transfused were exposed was not significantly reduced. Data show no significant difference in risk of stage ≥ 3 retinopathy of prematurity (ROP) with early EPO (typical RR 1.24, 95% CI 0.81 to 1.90; typical RD 0.01, 95% CI -0.02 to 0.04; I2 = 0% (no heterogeneity) for RR; I2 = 34% (low heterogeneity) for RD; 8 studies, 1283 infants). Mortality was not affected, but results show significant reductions in the incidence of intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). The authors concluded that early administration of ESAs reduces the use of red blood cell (RBC) transfusions, the volume of RBCs transfused, and donor exposure after study entry. Small reductions are likely to be of limited clinical importance. Donor exposure probably is not avoided, given that all but one study included infants who had received RBC transfusions before trial entry. This update found no significant difference in the rate of ROP (stage ≥ 3) for studies that initiated EPO treatment at less than eight days of age, which has been a topic of concern in earlier versions of this review. Early EPO treatment significantly decreased rates of IVH, PVL, and NEC. Neurodevelopmental outcomes at 18 to 22 months and later varied in published studies. Ongoing research should evaluate current clinical practices that will limit donor exposure. Promising but conflicting results related to the neuro protective effect of early EPO require further study. Very different results from the two largest published trials and high heterogeneity in the analyses indicate that we should wait for the results of two ongoing large trials before drawing firm conclusions. Administration of EPO is not currently recommended because limited benefits have been identified to date. Use of darepoetin requires further study.

A review was performed to focus on harms in assessing the effects of erythropoiesis-stimulating agents (ESAs), alone or in combination, compared with placebo, no treatment or a different active treatment regimen when administered off-label to critically-ill people.[44] Of the 27,865 records identified, 39 clinical trials and 14 observational studies, including a total of 945,240 participants, were eligible for inclusion. Five studies are awaiting classification. Overall, we found 114 adverse events in 33 studies (30 RCTs and three observational studies), and mortality was reported in 41 studies (32 RCTs and nine observational studies). Most studies were at low to moderate risk of bias for harms outcomes. However, overall harm assessment and reporting were of moderate to low quality in the RCTs, and of low quality in the observational studies. We downgraded the GRADE quality of evidence for venous thromboembolism and mortality to very low and low, respectively, because of risk of bias, high inconsistency, imprecision and limitations of study design.It is unclear whether there is an increase in the risk of any adverse events (Bayesian risk ratio (RR) 1.05, 95% confidence interval (CI) 0.93 to 1.21; 3099 participants; 9 studies; low-quality evidence) or venous thromboembolism (Bayesian RR 1.04, 95% CI 0.70 to 1.41; 18,917 participants; 18 studies; very low-quality evidence).There was a decreased risk of mortality with off-label use of ESAs in critically-ill people (Bayesian RR 0.76, 95% CI 0.61 to 0.92; 930,470 participants; 34 studies; low-quality evidence). The authors concluded that low quality of evidence suggests that off-label use of ESAs may reduce mortality in a critical care setting. There was a lack of high-quality evidence about the harm of ESAs in critically-ill people. The information for biosimilar ESAs is less conclusive. Most studies neither evaluated ESAs' harm as a primary outcome nor predefined adverse events. Any further studies of ESA should address the quality of evaluating, recording and reporting of adverse events.

An analysis was performed to assess benefits and harms of CERA compared with other epoetins (darbepoetin alfa and epoetin alfa or beta) or placebo/no treatment or CERA with differing strategy of administration for anaemia in individuals with CKD.[43] Twenty-seven studies involving 5410 adults with CKD. Seven studies (1273 participants) involved people not requiring dialysis, 19 studies (4209 participants) involved people treated with dialysis and one

study (71 participants) evaluated treatment in recipients of a kidney transplant. Treatment was given for 24 weeks on average. No data were available for children with CKD. Studies were generally at high or unclear risk of bias from allocation concealment and blinding of outcomes. Only two studies masked participants and investigators to treatment allocation. One study compared CERA with placebo, nine studies CERA with epoetin alfa or beta, nine studies CERA with darbepoetin alfa, and two studies compared CERA with epoetin alfa or beta and darbepoetin alfa. Three studies assessed the effects of differing frequencies of CERA administration and five assessed differing CERA doses.There was low certainty evidence that CERA had little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), hypertension (RR 1.01, 95% CI 0.75 to 1.37; RR 1.00, 95% CI 0.79 to 1.28), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) compared to epoetin alfa/beta or darbepoetin alfa respectively. There was insufficient evidence to compare the effect of CERA to placebo on clinical outcomes. Only one low quality study reported that CERA compared to placebo might lead to little or no difference in the risk of major cardiovascular events (RR 2.97, 95% CI 0.31 to 28.18) and hypertension ((RR 0.73, 95% CI 0.35 to 1.52). There was low certainty evidence that different doses (higher versus lower) or frequency (twice versus once monthly) of CERA administration had little or no different effect on all-cause mortality (RR 3.95, 95% CI 0.17 to 91.61; RR 0.97, 95% CI 0.56 to 1.66), hypertension (RR 0.45, 95% CI 0.08 to 2.52; RR 0.85, 95% CI 0.60 to 1.21), and blood cell transfusions (RR 4.16, 95% CI 0.89 to 19.53; RR 0.91, 95% CI 0.51 to 1.62). No studies reported comparative treatment effects of different ESAs on health-related quality of life. The authors concluded that there is low certainty evidence that CERA has little or no effects on patient-centred outcomes compared with placebo, epoetin alfa or beta or darbepoetin alfa for adults with CKD. The effects of CERA among children who have CKD have not studied in RCTs.

This review aimed to evaluate the benefits and harms of different routes, frequencies and doses of epoetins (epoetin alpha, epoetin beta and other short-acting epoetins) for anaemia in adults and children with CKD not receiving dialysis. Fourteen randomized controlled trials (2616 participants) were included in the analysis.[39] Nine studies were multi-centre and two studies involved children. The risk of bias was high in most studies; only three studies demonstrated adequate random sequence generation and only two studies were at low risk of bias for allocation concealment. Blinding of participants and personnel was at low risk of bias in one study. Blinding of outcome assessment was judged at low risk in 13 studies as the outcome measures were reported as laboratory results and therefore unlikely to be influenced by blinding. Attrition bias was at low risk of bias in eight studies while selective reporting was at low risk in six included studies. Four interventions were compared: epoetin alpha or beta at different frequencies using the same total dose (six studies); epoetin alpha at the same frequency and different total doses (two studies); epoetin alpha administered intravenously versus subcutaneous administration (one study); epoetin alpha or beta versus other epoetins or biosimilars (five studies). One study compared both different frequencies of epoetin alpha at the same total dose and at the same frequency using different total doses.Data from only 7/14 studies could be included in our meta-analyses. There were no significant differences in final haemoglobin (Hb) levels when dosing every two weeks was compared with weekly dosing (4 studies, 785 participants: MD -0.20 g/dL, 95% CI -0.33 to -0.07), when four weekly dosing was compared with two weekly dosing (three studies, 671 participants: MD -0.16 g/dL, 95% CI -0.43 to 0.10) or when different total doses were administered at the same frequency (four weekly administration: one study, 144 participants: MD 0.17 g/dL 95% CI -0.19 to 0.53).Five studies evaluated different interventions. One study compared epoetin theta with epoetin alpha and found no significant differences in Hb levels (288 participants: MD -0.02 g/dL, 95% CI -0.25 to 0.21). One study found significantly higher pain scores with subcutaneous epoetin alpha compared with epoetin beta. Two studies (165 participants) compared epoetin delta with epoetin alpha, with no results available since the pharmaceutical company withdrew epoetin delta for commercial reasons. The fifth study comparing the biosimilar HX575 with epoetin alpha was stopped after patients receiving HX575 subcutaneously developed anti-epoetin antibodies and no results were available. Adverse events were poorly reported in all studies and did not differ significantly within comparisons. Mortality was only detailed adequately in four studies and only one study included quality of life data. The authors concluded that epoetin alpha given at higher doses for extended intervals (two or four weekly) is non-inferior to more frequent dosing intervals in maintaining final Hb levels with no significant differences in adverse effects in non-dialysed CKD patients. However the data are of low methodological quality so that differences in efficacy and safety cannot be excluded. Further large, well designed, RCTs with patient-centred outcomes are required to assess the safety and efficacy of large doses of the shorter acting ESAs, including biosimilars of epoetin alpha, administered less frequently compared with more frequent administration of smaller doses in children and adults with CKD not on dialysis.

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.[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 Hematopoietic Growth Factors provide recommendations for the evaluation of Hgb ≤ 11 g/dL or ≥ 2 g/dL below baseline in patients with cancer.[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 Myelodysplatic Syndromes (MDS) provides recommendations for use of ESA in the management of symptomatic anemia in MDS patients.[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[6], and also for myelodysplastic syndromes.[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.
- ESAs are not indicated for patients with cancer not receiving therapy, receiving non-myelosuppressive therapy or 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.[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-KDOQI 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)*

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Epogen, Procrit, and Retacrit (epoetin alfa biosimilar) 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.[4,5,38]

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.[1]

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

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]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare covers Erythropoiesis Stimulating Agents (ESAs) for the treatment of anemia in patients with chronic renal failure who are on dialysis. See the Medicare Benefit Policy Manual, Chapter 15, § 50.5.2- Erythropoietin (EPO) and the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

Medicare covers ESA treatment for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia when criteria are met. See the National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). Local Coverage Determinations (LCDs) exist; see the LCDs for Erythropoiesis Stimulating Agents (ESAs). (Accessed July 11, 2019)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	**Template Update** • Reorganized policy template: o Simplified and relocated *Application* section; previously titled *State Exceptions* o Relocated *Background* and *FDA* sections **Coverage Rationale** • Added language to indicate: o Coverage for Retacrit is contingent on criteria in the *Diagnosis-Specific Criteria* section of the policy; prior authorization is not required o Coverage for Epogen or Procrit is contingent on *Medical Necessity Criteria* and *Diagnosis-Specific Criteria* sections of the policy; in order to continue coverage, members already on these products will be required to change therapy to Retacrit unless they meet the *Medical Necessity Criteria* section of the policy o Treatment with Epogen or Procrit is medically necessary for the indications specified in this policy when one of the criteria below are met: ▪ Both of the following: - History of a trial of adequate dose and duration of Retacrit, resulting in minimal clinical response; and - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior than experienced with Retacrit or ▪ Both of the following: - History of failure, contraindication, or intolerance to Retacrit; and - Physician attests that, in their clinical opinion, the same failure,

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	contraindication, or intolerance would not be expected to occur with Epogen or Procrit **Applicable Codes** • Updated list of applicable HCPCS codes to reflect annual code edits; revised description for Q5105 and Q5106 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit 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 UnitedHealthcare Medical Benefit Drug Policies 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.