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PHARMACY/MEDICAL POLICY – 5.01.535

Erythropoiesis-Stimulating Agents

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Last Revised:	Jun. 8, 2026	None
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Introduction

Red blood cells are made inside the bone marrow. The process of making red blood cells is called "erythropoiesis". If there are not enough red blood cells in the body, a person is said to be anemic. The kidneys make a hormone called "erythropoietin" that stimulates the bone marrow to make more red blood cells. Drugs called ESAs (erythropoiesis-stimulating agents) are similar to our own erythropoietin. These drugs can be used to stimulate the bone marrow to make more red blood cells. This policy describes when the use of ESAs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Indication	Medical Necessity

Anemia due to chronic kidney disease (CKD)	**Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) may be considered medically necessary for the treatment of anemia associated with chronic kidney disease when all the following are met:**
	• The individual has been diagnosed with anemia associated with chronic kidney disease
	AND
	• Has had a hemoglobin (Hb) level less than 10 g/dL within the last month AND Hb levels will be repeated at least monthly during the maintenance phase of therapy
	AND
	• Meets 1 of the following:
	  ○ If the individual is currently receiving hemodialysis or peritoneal dialysis, the individual meets 1 of the following:
	  ▪ The individual has adequate iron stores as demonstrated by a transferrin saturation of at least 20% OR ferritin level greater than 400 ng/mL within the last month
	  ▪ Iron will be administered before treatment or concurrently
	OR
	  ○ If the individual is not currently receiving dialysis, the individual meets 1 of the following:
	  ▪ Transferrin saturation is at least 20% within the last month
	  ▪ Ferritin level is greater than 200 ng/mL within the last month
	Note: When ferritin levels are greater than 500 ng/mL, the test is unreliable as a basis for intravenous iron therapy, and other measures should be considered including erythropoiesis-stimulating agent (ESA) responsiveness, clinical status, Hb and TSAT levels.

Anemia due to other conditions	**Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) may be considered medically necessary when all the following are met:** • Meets 1 of the following:

Indication	Medical Necessity
	○ The individual has been diagnosed with a non-myeloid malignancy (see **Related Information**) and meets ALL the following: ▪ Is experiencing anemia due to chemotherapy treatment ▪ Has a hemoglobin (Hb) level less than 10 g/dL ▪ The treatment will be discontinued when the individual is no longer receiving chemotherapy **OR** ○ The individual requires treatment after an allogeneic bone marrow transplantation **OR** ○ The individual has been diagnosed with a myelodysplastic syndrome AND requires a reduction in the use of blood transfusions **OR** ○ The individual has been diagnosed with hepatitis C AND is experiencing anemia due to ribavirin treatment **AND** • The lowest dose of erythropoiesis-stimulating agent (ESAs) will be used to avoid red blood cell transfusions **AND** • The treatment will not be used to raise the Hb level more than 12 g/dL **Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) may be considered medically necessary when:** • The individual is diagnosed with HIV AND is experiencing anemia due to treatment with zidovudine **OR** • The individual requires surgery AND a reduction in the use of allogeneic blood transfusion

Indication	Investigational
• **Aranesp (darbepoetin alfa)** • **Epogen (epoetin alfa)** • **Mircera (methoxy polyethylene glycol-epoetin beta)** • **Procrit (epoetin alfa)** • **Retacrit (epoetin alfa-epbx)**	**The use of Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) is considered investigational for other indications, including but not limited to:** • Anemia after high-dose chemotherapy with autologous stem-cell support • Non-iatrogenic chronic anemia of cancer • Other cancer-associated anemia excepted as noted above **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in the policy for the treatment of anemia associated with chronic kidney disease (CKD) may be approved up to 12 months.** **All other indications for all drugs listed in the policy may be approved up to 6 months.**
Indications	**Ongoing Use**

Anemia due to chronic kidney disease (CKD)	**All drugs listed in the policy may be approved for anemia associated with chronic kidney disease (CKD) up to 12 months when:**
	• The individual's hemoglobin level is less than 12 g/dL
	AND
	• Has adequate iron stores demonstrated by 1 of the following:
	  ○ If currently receiving hemodialysis or peritoneal dialysis, has a transferrin saturation of at least 20% or ferritin level greater than 400 ng/mL; OR iron is administered concurrently
	  OR

	○ If not currently receiving dialysis, has a transferrin saturation of at least 20% or a ferritin level greater than 200 ng/mL
• **Myelodysplastic syndrome** • **Non-myeloid malignancies**	**All reviews for Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) may be approved for myelodysplastic syndrome or non-myeloid malignancies up to 6 months when:** • If the individual does not have improvement in hemoglobin (Hb) levels with erythropoiesis-stimulating agent (ESA) use, the individual has adequate iron stores **AND** • Hemoglobin level is less than 12 g/dL **AND** • Continues to require ESA treatment for the covered condition
All other uses	**All drugs listed in the policy for all other indications may be approved for up to 6 months when:** • Hemoglobin level less than 12 g/dL **AND** • Has adequate iron stores (if indicated) **AND** • Continues to require ESA treatment for the covered condition

Documentation Requirements

The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Recent (within the past month) hemoglobin level
- For individuals with chronic kidney disease:
  - Recent (within the past month) ferritin level or transferrin saturation
  - Whether or not the individual is receiving dialysis

Coding

Code	Description
HCPCS	
J0881	Injection, darbepoetin alfa (Aranesp), 1 mcg (non-ESRD use)
J0882	Injection, darbepoetin alfa (Aranesp), 1 microgram (for ESRD on dialysis)
J0885	Injection, epoetin alfa (Epogen, Procrit), (for non-ESRD use), 1000 units
J0887	Injection, epoetin beta (Mircera), 1 microgram, (for ESRD on dialysis)
J0888	Injection, epoetin beta (Micera), 1 microgram, (for non-ESRD use)
Q4081	Injection, epoetin alfa (Epogen, Procrit), 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

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Transferrin saturation calculation=serum iron level ÷ total iron binding capacity (TIBC) level x 100

Throughout this policy, unless otherwise stated:

- The term ESA refers to three drugs: epoetin alfa (brand names Epogen [Amgen, Thousand Oaks, CA] and Procrit [Janssen Product, LP, Titusville, NJ]), epoetin alfa-epbx (brand name Retacrit [Pfizer, New York, NY]) and darbepoetin alfa (brand name Aranesp [Amgen, Thousand Oaks, CA])
- Non-myeloid malignancies include solid tumors and the non-myeloid hematologic malignancies of myeloma, lymphoma, and chronic lymphocytic leukemia

Administration

ESAs and pegylated (PEG)-epoetin beta are to be administered according to current FDA-approved labeling for each product, using recommended hemoglobin (Hb) levels for

determining when to start, stop, and adjust the dose. This includes decreasing the dose of ESA as the Hb approaches the target level.

Before commencing ESA or PEG-epoetin beta therapy, the individual's iron stores, blood ferritin, and transferrin saturation should be evaluated, adjusted, and maintained within normal physiological 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 individuals with uncontrolled hypertension.

Discontinuation

Erythropoiesis-Stimulating Agents (ESA)

Individuals with myelodysplastic syndromes should be initially limited to a 3-month trial period with ESA. If no response to ESA is observed, ongoing therapy would be futile.

ESAs and PEG-Epoetin Beta

Individuals with chronic kidney disease (CKD) 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 (Hb) 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.

Epoetin Alfa and Darbepoetin Alfa REMS

Clinical studies have shown that treatment with epoetin alfa and darbepoetin alfa for individuals with cancer may result in shorter survival and/or increased risk of progression or recurrence. Additional studies of individuals with chronic kidney disease and hemoglobin levels 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, FDA implemented a Risk Evaluation and Mitigation Strategy (REMS) in 2011 under which providers and hospitals were required to counsel individuals, and each individual had to complete a provider acknowledgement form before treatment.

In April 2017, the FDA eliminated the REMS for Epogen/Procrit and Aranesp, stating 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."

PEG-epoetin beta does not have a REMS.

In 2012, the FDA approved a REMS for peginesatide, however this drug is no longer in use. Peginesatide is currently discontinued.

Evidence Review

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, eg, epoetin alfa, epoetin alfa-epbx, pegylated epoetin beta, darbepoetin) are produced using recombinant DNA technologies and have pharmacologic properties similar to endogenous erythropoietin. The primary clinical use of ESAs is to treat chronic anemia.

Background

Endogenous Erythropoietin and Anemia

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor synthesized by cells near the renal tubules in response to changes in the blood oxygen concentration. When an individual 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 EPO, which then acts on the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood hemoglobin (Hb) 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), many types of cancer treatment, other chronic diseases, and use of certain drugs.

The severity of anemia is defined by blood Hb concentration. Normal ranges are 12 to 16 g/dL in women and 14 to 18 g/dL in men. Mild anemia is defined as Hb 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

Erythropoiesis-stimulating agents 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 individuals with chronic renal failure (CRF) secondary to CKD[1]. Individuals with CRF 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 individuals with CRF reduces the need for red blood cell (RBC) transfusions and enhances physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms:

1. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B_{12}) essential for RBC production.
2. Antibodies and/or immunoregulatory abnormalities associated with certain tumor types (most commonly, B cell malignancies) may cause increased erythrocyte destruction (hemolysis).

3. Tumors may cause blood loss via tissue invasion (e.g., gastrointestinal bleeding from colon cancer).

4. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment.

5. In more advanced cases, there may be marrow replacement with tumor or amyloid.

6. However, marrow dysfunction can occur even in the absence of frank invasion.

7. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization, as well as a direct suppression of RBC production.

Cancer treatments also may cause anemia: (1) radical cancer surgery can result in acute blood loss; and (2) radiotherapy and many cytotoxic chemotherapeutic agents suppress marrow to varying degrees. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage; antimetabolites damage DNA indirectly; and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

RBC transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, this approach carries a risk for several potential adverse events. The highest adverse event risk (occurring in 1 per 432 whole blood units transfused) is for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (eg, type mismatch) are estimated to occur at a rate of 1 per 5,000 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), 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 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 TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated individuals.

Five ESA products have been licensed in the United States:

- Epoetin alfa is manufactured, distributed, and marketed by Amgen, Inc. under the proprietary name, Epogen. The same epoetin alfa product manufactured by Amgen Inc. is also marketed and distributed by Janssen Products, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit. Under a contractual agreement with Amgen, Janssen

Products LP has rights to develop and market Procrit for any indication other than for treatment of anemia associated with CRF in individuals on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all FDA-approved indications.

- A second ESA, epoetin alfa-epbx is manufactured by Hospira, Inc, which is a subsidiary of Pfizer Inc. Epoetin alfa-epbx is a biosimilar of Epogen/Procrit and has the identical FDA approved indications as Epogen/Procrit.
- A third ESA, darbepoetin alfa, is marketed solely by Amgen, under the proprietary name, Aranesp.
- The fourth ESA product, peginesatide, was codeveloped and commercialized by Affymax Inc. and Takeda Pharmaceuticals, and was marketed under the proprietary name, Omontys. In 2013, Affymax, Takeda, and the FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. The FDA currently lists peginesatide (Omontys) as discontinued.
- Epoetin beta is currently unavailable in the US However, a methoxy pegylated (PEG) form of epoetin beta, called "continuous erythropoietin receptor activator" or CERA, has a prolonged half-life that permits once monthly dosing. PEG-epoetin beta was FDA-approved in 2007 under the brand name Mircera. Mircera sales in the US were prohibited from 2009 until 2015 due to a copyright infringement lawsuit, however, Hoffmann-LaRoche is now manufacturing and supplying the drug to Galencia, and it is currently available.

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. All three ESAs have been studied and 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 FDA warnings. The evidence is also inconsistent in showing improvements in functional status and quality of life. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cancer-related anemia who receive epoetin alfa, epoetin alfa-epbx or darbepoetin, the evidence includes RCTs, comparative analyses, and systematic reviews of RCTs. The relevant outcomes are symptoms, morbid events, medication use, and treatment-related mortality and morbidity. The available trials have demonstrated an increase in hemoglobin concentration and a decrease in the need for blood transfusions. However, the evidence has also demonstrated increased mortality rates and possible tumor promotion, as well as increased risk of thromboembolic events when target hemoglobin levels were above 12 g/dL. Comparative analyses have shown that when the target hemoglobin level was lowered to 10 g/dL, individuals experienced increased hemoglobin and decreased risk for blood transfusions. Length of follow-up was short in the comparative analyses, and mortality and adverse events were therefore not addressed. Epoetin alfa, epoetin alfa-epbx and darbepoetin are the ESAs approved for use in the treatment of cancer-related anemia; pegylated epoetin beta is not FDA approved for this indication, because studies have demonstrated increased mortality and no significant improvement in clinical outcomes. The evidence is sufficient to determine qualitatively 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, epoetin alfa-epbx 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, epoetin alfa-epbx and darbepoetin are the ESAs approved for this use. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

There are no currently ongoing or unpublished trials that might influence this review as of September 2025.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate

reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 academic medical centers and 2 specialty societies while this policy was under review in 2012. Reviewers agreed with the current medically necessary indications. There was support for treatment of individuals with hepatitis C and ribavirin-related anemia. For investigational indications, reviewers agreed with the current policy statements.

Practice Guidelines and Position Statements

National Kidney Foundation

The National Kidney Foundation (2012) published the "Kidney Disease: Improving Global Outcomes clinical practice guidelines for anemia in chronic kidney disease" (CKD).[62] A consensus of an international group of experts created comprehensive, evidence-based guidance for the treatment of anemia in CKD. The Kidney Disease: Improving Global Outcomes recommendation on initiation and maintenance of erythropoiesis-stimulating agents (ESAs) was based on balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individuals (eg, stroke, vascular access loss, hypertension). Recommendations for treatment initiation and maintenance are listed in **Table 2**.

Table 2. Recommendations for Initial and Maintenance ESA Therapy for Anemia in CKD

Recommendation	LOR
Initial therapy	
"We recommend using ESA therapy with great caution, if at all, in CKD patients with:	
•active malignancy	1B
•… a history of stroke or	1B
•a history of malignancy	2C
"For adult CKD ND patients with Hb concentration ≥10.0 g/dl (≥100 g/l) we suggest that ESA therapy not be initiated."	2D
"For adult CKD ND patients with Hb concentration ≤10.0 g/dl (<100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior	2C

Recommendation	LOR
response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia."	
"For adult CKD 5D patients, we suggest 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 (90-100g/l)."	2B
Maintenance therapy	
"…we suggest 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
"…we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l)."	1A

CKD: Chronic Kidney Disease; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; LOR: level of recommendation; ND: nondialysis. 5D: Dialysis-dependent

American Society of Clinical Oncology American Society of Hematology, and National Comprehensive Cancer Network

Table 3 summarizes current clinical practice guidelines published jointly by the American Society of Clinical Oncology and the American Society of Hematology (updated in 2019)[11] and from the National Comprehensive Cancer Network (v.2.2020).[63]

Table 3. Summary of Guidelines on ESA Therapy to Treat Anemia in Cancer Individuals

Indications	ASCO/ASH 2019 Clinical Practice Guidelines	NCCN Guidelines (v.1.2025)
ESAs are indicated for:	• Depending on clinical circumstances, ESAs may be offered to individuals with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin (HgB) has declined to <10 g/dl. RBC transfusion is also an option, depending on the severity of anemia	• Based on individual preference and values, individuals undergoing palliative treatment or myelosuppressive chemotherapy without curative intent may be treated with ESAs using FDA-approved indications/dosing/dosing adjustments OR may be treated with RBC transfusions per provided guidelines

Indications	ASCO/ASH 2019 Clinical Practice Guidelines	NCCN Guidelines (v.1.2025)
	or clinical circumstances (Type: EB; EQ: high; SOR: strong)	
ESAs are NOT indicated for:	• Individuals with chemotherapy-associated anemia whose cancer treatment is curative in intent (Type: EB; EQ: intermediate; SOR: strong) • ESAs should not be offered to most individuals with nonchemotherapy-associated anemia. (Type: IC; EQ: low; SOR: strong)	• ESA treatment is not recommended when individuals are treated with myelosuppressive chemotherapy with curative intent. • ESA treatment is not recommended when individuals are not receiving therapy or palliative treatment, or those on non-myelosuppressive therapy
ESA treatment symptom outcomes	• Not discussed	• Not discussed
Hb levels for ESA initiation	• ESAs may be offered to individuals with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤500 IU/L (Type: EB; EQ: intermediate; SOR: moderate)	• If Hb is <11 g/dL or >2 g/dL below baseline, an evaluation for possible causes of anemia is suggested. If a cause is not identified, then anemia due to myelosuppressive chemotherapy is considered.
Span of ESA treatment	• Not discussed	• Physicians advised not to administer ESAs outside the treatment period of cancer-related chemotherapy
ESA dosing modifications	• It is recommended that starting and modifying doses of ESAs follow FDA guidelines, (Type: IC; EQ: intermediate; SOR: moderate)	• Dosing and titration directions for epoetin alfa and darbepoetin alfa are reproduced from FDA-approved labels; alternative dosing regimens are provided, e.g., every 2 or 3 weeks instead of weekly injections
Hb target	• Hb may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by individual and condition (Type: IC; EQ: intermediate: SOR: moderate)	• No Hb target is mentioned; notes that the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target Hb <12 g/dL
Iron	• Iron replacement may be used to improve HgB response and reduce RBC transfusions for individuals receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Type: EB; EQ: intermediate; SOR: weak)	• Iron studies and supplementation of functional iron deficiency are recommended for individuals treated with ESAs. These include serum iron, TIBC, and serum ferritin. Any individual with cancer who develops a sudden loss of response to ESAs, accompanied by severe anemia and a low reticulocyte count, should be evaluated for the etiology of loss of effect.

Indications	ASCO/ASH 2019 Clinical Practice Guidelines	NCCN Guidelines (v.1.2025)
Thromboembolic risk	• In individuals with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased. In all cases, blood transfusion is a treatment option that should be considered (Type: IC; EQ: low; SOR: moderate) • ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type EB; EQ: high; SOR: strong)	• Individuals with previous risk factors for thrombosis may be at higher risk when administered ESAs and should undergo risk assessment
Response to treatment	• ESAs should be discontinued in individuals who do not respond within 6-8 weeks, Individuals who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia (Type: IC; EQ: intermediate; SOR: strong)	• ESA therapy should be discontinued if an individual shows no response despite iron supplementation after 8 weeks of treatment. ESA dose-adjustment decisions are based on the goal of a gradual increase in Hb level that remains sufficient to avoid transfusion.

EB: evidence-based; EQ: evidence quality; SOR: strength of recommendation; IC: informal consensus; ASCO: American Society of Clinical Oncology; ASH: American Society of Hematology; ESA: erythropoiesis-stimulating agent; FDA: Food and Drug Administration; HgB: hemoglobin; NCCN: National Comprehensive Cancer Network; RBC: red blood cell; TIBC: total iron-binding capacity.

American Society of Nephrology

In 2012, The American Society of Nephrology released its evidence-based recommendations for the Choosing Wisely campaign to improve individual care and resource use.[64] The Society included the following among its top 5 recommendations: "Do not administer erythropoiesis-

stimulating agents to CKD individuals with hemoglobin levels ≥10 g/dL without symptoms of anemia."

Medicare National Coverage

The Centers for Medicare and Medicaid Services (CMS; 2007) released a decision memorandum on the use of ESAs for nonrenal disease indications (CAG-00383N), which has since been closed.[14]

CMS also determined that "ESA treatment for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is reasonable and necessary under the following specified conditions:

- The hemoglobin (Hb) level immediately prior to initiation or maintenance of ESA treatment is less than 10 g/dL (or the hematocrit [Hct] is <30%).
- The starting dose for ESA treatment is the recommended FDA label starting dose (no more than 150 U/kg 3 times weekly for epoetin alfa or epoetin alfa-epbx and 2.25 mcg/kg weekly for darbepoetin alpha). Equivalent doses may be given over other approved time periods.
- Maintenance of ESA therapy is the starting dose if the Hb level remains below 10 g/dL (or Hct is <30%) 4 weeks after initiation of therapy and the rise in Hb is ≥ 1 g/dL (Hct≥3%).
- For individuals whose Hb rises≤1 g/dL (Hct rise <3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10 g/dL after the 4 weeks of treatment (or the Hct is <30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the Hb rises <1 g/dL (Hct rise <3%) compared to pretreatment baseline by 8 weeks of treatment.
- Continued administration of the drug is not reasonable and necessary if there is a rapid rise in Hb > 1 g/dL (Hct >3%) over 2 weeks of treatment unless the Hb remains below or subsequently falls to < 10 g/dL (or the Hct is <30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
- ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen."

PEG-epoetin beta is not addressed in the decision memorandum or NCD.[65]

The decision by CMS allows local Medicare contractors to "continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD."

Regulatory Status

The major regulatory timelines for approval actions for new indications are summarized next:

- Epoetin alfa (Epogen/Procrit):
    - 1989: Approved for use in individuals with anemia due to CRF
    - 1991: Approved for use in zidovudine-treated, HIV-infected individuals
    - 1993: Approved for chemotherapy-induced anemia in individuals with non-myeloid malignancies
    - 1996: Approved for presurgical use in certain individuals undergoing surgery
- Epoetin alfa-epbx (Retacrit):
    - 2018: Biosmilar to Epogen/Procrit with the identical FDA approved indications as Epogen/Procrit
- Darbepoetin alfa (Aranesp):
    - 2001: Approved for use in individuals with anemia due to CRF
    - 2002: Approved for chemotherapy-induced anemia in individuals with non-myeloid malignancies
- Peginesatide (Omontys; Takeda Pharmaceuticals, Deerfield, IL, 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 postmarketing reports of serious hypersensitivity
- Methoxy polyethylene glycol (PEG) epoetin-beta (Mircera; Roche, Basel, Switzerland)
    - 2007: Approved for use in individuals with anemia due to CRF who are on dialysis or not on dialysis
    - 2009: Injunction prohibiting US sales until mid-2014 due to copyright infringement
    - 2015: Resumption of US sales

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65. Mircera (methoxy polyethylene glycol-epoetin beta). Prescribing Information. Vifor (International) Inc.; Gallen, Switzerland. Revised June 2024.

66. Procrit (epoetin alfa). Prescribing Information. Amgen Inc.; Thousand Oaks, CA. Revised April 2024.

67. Retacrit (epoetin alfa-epbx). Prescribing information. Pfizer; New York, NY. Revised June 2024.

History

Date	Comments
12/13/11	New Policy – Add to Prescription Drug section. Policy approved with 90-day hold for provider notification; the policy effective date is June 1, 2012.

Date	Comments
01/10/12	Replace Policy – Conditions for medically necessary treatment updated to apply only to those patients aged 18 years and older.
04/10/12	Replace policy. Updated to allow lower iron store requirements and longer intervals between checking iron stores, specifically for patients receiving ESAs that are not receiving hemodialysis. Policy effective date remains June 1, 2012.
09/24/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
01/10/13	Coding update. HCPCS code J0890, effective 1/1/13, added to policy.
10/14/13	Replace policy. Policy updated with literature review; no change in policy statement. Repeating references removed.
02/10/14	Scope updated to indicate that this policy not part of Medicare Advantage.
04/14/14	Annual review. Policy statement updated to indicate an additional requirement of adequate B12 level (200 pg/ml) as a treatment criterion for those over 18 years of age. When treating those with chronic kidney disease, the following criteria were added: Hb level of 10 g/dL, and iron store threshold levels were differentiated for those receiving hemodialysis versus those not receiving hemodialysis, with quarterly documentation required for continued treatment. When treating cancer patients, treatment criterion include Hb level above 10 g/dL. Policy Guidelines section updated with Risk Evaluation and Mitigation Strategy (REMS) information. Peginesatide (Omontys) added to the policy as an ESA agent. Rationale and Description sections updated extensively. References removed, added and renumbered. Coding section update removing ICD-9 and ICD-10 diagnosis and procedure codes; these are not part of the adjudication of this policy.
05/12/14	Interim update. Policy statement revised: treatment initiation criterion of an adequate B12 levels (200 pg/ml) removed. This is not generally performed by the local provider community and is not considered a necessary prerequisite to treatment. Coding update: Remove HCPCS codes Q2047 and Q4081 (these are not utilized, J0881-0890 are listed on the policy and are specific to the policy).
11/10/14	Interim update. This policy is updated with a current literature review and includes the newly marketed drug pegylated (PEG) – epoetin beta.
01/05/15	Coding update. New HCPCS codes J0887 and J0888, effective 1/1/15, added to the policy.
04/14/15	Annual review. Policy section updated clarifying target Hb level ranges within the medical necessity criteria; for use in those with chronic kidney disease, adjustment made to ferritin level threshold levels; for use in cancer patients, added that documentation of iron stores is indicated only if there is no improvement in hemoglobin level with ESA use.
02/04/16	Coding update. Added Q4081.
06/01/16	Annual Review, approved May 10, 2016. Policy updated with literature review through November 2015; references added. Policy statements unchanged.

Date	Comments
09/01/16	Interim Review, approved August 9, 2016. Added peritoneal dialysis to chronic kidney disease policy statement for clarification.
01/01/17	Interim Review, approved December 13, 2016. Clarification added to chronic kidney disease policy statement, "For ongoing ESA therapy, Hb level below 12 g/dL is considered acceptable as 11.0 to 11.9 is the target range for Hb level".
04/11/17	Policy moved into new format; no change to policy statements. Evidence Review section reformatted.
06/13/17	Coding update; removed HCPCS code J0886 as it was terminated 1/1/16.
11/01/17	Annual Review, approved October 19, 2017. Updated guidelines from KDIGO. Removed HCPCS code J0890.
03/01/18	Annual Review, approved February 27, 2018. Policy updated with literature review through August 2017; references 21-26, 44, and 46-50 added. Policy statements unchanged. Removed CPT codes 96365, 96372.
12/01/18	Interim Review, approved November 21, 2018. Added the biosimilar, Retacrit (epoetin alfa-epbx) to policy. Added HCPCS codes Q5105 and Q5106.
04/01/19	Minor update, added Documentation Requirements section.
01/01/20	Annual Review, approved December 10, 2019. Policy updated with literature review through August 2019; no references added, references on ASCO and NCCN updated. Policy statements unchanged.
01/01/21	Annual Review, approved December 1, 2020. Policy updated with literature review through August 27, 2020; references added. Policy statements unchanged.
06/01/21	Annual Review, approved May 20, 2021. Updated references and policy statements unchanged.
12/01/22	Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/23	Annual Review, approved July 10, 2023. No changes to the policy statements.
07/01/24	Annual Review, approved June 24, 2024. No changes to the policy statements. Policy statements re-formatted to improve comprehension.
01/01/25	Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
07/01/25	Annual Review, approved June 23, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.
07/01/26	Annual Review, approved June 8, 2026. Policy updated with literature review through September 8, 2025; no references added. Removed reference to non-formulary exception reviews. Separated initial and continuing authorization criteria for all drugs

Date	Comments
	used to treat anemia associated with chronic kidney disease (CKD) from other indications, and updated initial and ongoing approval durations for treatment of anemia associated with CKD from 6 months to 12 months.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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