Policy Number	**RX501.069**
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Erythropoiesis-Stimulating Agents (ESAs)

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Related Policies (if applicable)
RX502.061: Oncology Medications

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: A form is available for optional use to assist in requesting review for consideration of coverage of Erythropoiesis-Stimulating Agents (ESAs). The form is available on the Provider/Forms page of the applicable Blue Cross Blue Shield web site, i.e., BCBSIL.com, BCBSMT.com, BCBSNM.com, BCBSOK.com, or BCBSTX.com.

NOTE 2: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications.

General Criteria for Erythropoiesis-Stimulating Agents (ESAs)

Erythropoiesis-stimulating agents (ESAs) **may be considered medically necessary**, when **ALL** of the following criteria are met:

A. Prior to starting ESA therapy, the individual's iron stores should be evaluated, and blood ferritin should be at least 100 ng/mL (nanograms per milliliter) OR transferrin saturation should be at least 20%—initial and ongoing ESA therapy should not be administered unless iron stores are maintained; **AND**
B. The ESA dose should be the lowest dose that will gradually increase hemoglobin (Hb) concentration to the lowest level sufficient to avoid the need for red blood cell (RBC) transfusion; **AND**
C. Blood pressure is adequately controlled and closely monitored before and during ESA therapy; **AND**
D. **Drug-specific criteria listed below must be met.**

Epoetin Alfa (Epogen®, Procrit®), Epoetin alfa-epbx (Retacrit®)—Drug-Specific Criteria

When the General Criteria (listed above) are met, the use of epoetin alfa or epoetin alfa-epbx **may be considered medically necessary** for treatment of anemia:

1. Associated with chronic kidney disease (including end-stage renal disease—ESRD) (See **NOTE 3**); **OR**
2. Related to therapy with AZT (zidovudine) in human immunodeficiency virus (HIV)-infected individuals, when the endogenous serum erythropoietin level is ≤500 mUnits/ml; **OR**
3. To reduce the need for allogeneic blood transfusion in pre-operative surgery individuals who meet **all** of the following criteria:
   a) Scheduled for elective, non-cardiac, non-vascular surgery, **and**
   b) Hb <13 g/dL, **and**
   c) Not a candidate for autologous blood transfusion, **and**

d) High risk for significant perioperative blood loss; **OR**

4. Associated with Hepatitis C that is being treated with the combination of ribavirin and interferon alfa or ribavirin and peg interferon, **AND**:
   a) Other causes of anemia have been ruled out, **and**
   b) Individual has failed to respond (i.e., severe anemia) within two weeks after reducing the dose of Ribavirin by 200 mg/day from the initial dose (**NOTE 4**: Use of erythropoietin may be considered prior to dose reduction for the following: 1) documented evidence of cirrhosis, or 2) post liver transplant, or 3) HIV co-infection), **and**
   c) Hb<10 g/dL, or individual is symptomatic and has Hb <11 g/dL.

Darbepoetin Alfa (Aranesp®)—Drug-Specific Criteria
When the General Criteria (listed above) are met, the use of darbepoetin alfa **may be considered medically necessary** for treatment of anemia associated with chronic kidney disease (including end-stage renal disease—ESRD) (See **NOTE 3**).

Pegylated (PEG)-epoetin beta (Mircera®)—Drug Specific Criteria
When the General Criteria (listed above) are met, Pegylated (PEG)-epoetin beta **may be considered medically necessary** for treatment of anemia associated with chronic kidney disease (CKD) (See **NOTE 3**).

The use of PEG-epoetin beta (Mircera) **is considered experimental, investigational and/or unproven** for all other indications.

NOTE 3: For use in chronic kidney disease (including end-stage renal disease-[ESRD]), therapy may be initiated to reduce the need for red cell transfusions when Hb has dropped below 10 g/dL (no target Hb is recommended, but levels of 11 g/dL or greater should be avoided).

The use of an erythropoiesis-stimulating agent (ESA) **is considered experimental, investigational and/or unproven for any other indication**, including but not limited to the treatment of:

- Aplastic anemia; or
- Any other type of anemia (except as noted above) including, but not limited to, anemia secondary to:
  - Deficiency (e.g., iron, folate, B12);
  - Hemolysis;
  - Bleeding (e.g., occult, gastrointestinal);
  - Hemolytic disease (e.g., sickle cell anemia, thalassemia, porphyria);
  - Gaucher's disease;
  - HIV, when anemia is due to factors other than AZT (zidovudine) therapy (e.g., iron or folate deficiency, hemolysis, gastrointestinal bleeding, etc.); or
  - Pregnancy.

Policy Guidelines

None.

Description

Endogenous erythropoietin is a glycoprotein hematopoietic growth factor that regulates hemoglobin levels in response to changes in the blood oxygen concentration. Erythropoiesis-stimulating agents (ESAs) (e.g., epoetin alfa, pegylated epoetin beta, darbepoetin) are produced using recombinant deoxyribonucleic acid (DNA) technologies and have pharmacologic properties similar to endogenous erythropoietin. The primary clinical use of ESAs is to treat chronic anemia.

Endogenous Erythropoietin and Anemia

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

The severity of anemia is defined by blood hemoglobin concentration. Normal ranges are 12 to 16 g/dL in women and 14 to 18 g/dL in men. Mild anemia is defined as hemoglobin from 10 g/dL to the lower limit of normal ranges, moderate anemia is 8 to 10 g/dL, and severe anemia is 8 g/dL or less.

Treatment

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

Red blood cell transfusion is the traditional approach to ameliorate anemia symptoms quickly. However, this approach carries a risk for several potential adverse events. The highest adverse event risk (1 per 432 whole blood units transfused) is for transfusion-related acute lung injury. Adverse events due to errors in transfusion (e.g., type mismatch) are estimated to occur at a

rate of 1 per 5000 to 10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), human immunodeficiency virus (HIV) (<1 in 1,000,000), and bacterial contaminants (1 per 10,000 to 100,000) have fallen dramatically since the early 1990s. Therefore, although the initial impetus to commercialize erythropoietin replacement products was based on a reduction in the risks associated with blood transfusion, current practices have mitigated many of those risks. Nonetheless, blood shortages, transfusion errors, and risks of alloimmunization and transfusion-related acute lung injury provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Table 1 summarizes the 4 ESA products that have been licensed in the U. S.; however, peginesatide is no longer manufactured.

Epoetin alfa and epoetin beta have the same amino acid sequence as endogenous erythropoietin but differ from each other in glycosylation; clinical effects are considered interchangeable. However, the epoetins and darbepoetin all have pharmacologic actions similar to those of the endogenous hormone. When given to individuals with functioning erythropoiesis, each binds to and activates the human erythropoietin receptor and thus increases the number of RBCs and the blood concentration of hemoglobin. Both brands of epoetin alfas, PEG-epoetin beta, and darbepoetin alfa are approved by the U.S. Food and Drug Administration (FDA) to treat anemia in patients with CKD who are on or are not on dialysis. Epoetin alfa and darbepoetin alfa also are approved for other indications.

Regulatory Status

Table 1 summarizes the major regulatory timelines for approval actions for new indications of ESAs.

Table 1. Erythropoiesis-Stimulating Agents Approved by the U.S. Food and Drug Administration

Drug	Manufacturer	Approval Date	Indication
Epoetin Alfa			
Epogen®	Amgen	1989	Approved for use in patients with anemia due to CRF.
		1991	Approved for use in zidovudine-treated, HIV-infected patients.
		1993	Approved for chemotherapy-induced anemia in patients with non-myeloid malignancies.
		1996	Approved for presurgical use in certain patients undergoing surgery.

Procrit®	Janssen Products	See all dates and indications for Epogen®	
Darbepoetin Alfa			
Aranesp®	Amgen	2001	Approved for use in patients with anemia due to CRF.
		2002	Approved for chemotherapy-induced anemia in patients with non-myeloid malignancies.
Peginesatide			
Omontys®	Takeda and Affymax	2012	Approved for use in adults with anemia due to CKD who are on dialysis.
		2013	Voluntary recall of all lots due to post-marketing reports of serious hypersensitivity.
Methoxy Polyethylene Glycol Epoetin Beta			
Mircera®	Vifor	2007	Approved for use in patients with anemia due to CRF who are on dialysis or not on dialysis.
		2009	Injunction prohibiting U.S. sales until mid-2014 due to copyright infringement.
		2015	Resumption of U.S. sales.

CKD: chronic kidney disease; CRF: chronic renal failure.

Information on the associated Biosimilar Product Retacrit (epoetin alfa-epbx) is noted below.

Risk Evaluation and Mitigation Strategy

Studies of patients with CKD and hemoglobin greater than 11 g/dL found that treatment with epoetin alfa and darbepoetin alfa resulted in increased risks of mortality or cardiovascular adverse events or stroke. In response to this data, the FDA implemented a risk evaluation and mitigation strategy (REMS) in 2011 under which providers and hospitals were required to counsel patients and each patient had to complete a provider acknowledgment form before treatment.

In April 2017, the FDA eliminated the risk evaluation and mitigation strategy for Epogen®/Procrit® and Arenesp®, citing that "the risks can be communicated by the current product prescribing information" and that "The appropriate use of ESAs is supported by the Centers for Medicare and Medicaid Services' (CMS) National Coverage Determination, the American Society of Clinical Oncology, the American Society of Hematology clinical guidelines, which are evidence-based guidelines intended to provide a basis for the standard of care in clinical oncology."

There is no REMS for PEG-epoetin beta.

In 2012, the FDA approved a REMS for peginesatide with a communication plan as its only component. The plan's goal was to inform all health care professionals who might prescribe the drug that peginesatide is indicated only for adults with chronic kidney disease on dialysis, as well as to warn health care professionals of potentially fatal risks associated with its use in patients with chronic kidney disease not on dialysis. Peginesatide is currently discontinued.

Postapproval U.S. Food and Drug Administration Regulatory Actions

In 2006, the FDA issued an advisory on the serious cardiovascular risks from ESA therapy in patients with CKD, as evidenced in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and the Normal Hematocrit Cardiac Trial (NHCT) studies. (1) Subsequently, the FDA received reports of increased risks associated with ESAs used to treat anemia in cancer patients who were receiving or not receiving chemotherapy, as well as a report of thrombotic risks in patients receiving ESAs in the peri-surgical setting.

Regarding dosage information, periodic reassessment of ESA safety has determined that clinical data do not support a therapeutic hemoglobin target free of risk for mortality. Consequently, revised "Dosage and Administration" sections of the product label deleted any specific therapeutic hemoglobin or hematocrit "target" range for ESAs. Instead, revised labels recommended that prescribers use the lowest ESA dose that will gradually increase hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusion. For anemic chronic renal failure patients, this recommendation was primarily based on the NHCT and the CHOIR study findings, as well as the lack of data for any specific hemoglobin or hematocrit threshold or range. Clinical data did not identify specific hemoglobin or hematocrit levels that directly correlated with a "....reduction in the need for red blood cell transfusion," the main treatment benefit supporting ESA efficacy. Label revisions allowed prescribers to use their clinical judgment in determining the "…lowest level sufficient to avoid the need for red blood cell transfusion." These data prompted a reassessment of the safety information contained in the labeling for Mircera (2018), (2) Aranesp (2019), (3) Epogen (2018), (4) and Procrit (2018) (5) and culminated in the approval of revised labels. These revisions clarified the evidence for safety and effectiveness of these products and provided more explicit directions and recommendations for their use.

These recommendations were consistent with those made by the FDA in May 2007 and in September 2007. Revisions included strengthened *boxed warnings* and "*Warnings and Precautions*" sections, and changes to the "*Indications and Usage*," "*Clinical Trials Experience*," and "*Dosage and Administration*" sections of the product labels. The revised boxed warnings and limitations of use shown next reflect current labeling for these ESAs. (2, 3, 4, 5)

This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications.

Chronic Renal Failure

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Epogen/Procrit, Mircera, or Aranesp dose sufficient to reduce the need for RBC transfusions.

Perisurgery (Epogen and Procrit Only)
- Due to increased risk of deep venous thrombosis, prophylaxis for deep venous thrombosis is recommended.

Limitations of Use
Epogen, Procrit, and Aranesp have not been shown to improve quality of life, fatigue, or patient well-being (for any indication).

Epogen, Procrit, and Aranesp are not indicated for use:
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Epogen and Procrit also are not indicated for use:
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.

Retacrit
In May 2018, Retacrit (epoetin alfa-epbx; Pfizer) was approved by the FDA as a biosimilar of epoetin alfa for the treatment of anemia due to CKD in patients on dialysis and not on dialysis, zidovudine in patients with HIV-infection and the effects of concomitant myelosuppressive chemotherapy. Retacrit is also indicated for the reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

<u>Administration</u>
ESAs and pegylated (PEG) epoetin beta are to be administered according to current FDA-approved labeling for each product, using recommended hemoglobin levels for starting, stopping, and dose adjustment. This includes decreasing the dose of ESA as the hemoglobin approaches the target level.

Before commencing ESA or PEG-epoetin beta therapy, the patient's iron stores, blood ferritin, and transferrin saturation should be evaluated, adjusted, and maintained within normal physiologic limits. ESA or PEG-epoetin beta therapy should not be administered without adequate iron stores.

Blood Pressure Monitoring

Blood pressure should be adequately controlled before initiation of ESA therapy and closely monitored and controlled during treatment. ESAs and PEG-epoetin beta are contraindicated in patients with uncontrolled hypertension.

Erythropoiesis-Stimulating Agents and Pegylated Epoetin Beta; Discontinuation
Individuals with chronic kidney disease who do not respond adequately over a 12-week dose escalation period should not have their ESA or PEG-epoetin beta dose increased further. Increasing ESA or PEG-epoetin beta dose further is unlikely to improve response and may increase risks; the lowest ESA or PEG-epoetin beta dose that maintains adequate hemoglobin to avoid recurrent red blood cell transfusions should be used. Other causes of anemia should be evaluated. If responsiveness does not improve, discontinue ESA or PEG-epoetin beta therapy.

Rationale

This medical policy was created in December 2008 and has been updated regularly with literature searches of the PubMed database. The most recent literature update was performed through March 7, 2024.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Information on the use of Erythropoiesis-Stimulating Agents (ESAs) in chronic renal failure (CRF) was obtained from several sources, including a meta-analysis by Strippoli et al. (2004) evaluating blood hemoglobin targets for patients with CRF-associated anemia. (6) The FDA-approved labels for ESAs available in the United States comprised additional data sources for

this policy, in particular, recommended dosing information for the different clinical settings covered.

Chronic Kidney Disease and Anemia

Clinical Context and Therapy Purpose

The purpose of epoetin alfa, pegylated (PEG)-epoetin beta or darbepoetin is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with anemia related to chronic kidney disease (CKD).

The following PICO was used to select literature to inform this policy.

Population

The relevant population of interest is individuals with CKD-related anemia.

Interventions

The therapies being considered are epoetin alfa, pegylated epoetin beta, and darbepoetin.

Comparators

The following practice is currently being used to treat anemia related to CKD: standard of care.

Outcomes

The general outcomes of interest are symptoms, morbid events, medication use, treatment-related mortality, and treatment-related morbidity. Follow-up at 1 and 3 years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Epoetin Alfa, Epoetin Beta, and Darbepoetin

Pivotal Trials

At initial approval of epoetin in 1989, the primary objective of treatment was to raise hemoglobin concentration sufficiently to avoid transfusion, with a target range of 9 to 10 g/dL in anemic patients with CKD. The first National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines in 1997 recommended a hemoglobin concentration of 11 g/dL, a level that was increased in the 2007 NKF-KDOQI anemia guidelines to 11 to 13 g/dL. (7) With increased experience in the use of ESAs, it became unclear whether higher hemoglobin target concentrations, including normalization, would yield additional benefits such as physical

function and improved cardiovascular outcomes. Clinical doubts were raised with the publication of the first large RCT of hemoglobin normalization using epoetin alfa in hemodialysis patients (Normal Hematocrit Cardiac Trial [NHCT]). (8) The NHCT, reported by Besarab et al. (1998), showed a trend toward increased mortality risk and significantly increased the risk for vascular access thrombosis with ESA treatment to a hematocrit (Hct) target of 42%. Subsequently, 4 published RCTs in hemodialysis patients with end-stage renal disease (ESRD) and 8 in nondialysis patients with CKD found improved physical function at higher hemoglobin targets, but none demonstrated significant improvements in cardiovascular end points or mortality. (9)

The Epogen/Procrit labeling was modified in 1996 to include results of NHCT, which showed a higher mortality rate for anemic dialysis patients randomized to an Hct of 42%, compared with an Hct of 30%. The CHOIR study, reported by Singh et al. (2006), found worse cardiovascular outcomes for anemic CRF patients who were not undergoing dialysis and who were randomized to a target hemoglobin level of 13.5 g/dL or to a hemoglobin level of 11.3 g/dL. (10) Subsequent analyses of CHOIR outcomes showed shorter times to progression of kidney disease and higher rates of renal replacement therapy and death among patients randomized to the higher hemoglobin target. (11) The Cardiovascular Reduction Early Anemia Treatment Epoetin β (CREATE) study, reported by Drueke et al. (2006), was similar to CHOIR but enrolled fewer patients. (12) The CREATE trial did not demonstrate statistically significant differences in adverse cardiovascular outcomes for the higher hemoglobin group, but the general trend of major cardiovascular outcomes was similar to the CHOIR findings. In the Trial to Reduce Cardiovascular Events With Aranesp® Therapy (TREAT) study, Pfeffer et al. (2009) randomized 4038 patients with type 2 diabetes, hemoglobin levels of 11 g/dL or less, and CKD not on dialysis. (13) Patients in 1 arm were treated with darbepoetin to a target hemoglobin level of 13 g/dL, and those in the other arm received darbepoetin only if hemoglobin fell below 9 g/dL. Risks for 2 endpoints did not differ significantly between arms: death or a cardiovascular event (hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.94 to 1.17; p=0.41) and death or ESRD (HR=1.06; 95% CI, 0.95 to 1.19; p=0.29). However, fatal or nonfatal stroke was significantly increased among patients randomized to the higher hemoglobin target (HR=1.92; 95% CI, 1.38 to 2.68; p<0.001). Multivariate analysis found no statistically significant correlations between increased stroke risk and any baseline characteristic; effects on blood pressure, hemoglobin, or platelet count; or darbepoetin dose. (14)

Systematic Reviews

Tables 2 and 3 summarize the characteristics and results of the systematic reviews assessed. A brief narrative of each review is provided below the tables. The systematic review by Amato et al. (2018), discussed below, is not included in the tables due to the heterogeneity of outcome measures. (15)

Table 2. Characteristics of Systematic Reviews Assessing Chronic Kidney Disease and Anemia

Study	Dates	Trials	Participants	N (Range)	Design	Duration

Chung et al. (2023) (16)	Through April 2022	117	Patients with anemia and CKD	25,237	RCT	NR
Roger et al. (2017) (17)	1995-2007	7	Patients with CKD on dialysis	615	RCT	NR
Cody and Hodson (2016) (18)	1989-2008	19	Patients with anemia and CKD	993 (8-186)	RCT and quasi-RCT	8 wk-36 mo
Collister et al. (2016) (19)	1995-2014	17	Patients with anemia and CKD	NR	RCT	NR
Palmer et al. (2014) (20)	2002-2011	21	Patients with anemia and CKD	8328 (18-507)	RCT and quasi-RCT	Varied
Vinhas et al. (2012) (21)	1998-2009	5	Patients with anemia and CKD	7904 (596-4038)	RCT	14-36 mo

CKD: chronic kidney disease; mo: months; NR: not reported; RCT: randomized controlled trials; wk: week.

Table 3. Results of Systematic Reviews Assessing Chronic Kidney Disease and Anemia

Study	**VAT**	**Stroke**	**Progress to ESRD**	**All-Cause Mort-ality**	**Need Blood Trans-fusion**	**Hb, g/L**	**Hct, %**	**HRQOL**	**ESA Dose Reduc-tion, %**
Chung et al. (2023) (16)			NR			NR	NR	NR	NR
Epoetin alfa vs. placebo									
OR	1.74	2.25		0.79	0.28				
95% CI	0.63 to 4.80	0.83 to 6.15		0.51 to 1.22	0.13 to 0.61				
Epoetin beta vs. placebo									
OR	2.20	1.10		0.69	0.19				
95% CI	0.82 to 5.92	0.16 to 7.77		0.40 to 1.20	0.08 to 0.47				
Darbepoetin vs. placebo									
OR	1.47	2.03		0.99	0.27				

95% CI	0.55 to 3.95	1.49 to 2.77		0.81 to 1.21	0.11 to 0.67				
Roger et al. (2017) (17)	NR	NR	NR	NR	NR	NR	NR	NR	23 (7 to 55)
Weighted change (range)									-23 (-7 to -55)
Cody and Hodson (2016) (18)	NR	NR	NR	NR				NR	NR
MD					-	1.90	9.85		
RR					0.32	-	-		
95%CI					0.12 to 0.83	- 2.34 to - 1.47	8.35 to 11.34		
Collister et al. (2016) (19)	NR	NR	NR	NR	NR	NR	NR		NR
SF-36 (95% CI)								(0)	
KDQ (95% CI)								0.5 (-2.2 to 1.2)	
Palmer et al. (2014) (20)	NR	NR	NR			NR	NR	NR	NR
RR				1.05	0.60				
95% CI				0.93 to 1.19	0.53 to 0.69				
Vinhas et al. (2012) (21)					NR	NR	NR	NR	NR
n/N	2/1829	4/7305	3/6073	5/7902					
RR[a]	1.34	1.74	1.09	1.15					
95% CI	1.16 to 1.55	1.32 to 2.28	0.99 to 1.20	098 to 1.35					

CI: confidence interval; ESA: erythropoiesis-stimulating agent; ESRD: end-stage renal disease; Hb: hemoglobin; Hct: hematocrit; HRQOL: health-related quality of life; KDQ: Kidney Dialysis Questionnaire; MD: mean difference; n/N: number of trials/number of patients; NR: not reported; RR: relative risk; SF-36: Short Form-36 Health Survey; VAT: vascular access thrombosis.

[a] Relative risk for outcome at higher Hb targets (13.0-15.0 g/dL) vs lower Hb targets (9.5-11.5 g/dL).

Chung et al. (2023) updated a Cochrane meta-analysis comparing ESAs in patients with anemia related to CKD. (16) Despite the large number of studies (N=117), the studies were at high or unclear risk of bias. Overall, epoetin alfa and beta "may be superior" to placebo (low certainty evidence), and darbepoetin was deemed "probably superior" to placebo (moderate certainty evidence) for prevention of blood transfusion. Effects on death were uncertain for epoetin alfa or epoetin beta, and there was probably no difference between darbepoetin and placebo. Epoetin alfa and beta increased the odds of hypertension compared with placebo, but darbepoetin had uncertain effects on hypertension. All other comparisons were uncertain.

Amato et al. (2018) published a systematic review and meta-analysis comparing ESA biosimilars with originators in patients with anemia due to CKD. (15) Thirty RCTs (N=7843 patients) were included. When comparing epoetin alfa with biosimilar, epoetin alfa with darbepoetin alfa, epoetin beta with methoxy polyethylene glycol-epoetin beta, and darbepoetin alfa with methoxy polyethylene glycol-epoetin beta, no differences were observed for any outcome except for favorable results for blood transfusion for darbepoetin alfa compared with epoetin alfa. Besides 2 studies comparing epoetin beta and methoxy polyethylene glycol-epoetin beta (moderate), all included studies were judged to have low to very low quality of evidence. The review was limited to bibliographic sources mentioned in methodologic sections.

Roger et al. (2017) published a systematic review on the use of intravenous iron to optimize ESA response and reduce ESA dose in patients with CKD on dialysis. (17) The literature search, conducted through December 2014, identified 7 RCTs (N=615 patients) for inclusion. Quality of the studies was assessed using the risk of bias criteria outlined by Cochrane. Few studies provided randomization details, and almost half did not conduct intention-to-treat analyses. Results from a meta-analysis showed a statistically significant reduction in ESA dose when optimal iron (defined as 100-200 mg/wk) was administered with the ESA.

A Cochrane review by Cody et al. (2016) evaluated the use of ESAs as treatment for anemia due to CKD in patients not requiring dialysis. (18) This review updated a 2005 review, which updated the initial 2001 review. The literature search, conducted through June 2015, identified 4 additional studies to include in the update, for a total of 19 studies (N=993 patients). Selected studies were assessed for bias in selection, performance, detection, attrition, and reporting. Risk of bias was determined to be mostly unclear among the studies. ESAs were found to improve hemoglobin and Hct levels significantly and reduce the need for blood transfusions in predialysis patients significantly. Improvements were also found in quality of life and exercise capacity in the treatment group. Follow-up times of the studies were not sufficient to determine the effect of ESAs on CKD progression or the timing of dialysis initiation.

Collister et al. (2016) focused on studies of ESAs for treating patients with anemia due to CKD-that reported validated quality of life outcomes. (19) The literature search, conducted up to November 2015, identified 17 studies for inclusion. Four studies included only patients on dialysis, 12 studies included only nondialysis patients, and another included both. Comparisons were between erythropoietin alfa and placebo (3 studies), darbepoetin and placebo (2 studies), erythropoietin alfa and darbepoetin (1 study), and erythropoietin alfa and erythropoietin alfa

(11 studies). Follow-up ranged from 8 weeks to 36 months. Quality of life outcomes included the 36-Item Short-Form Health Survey (SF-36; 13 studies) and Kidney Dialysis Questionnaire (KDQ; 4 studies). The SF-36 consists of 8 domains: physical function, physical role, bodily pain, general health, vitality, emotional role, social function, and mental health. A minimum clinically important difference (MCID) in the SF-36 is a 5-point change. The KDQ has 5 dimensions: fatigue, depression, relationships with others, frustration, and physical symptoms. An MCID in KDQ is a 0.5-point change. Study quality was assessed using the Cochrane Risk of Bias tool. Only 4 studies had low risk of bias. Many did not adequately conceal allocation, which could have influenced results of subjective quality of life measures. Meta-analyses of the 13 studies using the SF-36 outcome found MCIDs in 2 domains, though the differences were not statistically significant (95% CI, -5.6 to 0.4 for physical function; 95% CI, -5.1 to 3.7 for physical role). Meta-analyses including only the 4 studies with low risk of bias reported nonsignificant results as well. Meta-analysis of the 4 studies using the KDQ outcome found MCIDs in 3 dimensions, though the differences again were not statistically significant (95% CI, -2.2 to 1.2 for physical symptoms; 95% CI, -1.6 to 0.5 for fatigue; 95% CI, -1.1 to 0.8 for depression).

A Cochrane review by Palmer et al. (2014) evaluated darbepoetin for the treatment of anemia due to CKD. (20) The literature search, conducted through January 2014, identified 21 studies (N=8328 patients) for inclusion. Comparators with darbepoetin included placebo (1 study), epoetin alfa or beta (8 studies), and PEG-epoetin beta (4 studies). The remaining studies compared different dosages of darbepoetin and different methods of administration (intravenous vs subcutaneous). Risk of bias, based on randomization, concealment, incomplete data, and blinding, was considered high or unclear among the included studies. The single study comparing darbepoetin with placebo found that the treatment significantly reduced the need for blood transfusions, but did not affect all-cause mortality, or the 36-Item Short-Form Health Survey (SF-36) energy or physical functioning scores. Studies comparing method of administration found no significant differences in need for blood transfusions or adverse events between intravenous and subcutaneous methods. Results from studies comparing darbepoetin with other ESAs are discussed in the Comparative Efficacy of Different ESAs section below.

A meta-analysis by Vinhas et al. (2012) included only large RCTs (n>500) with a minimum follow-up of 1 year. (21) Outcomes of interest were vascular access thrombosis, stroke, progression to ESRD, and all-cause mortality. Five trials (N=7902 patients), including the CHOIR, CREATE, NHCT, and TREAT trials, were selected. As shown in Table 4, higher hemoglobin targets were associated with increased risks of vascular access thrombosis and stroke but not with progression to ESRD or all-cause mortality.

Table 4. Meta-Analytic Results

Outcome	Number of Trials/Patients	Relative Risk[a]	95% CI	I^2% [b]
Vascular access thrombosis	2/1829	1.34	1.16 to 1.55	0
Stroke	4/7305	1.74	1.32 to 2.28	0

Progression to end-stage renal disease	3/6073	1.09	0.99 to 1.20	0
All-cause mortality	5/7902	1.15	0.98 to 1.35	0

Adapted from Vinhas et al. (2012). (21)
CI: confidence interval.
[a] Relative risk for outcome at higher hemoglobin targets (13.0-15.0 g/dL) vs. lower hemoglobin targets (9.5-11.5 g/dL).
[b] Describes the proportion of total variation across studies due to heterogeneity rather than chance.

Randomized Controlled Trials

Saglimbene et al. (2017) published an RCT investigating whether a lower dose of ESA could reduce the risk of death and other adverse events in patients with anemia due to CKD. (22) Patients were randomized to a fixed low-dose ESA (n=324) (epoetin alfa or beta 4000 IU or darbepoetin alfa 20 µg weekly) or a fixed high-dose ESA (n=332) (epoetin alfa or beta 18,000 IU or darbepoetin alfa 90 µg weekly) and were followed at 6 and 12 months. Primary outcomes were serum transferrin, ferritin, albumin, and C-reactive protein. Secondary outcomes were a composite of death or cardiovascular event, all-cause mortality, other adverse events, blood transfusion, and health-related quality of life. There were no significant differences at final follow-up in any of the primary outcomes between the low- and high-dose ESA groups. Significant differences were not detected between the groups in all-cause mortality, nonfatal or fatal myocardial infarction, thrombosis, or hospitalizations due to cardiovascular events. Risk estimates could not be calculated for stroke or seizures due to no events in one or both treatment groups. Patients in the low-dose ESA group reported significantly higher quality of life scores in emotional and physical functioning domains compared with patients in the high-dose ESA group. Patients in the low-dose group were at a significantly higher risk of blood transfusions than patients in the high-dose group.

<u>Pegylated Epoetin Beta</u>

Pivotal Trials

The FDA's 2007 approval of PEG-epoetin beta (Mircera) was based on 6 phase 3, international, open-label, RCTs in patients with anemia due to CKD (see Table 5). In 2 trials (n=505 patients), patients did not receive ESA therapy (correction trials), and in 6 trials (n=1894 patients), hemoglobin was stable on maintenance ESA therapy (maintenance trials). All but 1 trial (Administration of C.E.R.A. in CKD Patients to Treat Anemia with a Twice-Monthly Schedule [ARCTOS]) enrolled dialysis-dependent patients. The primary efficacy outcome in all trials was maintenance of hemoglobin levels over 24 to 52 weeks, adjusted for baseline hemoglobin and center, in the intention-to-treat and per-protocol patient samples. For this outcome, the trials demonstrated noninferiority of PEG-epoetin beta once or twice monthly to epoetin (alfa or beta) 1 to 3 times weekly (C.E.R.A. Administered Intravenously for Anemia Correction and Sustained Maintenance in Dialysis [AMICUS], Maintenance of Haemoglobin Excels with IV Administration of C.E.R.A. [MAXIMA], Patients Receiving C.E.R.A. Once a month for the mainTenance Of Stable hemoglobin [PROTOS], Targeting Sustained Haemoglobin in Dialysis with IV and SC C.E.R.A. Administration [RUBRA]) and to darbepoetin weekly or twice monthly (ARCTOS, Stabilizing haemoglobin TaRgets indialysis following IV C.E.R.A. Treatment for

Anaemia [STRIATA]). In the correction trials (ARCTOS, AMICUS), the median time to response was longer in the PEG-epoetin beta groups (43 days vs 57 days, respectively) compared with the darbepoetin (29 days) and epoetin (31 days) groups.

Target hemoglobin ranges in these trials included levels that have since been associated with increased mortality in CKD (i.e., >11 g/dL). (23) The FDA's summary review of safety (based on 1789 PEG-epoetin beta-treated patients [64% for >1 year] and 948 ESA-treated patients) reported that mortality was similar between the 2 groups (10% vs 11%, respectively). Incidence of serious adverse events also was similar between groups (37% vs 40%, respectively), although serious bleeding events (5.2% vs 4%), serious gastrointestinal bleeding events (1.2% vs 0.2%), and thrombocytopenia less than 100×10^9 platelets/L (7.5% vs 4.4%) occurred more commonly in PEG-epoetin beta-treated patients. The FDA reviewers attributed these imbalances to the greater proportion of patients on hemodialysis in the PEG-epoetin beta group (84% vs 80%) and considered the risks of hemorrhage and thrombocytopenia similar to or slightly increased above that for other ESAs. Trials excluded patients with poorly controlled hypertension; 27% of enrolled patients required increases in antihypertensive therapy.

Table 5. Pivotal Trials of PEG-Epoetin Beta

Study (Trial)	**N**	**Initial dose**	**Results**	
			Percent Responders[a]	**Mean ΔHb,[b] g/dL**
Correction trials in patients not receiving ESA therapy				
Macdougall et al. 2008 (ARCTOS) (24) [c]				
PEG-epoetin beta	162	0.6 µ/kg SC every 2 wks	98	2.15
Darbepoetin	162	0.45 µ/kg SC every wk	96	2.00
P			<0.001[d]	<0.001[e]
Klinger et al. 2007 (AMICUS) (25)				
PEG-epoetin beta	135	0.4 µ/kg IV every 2wks	93	2.70
Epoetin alfa/beta	46	Per product label IV 3 times per wk	91	2.56
P			<0.001[d]	<0.001[e]
Maintenance trials in patients receiving ESA therapy				
Canaud et al. 2008 (STRIATA) (26)				
PEG-epoetin beta IV every 2 wks	157		66	0.06
Darbepoetin IV every 1 to 2 wks	156		72	-0.12
P		• PEG-epoetin beta dose	0.25	<0.001[e]
Spinowitz et al. 2008 (RUBRA) (27)				

PEG-epoetin beta SC/IV every 2 wks	168	based on maintenance ESA dose • Comparator ESA dose was continuation of maintenance dose	69	0.09
Epoetin alfa/beta SC/IV every 1 to 2 wks	168		68	-0.03
P			-[h]	<0.001[e]
Levin 2007 et al. (MAXIMA) (28)				
PEG-epoetin beta IV every 2 wks	223		---	-0.71
PEG-epoetin beta IV every 4 wks	224		---	-0.25
Epoetin alfa/beta IV 1 to 3 times per wk	226		---	-0.75
P vs control			---	<0.001[e, f]
Sulowicz et al. 2007 (PROTOS) (29)				
PEG-epoetin beta SC every 2 wks	190		76	-0.03
PEG-epoetin beta SC every 4 wks	191		66	-0.13
Epoetin alfa/beta SC 1 to 3 times per wk	191		72	-0.11
P vs control			-[g]	<0.001[e, f]

ESA: erythropoiesis-stimulating agents; Hb: hemoglobin; IV: intravenous; PEG: pegylated; SC: subcutaneous; wks: weeks.

[a] Defined as:

- ARCTOS: Hb level ≥11 g/dL and increased ≥1.0 g/dL from baseline at 28 wk; target Hb 11-13 g/dL
- AMICUS: Hb level ≥11 g/dL and increased ≥1.0 g/dL from baseline at 24 wk; target Hb 11-13 g/dL
- PROTOS, STRIATA: Mean Hb within ±1 g/dL of baseline values through 52 wk; target Hb 10-13.5 g/dL

[b] Change from baseline Hb at 24 wk (AMICUS), 28 wk (ARCTOS), 36 wk (MAXIMA, STRIATA, RUBRA), or 52 wk (PROTOS).

[c] Patients with stage 3 or 4 chronic kidney disease (creatinine clearance <59 mL/min) who were not on dialysis.

[d] For noninferiority to a predefined minimum of 60%.

[e] For noninferiority to comparator; noninferiority margin for difference in mean Hb level (PEG-epoetin beta - comparator), -0.75 g/dL.

[f] Both comparisons.

[g] Trial investigators did not report statistical testing. Neither PEG-epoetin beta group differed statistically from comparator.
[h] Trial investigators did not report statistical testing. There was no statistical difference between groups.

Other Randomized Controlled Trials
Since FDA approval, other short-term trials (24-40 weeks; N=841) have replicated the findings of the pivotal correction trials in patients on hemodialysis (30) and not on hemodialysis, (31 32) and of the pivotal maintenance trials in patients on hemodialysis. (33, 34) Of 324 non-dialysis patients in the ARCTOS correction trial, 296 (91%) entered a 24-week extension study. (35) Patients who responded to PEG-epoetin beta biweekly (n=145) were re-randomized 1:1 to biweekly or monthly dosing to maintain hemoglobin levels between 11 g/dL and 13 g/dL. Mean hemoglobin levels were 11.9 g/dL, 11.7 g/dL, and 11.9 g/dL in the PEG-epoetin biweekly, PEG-epoetin monthly, and darbepoetin (weekly or biweekly) groups (n=151), respectively. Within-patient variation in hemoglobin levels was similar across groups.

Locatelli et al. (2020) conducted a noninferiority RCT (MIRCERA PASS) evaluating cardiovascular safety and all-cause mortality between PEG-epoetin beta compared to other ESAs (epoetin alfa/beta and darbepoetin) in patients with anemia of CKD (N=2818) when targeting hemoglobin levels of 10 to 12 g/dL. (36) The primary endpoint, a composite of all-cause mortality, nonfatal myocardial infarction or nonfatal stroke, occurred in 45.4% of patients in the PEG-epoetin beta group compared to 45.7% of patients in the control group (HR=1.03; 95% CI, 0.93 to 1.15, p=0.004 for noninferiority).

Systematic Reviews
A Cochrane review by Hahn et al. (2014) included random-effects meta-analyses of the 5 trials that enrolled dialysis patients listed in Table 5 and reported no statistical between-group differences in final hemoglobin level (vs epoetin), overall mortality, blood transfusions, or adverse events due to hypertension or vascular access thrombosis. (37) In the STRIATA trial, final hemoglobin level was statistically higher in the PEG-epoetin group compared with the darbepoetin group (mean difference, 0.30 g/dL; 95% CI, 0.05 to 0.55). Risk of bias was rated as low to moderate, and statistical heterogeneity was low to moderate (I^2 range, 0%-34%).

<u>Comparative Efficacy of Different Erythropoiesis-Stimulating Agents</u>
A systematic review by Wilhelm-Leen et al. (2015) evaluated mortality risk rates for darbepoetin alfa and epoetin alfa in patients with CKD. (38) The literature search, conducted up to October 2014, identified 10 studies (N=2149 patients) comparing darbepoetin alfa with epoetin alfa for inclusion. Eight studies included patients on dialysis and two included patients not requiring dialysis. No quality assessment of the studies was discussed. Meta-analyses found no significant difference in mortality rates between patients receiving darbepoetin alfa and patients receiving epoetin alfa.

A Cochrane network meta-analysis, published by Palmer et al. (2014), used indirect comparisons via network meta-analysis to evaluate comparative efficacy. (39) This analysis included RCTs published through February 2014 that compared 1 ESA with placebo, no

treatment, or another ESA for the treatment of CKD. A total of 56 studies (N=15,596 patients) were selected, the majority of which were judged to have a high or uncertain risk of bias. While all ESAs were found to be better than placebo in reducing the need for blood transfusions, the network meta-analysis did not detect differences in efficacy of the various agents in preventing blood transfusions. Very few studies included patient-reported outcomes (e.g., quality of life or energy level) and, as a result, the evidence base was insufficient to draw conclusions on the comparative efficacy of the different ESAs on these functional outcomes. Data were also limited on mortality outcomes (e.g., all-cause and cardiovascular) and myocardial infarction, stroke, and hypertension. Overall, due to the limitations of the data, reviewers could not determine whether one ESA was safer or more effective than another ESA. A 2023 update to this meta-analysis by Chung et al. found similar results to the initial meta-analysis, the differences between ESAs and placebo are summarized in Table 3. (16) The comparative effects of the various ESAs were uncertain.

A systematic review by Alsalimy et al. (2014) evaluated the efficacy of PEG-epoetin beta and darbepoetin for treatment of anemia in patients with CKD who are not dialysis-dependent. (40) Reviewers included 4 RCTs (N=1155 patients) and concluded that there were no differences between PEG-epoetin beta and darbepoetin on the change in hemoglobin levels.

A Cochrane review by Palmer et al. (2014) evaluated darbepoetin for treating anemia; it included 8 trials (N=2051 patients) that compared darbepoetin with epoetin (alfa or beta) in adults with anemia due to CKD. (20) No statistically significant differences between ESAs were observed in random-effects meta-analyses of final hemoglobin level or mean change in hemoglobin level, overall mortality, cardiovascular events or cardiovascular mortality, blood transfusions, or adverse events due to hypertension or vascular access thrombosis. Risk of bias was rated as moderate to high, and statistical heterogeneity was minimal (I^2=0%) for all outcomes.

Section Summary: Chronic Kidney Disease and Anemia

Three ESAs are FDA-approved for use in patients with CRF: epoetin alfa, PEG-epoetin beta, and darbepoetin alfa. Placebo-controlled trials have established that epoetin alfa and darbepoetin alfa effectively increase hemoglobin concentrations and decrease the need for blood transfusions. Evidence does not support an improvement in other clinical outcomes such as mortality and morbidity. The evidence is also inconsistent in showing significant improvements in functional status or quality of life. Some trials and a meta-analysis published in 2012 reported increased cardiovascular events and/or increased mortality in patients treated with ESAs. These trials have treated to a hemoglobin level of 12 g/dL or higher. The optimal recommended target hemoglobin has been lowered, though there is no evidence that treating to lower hemoglobin levels avoids adverse events. Recent meta-analyses have addressed ESA administration issues. One meta-analysis reported that intravenous and subcutaneous ESA administration methods were equally effective in reducing the risk of blood transfusions and had similar adverse event profiles. Another meta-analysis showed that significantly lower ESA doses could be used when iron was administered with the ESAs. A recent RCT has reported that patients receiving lower ESA doses experienced significantly higher quality of life scores but were at higher risk of

needing blood transfusions than patients receiving higher ESA doses. Differences in all-cause mortality and cardiovascular events were not detected among the patients receiving low ESA doses compared with those receiving high ESA doses.

PEG-epoetin beta has shown noninferiority to epoetin and darbepoetin for correcting or maintaining hemoglobin levels in RCTs of patients on dialysis or not on dialysis. In meta-analyses of trials involving dialysis patients, no statistical differences were reported in overall mortality, blood transfusions, or adverse events due to hypertension or venous access thrombosis. Evidence on the comparative effectiveness of the different agents is lacking. A Cochrane network meta-analysis did not detect differences in efficacy or adverse events among the different ESAs due to limited comparative evidence.

Hepatitis C Infection and Ribavirin-Related Anemia

Clinical Context and Therapy Purpose

The purpose of epoetin alfa or darbepoetin is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with anemia related to use of ribavirin to treat hepatitis C infection.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with hepatitis C infection treated with ribavirin who develop ribavirin-related anemia.

Interventions

The therapy being considered is epoetin alfa.

Standard treatment for hepatitis C infection includes ribavirin. Anemia related to ribavirin use often is the limiting step in treatment. Options for treatment of ribavirin-related anemia are a reduction in the dose of ribavirin and use of ESAs and/or blood transfusions as needed. However, a reduction in ribavirin dose has been associated with less favorable response rates, and some experts use ESAs to maintain full-dose ribavirin.

Comparators

The following practice is currently being used to treat anemia in those with hepatitis C infection: standard of care.

Outcomes

The general outcomes of interest are the QOL and medication use. Treatment of 8 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

An RCT by Shiffman et al. (2007) evaluated ESAs for anemia in patients with hepatitis C who were treated with ribavirin. (41) This trial randomized 150 patients to 3 groups at the onset of treatment: 1) ribavirin at standard dose; 2) ribavirin at standard dose plus epoetin alfa; and 3) ribavirin at higher dose plus epoetin alfa. Primary end points were a reduction in ribavirin dose and the proportion of patients with a sustained virologic response. Fewer patients treated with epoetin required dose reduction (10%) compared with patients not treated with epoetin (40%, $p<0.05$), but the proportion of patients with sustained virologic response did not differ between groups.

At least 2 controlled trials have randomized patients with hepatitis C virus and ribavirin-related anemia to epoetin alfa or usual care. The larger of these was conducted by Afdhal et al. (2004). (42) This trial included 185 patients with a hemoglobin level of 12 g/dL or less who were randomized to 8 weeks of epoetin alfa at a dose of 40,000 units weekly or placebo. Outcomes included the proportion of patients who were able to maintain full-dose treatment with ribavirin, mean hemoglobin level, and quality of life as measured by SF-36. More patients in the epoetin group (88%) than in the placebo group (60%, $p<0.001$) maintained full-dose ribavirin. Increase in mean hemoglobin level was higher in the epoetin group (2.2 g/dL) than in the usual care group (0.1 g/dL, $p<0.001$). Improvement in quality of life was significantly greater for the epoetin group on 7 of 8 domains, with incremental improvement ranging from 1.3 to 10.0 for patients on epoetin. Similar improvements were reported for patients from the placebo group who switched to epoetin alfa in the open-label phase, which followed the 8-week randomized trial.

An RCT by Dieterich et al. (2003) (43) was similar in design to the Afdhal trial. Dieterich et al. enrolled 64 patients with hepatitis C and ribavirin-related anemia, as defined by a hemoglobin level of 12 g/dL or less. Patients were followed for 16 weeks and randomized to epoetin alfa 40,000 units weekly or standard of care for anemia management (ribavirin dose reduction or discontinuation, or transfusions). Primary end points were ribavirin dose and hemoglobin level. The mean ribavirin dose decreased less in the epoetin group (-34 mg/d) than in the usual care group (-146 mg/d), but this difference was not statistically significant ($p=0.06$). More patients in the epoetin group (83%) than in the usual care group (54%, $p=0.02$) maintained full-dose ribavirin. The mean hemoglobin level was higher in the epoetin group (13.8 g/dL) than in the usual care group (11.4 g/dL; $p<0.001$).

Section Summary: Hepatitis C Infection Treated and Ribavirin-Related Anemia

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

Anemia due to Zidovudine-treated patients with HIV-Infection (44, 45, 46)
The safety and efficacy of epoetin alfa were evaluated in 4 placebo-controlled studies enrolling 297 anemic patients (hemoglobin < 10 g/dL) with HIV-infection receiving concomitant therapy with zidovudine. In the subgroup of patients (89/125 epoetin alfa and 88/130 placebo) with pre-study endogenous serum erythropoietin levels ≤ 500 mUnits/mL, epoetin alfa reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group. Among those patients who required RBC transfusions at baseline, 43% of patients treated with epoetin alfa versus 18% of placebo-treated patients were RBC transfusion-independent during the second and third months of therapy. Epoetin alfa therapy also resulted in significant increases in hemoglobin in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant reduction ($p < 0.003$) in RBC transfusion requirements in patients treated with epoetin alfa (n = 51) compared to placebo-treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving epoetin alfa in doses from 100 to 200 Units/kg 3 times weekly achieved a hemoglobin of 12.7 g/dL without administration of RBC transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose pre-study endogenous serum erythropoietin levels were > 500 mUnits/mL, epoetin alfa therapy did not reduce RBC transfusion requirements or increase hemoglobin compared to the corresponding responses in placebo-treated patients.

Surgery Patients (44, 45, 46)
The safety and efficacy of epoetin alfa were evaluated in a placebo-controlled, double-blind study (S1) enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Patients were stratified into 1 of 3 groups based on their pretreatment hemoglobin [≤ 10 g/dL (n = 2), > 10 to ≤ 13 g/dL (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg epoetin alfa, 100 Units/kg epoetin alfa, or placebo by subcutaneous injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery. All patients received oral iron and a low-dose, postoperative warfarin regimen.

Treatment with epoetin alfa 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic RBC transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13 g/dL; 5/31 (16%) of patients treated with epoetin alfa 300 Units/kg, 6/26 (23%) of patients treated with epoetin alfa

100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused. There was no significant difference in the number of patients transfused between epoetin alfa (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if epoetin alfa is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per epoetin alfa-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p = 0.028). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with epoetin alfa.

Epoetin alfa was also evaluated in an open-label, parallel-group study (S2) enrolling 145 patients with a pretreatment hemoglobin level of ≥ 10 to < 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program. Patients were randomly assigned to receive 1 of 2 subcutaneous dosing regimens of epoetin alfa (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery, and for 4 days after surgery). All patients received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than that observed in the 300 Units/kg daily group. The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the 2 treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar RBC transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group]. The mean number of units transfused per patient was approximately 0.3 units in both treatment groups.

Summary of Evidence

For individuals who have chronic kidney disease (CKD) and anemia who receive epoetin alfa, epoetin alfa-epbx, pegylated epoetin beta, or darbepoetin, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, medication use, and treatment-related mortality and morbidity. Epoetin alfa, epoetin alfa-epbx, pegylated epoetin beta, or darbepoetin Erythropoiesis-Stimulating Agents (ESAs) have been approved for this use. Most of the evidence has demonstrated an increase in hemoglobin (and a decrease in blood transfusions but has failed to demonstrate any significant improvement in clinical outcomes such as mortality and morbidity. Many studies have demonstrated increased mortality risk and increased risk for venous access thrombosis and stroke, prompting the U.S. Food and Drug Administration (FDA) warnings. The evidence is also inconsistent in showing improvements in functional status and quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatitis C infection treated with ribavirin who receive epoetin alfa or darbepoetin, the evidence includes RCTs. Relevant outcomes are quality of life and medication use. Evidence from RCTs has demonstrated that treatment with ESAs improves the ability to maintain full-dosing of ribavirin, because anemia is often a limiting effect for treatment. There may also be a positive effect on quality of life, although this is less certain. Epoetin alfa and darbepoetin are the ESA's approved for this use. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who receive the biosimilar product Retacrit (epoetin alfa-epbx), the FDA's approval of Retacrit is based on a review of comparisons of extensive structural and functional characterization, animal data, human pharmacokinetic and pharmacodynamic data, and clinical immunogenicity between Retacrit and U.S. -Licensed Epogen/Procrit demonstrating that Retacrit is highly similar to Epogen/Procrit and that there is no clinically meaningful differences between the products. The FDA approved Retacrit as a biosimilar to Epogen/Procrit for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis and to treat anemia due to the use of zidovudine in patients with human immunodeficiency virus (HIV) infection. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0881, J0882, J0885, J0887, J0888, J0890, Q4081, Q5105, Q5106, S9537

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2024	Document updated with literature review. Coverage unchanged. Reference 16 added; others updated.
06/15/2023	Document updated with literature review. The following changes were made to the Coverage: The Drug specific criteria for Epoetin alfa-epbx (Retacrit®) was removed and Epoetin alfa-epbx (Retacrit®) was added to the Drug Specific criteria addressing Epoetin Alfa (Epogen®, Procrit®). References 46 and 47 were added; other references were updated; and 2 references were removed.
04/15/2022	Reviewed. No changes.
08/01/2021	Document updated with literature review. The following changes were made to the Coverage: 1) Modified the list of medically necessary indications including removal of oncological indications and authorization limits from this policy; 2) Modified examples of indications listed in the experimental, investigational and/or unproven list. 3) Added NOTE 2: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications. 4) Wording clarified from chronic kidney failure to chronic kidney disease. The following references were added: 36, 45 and 46; others updated.
01/15/2021	Reviewed. No changes.

12/01/2019	Document updated with literature review. The following changes to Coverage were made: 1) Added criteria for the biosimilar Retacrit™ (epoetin alfa-epbx) as well as authorization limits. 2) Added NOTEs 2 and 3 to clarify criteria for use in cancer patients and patients with chronic kidney failure. The following references were added: 3-6, 25-28, 31, 47, 50-51, 53-55, 60, 64-67.
02/15/2018	Document updated with literature review. The following changes to Coverage were made: Peginesatide (Omontys®)—Drug Specific Criteria was removed. The following Coverage statement was added: The use of PEG-epoetin beta (Mircera) is considered experimental, investigational and/or unproven for all other indications.
06/01/2016	Reviewed. No changes.
09/15/2015	Document updated with literature review. The following was added to Coverage: When the General Criteria are met, Pegylated (PEG)-epoetin beta may be considered medically necessary for treatment of anemia associated with chronic kidney disease (CKD). Authorization limit of "every 24 weeks for chronic renal failure" was removed for Epogen, Procrit and Aranesp.
07/01/2014	Reviewed. No changes.
06/01/2013	Document updated with literature review. Coverage unchanged. Rational completely revised.
07/01/2012	CPT/HCPCS codes updated. The following was added regarding a new FDA approved drug: "Peginesatide (Omontys) may be considered medically necessary for treatment of anemia due to chronic kidney disease in adult patients on dialysis." Also, the following general criteria bullet was added: "For use in chronic kidney failure (including end-stage renal disease-ESRD), therapy may be initiated to reduce the need for red cell transfusions when Hgb has dropped below 10 g/dL (no target Hgb is recommended, but levels of 11 g/dL or greater should be avoided)." Two general criteria bullets were merged into the following one bullet: "For use in cancer patients, ESA therapy should not be initiated until the Hgb (hemoglobin) level is approaching or has fallen below 10 g/dL; and ESA therapy should not be used to raise the Hgb level above 12 g/dL."
04/15/2012	The following change(s) were made: Normal thyroid function and control of hypertension were removed from the Coverage criteria and were placed in the Rationale section.
09/01/2011	The general criteria for ESA therapy changed from needing both blood ferritin and transferrin saturation to needing either blood ferritin OR transferrin saturation. The following statement was added to the documentation requirements for continued ESA therapy: Documentation should include the current Hgb and current test(s) for iron stores (i.e., blood ferritin OR transferrin saturation).
01/01/2011	Document updated with literature review. The following changes were made: 1) ESAs may be considered medically necessary in cancer patients

	with metastatic non-myeloid malignancies who are undergoing myelosuppressive chemotherapy, anemia is caused by the chemotherapy, anemia is not due to other factors, and anticipated outcome of myelosuppressive therapy is not cure; 2) For ESAs related to AZT in HIV-infected patients, requirement was added that the endogenous serum erythropoietin level is ≤ 500 mUnits/ml; 3) Aplastic anemia and any other type of anemia were added to the list of examples of experimental, investigational and unproven indications; 4) Continued therapy requires clinical documentation of ongoing need every 12 weeks for treatment of anemia secondary to chemotherapy, and every 24 weeks for chronic renal failure; 5) A form is available for optional use to assist in requesting review for consideration of coverage of ESAs. The form is available on the Provider / Forms page of the applicable Blue Cross Blue Shield web site.
11/15/2008	New medical document