09-J0000-31

Original Effective Date: 06/15/00

Reviewed: 06/11/25

Revised: 04/15/26

Subject: Erythropoiesis Stimulating Agents

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DESCRIPTION:

Erythropoietin is a glycoprotein responsible regulating the production of red blood cells (RBCs) by stimulating the division and differentiation of erythroid progenitor cells in the bone marrow. Erythropoiesis stimulating agents (ESAs) are recombinant forms of erythropoietin and have the same biological activity as endogenous erythropoietin. Currently, there are five commercially available ESAs in the United States: epoetin alfa (Epogen® and Procrit®), epoetin alfa-epbx (Retacrit®), darbepoetin alfa (Aranesp®), and methoxy polyethylene glycol-epoetin beta (MPG-epoetin beta)(Mircera®). Epoetin alfa was granted orphan designation by the FDA for the treatment of anemia associated with HIV infection or HIV treatment (1991), myelodysplastic syndrome (1993), and anemia associated with end stage renal disease (1986). While all ESAs share the same mechanism of action, darbepoetin alfa has two additional carbohydrate chains to give it a longer half-life. In 2007 the FDA approved MPG-epoetin beta (Mircera®) for the treatment of anemia associated with chronic renal failure. MPG-epoetin beta is a pegylated version of recombinant human erythropoietin developed by Hoffman-La Roche. However, due to infringement on an Amgen patent, Hoffman-La Roche was not able to commercially release their product until mid-2014. Additionally, as of March 2015, MPG-epoetin beta is only being distributed to Fresenius Medical Care dialysis centers.

POSITION STATEMENT:

NOTE: Epogen, Procrit, and Retacrit are the preferred erythropoiesis stimulating agents for all indications except anemia due to chronic kidney disease in members on dialysis. For initiation of therapy for all indications except anemia due to chronic kidney disease on dialysis, darbepoetin alfa [Aranesp] will require an inadequate response or contraindication to the preferred agents (Epogen, Procrit, and Retacrit).

Initiation of an erythropoiesis stimulating agent (ESA) (e.g., epoetin alfa [Procrit, Epogen], epoetin alfa-epbx [Retacrit], darbepoetin alfa [Aranesp], Methoxy polyethylene glycol-epoetin beta [Mircera]) meets the definition of **medical necessity** when **ALL** of the following are met:

1. Within the last 4 weeks, evaluation of the member's iron status includes **BOTH** of the following (unless member is receiving concurrent intravenous iron):
    a. Transferrin saturation is 20% or more
    b. Ferritin is 100 ng/mL or more
2. Within the last 4 weeks, member's hemoglobin is less than 10 g/dL or hematocrit is less than 30% (unless receiving for anemia of prematurity or otherwise specified in Table 1 [e.g., peri-surgery]).
3. Other causes of anemia (e.g., hemolysis, bleeding) have been ruled out.
4. The ESA will not be used in combination with daprodustat (Jesduvroq) or vadadustat (Vafseo)*
5. ESA is administered for treatment of the indications listed in table 1 and **ALL** of the indication-specific criteria.

Table 1:

Indications and Specific Criteria for ESA Therapy Initiation		
Indication	**Specific Criteria**	**Maximum Allowable Dose**
Epoetin alfa (i.e., Procrit and Epogen) and epoetin alfa-epbx (Retacrit)		
Anemia due to CKD	**ONE** of the following: 1. Member is on dialysis 2. Member is not on dialysis and **BOTH** of the following apply: a. The rate of hematocrit decline indicates the likelihood of requiring a blood transfusion b. Reducing the risk of alloimmunization and/or other blood transfusion-related risk is a goal 3. Member is less than 18 years of age	60,000 units weekly
Zidovudine-induced anemia	**BOTH** of the following: 1. The member's endogenous serum erythropoietin level is 500 mUnits/ mL or less 2. The dose of zidovudine does not exceed 4200 mg weekly	60,000 units weekly
Chemotherapy-induced anemia	**ALL** of the following: 1. Member is diagnosed with a non-myeloid, non-erythroid malignancy (e.g., solid tumors, myeloma, lymphoma)	60,000 units weekly

	2. The anticipated outcome of chemotherapy is not cure 3. Member is on myelosuppressive chemotherapy or has received myelosuppresive chemotherapy in the past 2 months	
Peri-surgery	**ALL** of the following: 1. Member is scheduled to undergo elective, non-cardiac, non-vascular surgery 2. Member's hemoglobin is greater than 10 g/dL but less than or equal to 13 g/dL (or hematocrit greater than 30% but less than or equal to 39%) 3. Member is expected to require more than 2 units of blood during surgery 4. Member is unwilling or unable to provide autologous blood donation	Either of the following: • 300 units/kg/ day x 15 days • 600 units/kg/ week x 3 weeks
Anemia of Prematurity	**ONE** of the following: 1. Member's birth weight is less than 1800 grams 2. Member's gestational age at the time of birth is less than 35 weeks	1500 units/kg weekly
Anemia associated with Myelodysplastic syndromes (MDS)	The member has lower risk disease (IPSS-R, very low, low, intermediate; IPSS, low or intermediate-1) when used as a single agent or in combination with either lenalidomide or G-CSF for **ONE** of the following: • The member's endogenous serum erythropoietin level is 500 mUnits/ mL or less • The member has symptomatic anemia	60,000 units twice weekly
Anemia associated with Myeloproliferative neoplasms (Primary MF, Post-PV MF, Post-ET MF)	The member's endogenous serum erythropoietin level is less than 500 mUnits/ mL	60,000 units weekly
Anemia associated with Hepatitis C management	Member is receiving concomitant therapy with ribavirin and **EITHER** of the following 1. Interferon-alfa 2. Peg-interferon alfa	60,000 units weekly

Anemia associated with RA treatment	Member is prescribed concomitant therapy for the treatment of RA that is known to cause anemia (e.g., methotrexate)	60,000 units weekly
Darbepoetin alfa (Aranesp)		
Anemia due to CKD	**ONE** of the following: 1. Member is on dialysis 2. Member is not on dialysis and **BOTH** of the following apply: a. The rate of hematocrit decline indicates the likelihood of requiring a blood transfusion b. Reducing the risk of alloimmunization and/or other blood transfusion-related risk is a goal 3. Member is less than 18 years of age	Any of the following: • 500 mcg every 21 days • 300 mcg every 14 days • 200 mcg every 7 days
Chemotherapy-induced anemia	**ALL** of the following: 1. Member is diagnosed with a non-myeloid, non-erythroid malignancy 2. The anticipated outcome of chemotherapy is not cure 3. Member is on myelosuppressive chemotherapy or has received myelosuppressive chemotherapy in the past 2 months	
Anemia associated with MDS	The member has lower risk disease (IPSS-R, very low, low, intermediate; IPSS, low or intermediate-1) when used as a single agent or in combination with either lenalidomide or G-CSF for **ONE** of the following: • The member's endogenous serum erythropoietin level is 500 mUnits/ mL or less • The member has symptomatic anemia	
Anemia associated with Myeloproliferative neoplasms (Primary MF, Post-PV MF, Post-ET MF)	The member's endogenous serum erythropoietin level is less than 500 mUnits/ mL	

Anemia associated with RA treatment	Member is prescribed concomitant therapy for the treatment of RA that is known to cause anemia (e.g., methotrexate)	
Anemia associated with Hepatitis C management	Member is receiving concomitant therapy with ribavirin and **EITHER** of the following 1. Interferon-alfa 2. Peg-interferon alfa	
Anemia of Prematurity	**ONE** of the following: 1. Member's birth weight is less than 1800 grams 2. Member's gestational age at the time of birth is less than 35 weeks	• 10 mcg/kg every 7 days
Methoxy polyethylene glycol-epoetin beta (Mircera)		
Anemia due to CKD	**BOTH** of the following: 1. Member has an inadequate response to or contraindication to epoetin alfa [Procrit, Epogen, and Retacrit] 2. **ONE** of the following: a. Member is on dialysis b. Member is not on dialysis and **BOTH** of the following apply: • The rate of hematocrit decline indicates the likelihood of requiring a blood transfusion • Reducing the risk of alloimmunization and/or other blood transfusion-related risk is a goal c. Member is less than 18 years of age	Either of the following: • 600 mcg every 4 weeks • 300 mcg every 2 weeks
ESA, erythropoiesis stimulating agent; CKD, chronic kidney disease; G-CSF, granulocyte colony stimulating factor; IPSS-R, Revised International Prognostic Scoring System; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MF, myelofibrosis: Post-PV MF, post polycythemia vera myelofibrosis; Post-ET MF, post essential thrombocythemia myelofibrosis; RA, rheumatoid arthritis Duration of Approval for Peri-surgery: 21 days Duration of Approval all other indications: 6 months		

Continuation of an erythropoiesis stimulating agent (e.g., epoetin alfa, epoetin alfa-epbx, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta) meets the definition of **medical necessity** when **ALL** of the following criteria are met:

1. The member has a beneficial clinical response to therapy (defined as a rise in hemoglobin of 1 g/dL or more compared to pre-treatment baseline within 12 weeks of therapy initiation for anemia of chronic kidney disease or within 8 weeks of therapy initiation for all other indications) and **EITHER** of the following:
    a. Member has been approved by Florida Blue or another healthplan in the past 6 months
    b. Member has previously met Florida Blue's initial criteria for coverage in the past 6 months
2. Within the past 3 months, evaluation of the member's iron status includes **BOTH** of the following(unless member is receiving concurrent intravenous iron):
    a. Transferrin saturation is 20% or more
    b. Ferritin is 100 ng/mL or more
3. The ESA will not be used in combination with daprodustat (Jesduvroq) or vadadustat (Vafseo)*
4. ESA is administered for treatment of the indications listed in table 2 and **ALL** of the indication-specific criteria are met

TABLE 2:

Indications and Specific Criteria for ESA Therapy Continuation	
Indication	**Specific Criteria†**
Epoetin alfa (i.e., Procrit and Epogen) and epoetin alfa-epbx [Retacrit]	
Anemia due to CKD	**ONE** of the following 1. On dialysis: hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Not on dialysis: hemoglobin is 10 g/dL or less (or hematocrit 30% or less) 3. Less than 18 years of age: hemoglobin is 12 g/dL or less (or hematocrit 36% or less)
Zidovudine-induced anemia	**BOTH** of the following 1. Hemoglobin is 12 g/dL or less (or hematocrit 36% or less) 2. Zidovudine dose is 4200 mg/week or less
Chemotherapy-induced anemia	**ALL** of the following 1. Hemoglobin is 10 g/dL or less (or hematocrit 30% or less) 2. Member is on myelosuppresive chemotherapy or has received myelosuppresive chemotherapy in the past 2 months

Anemia of Prematurity	Hemoglobin is 11 g/dL or less (or hematocrit 33% or less)
Anemia associated with MDS	Hemoglobin is 12 g/dL or less (or hematocrit 36% or less)
Anemia associated with Myeloproliferative neoplasms (Primary MF, Post-PV MF, Post-ET MF)	Hemoglobin is 11 g/dL or less (or hematocrit 33% or less)
Anemia associated with RA treatment	**BOTH** of the following: 1. Hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Member is prescribed concomitant therapy for the treatment of RA that is known to cause anemia (e.g., methotrexate)
Anemia associated with Hepatitis C management	**BOTH** of the following 1. Hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Member is receiving concomitant therapy with ribavirin and **EITHER** of the following: a. Interferon-alfa b. Peg-interferon alfa
Darbepoetin alfa (Aranesp)	
Anemia due to CKD	**ONE** of the following: 1. On dialysis: hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Not on dialysis: hemoglobin is 10 g/dL or less (or hematocrit 30% or less) 3. Less than 18 years of age: hemoglobin is 12 g/dL or less (or hematocrit 36% or less)
Chemotherapy-induced anemia	**ALL** of the following 1. Hemoglobin is 10 g/dL or less (or hematocrit 30% or less) 2. Member is on myelosuppressive chemotherapy or has received myelosuppressive chemotherapy in the past 2 months
Anemia of Prematurity	Hemoglobin is 11 g/dL or less (or hematocrit 33% or less)
Anemia associated with MDS	Hemoglobin is 12 g/dL or less (or hematocrit 36% or less)

Anemia associated with Myeloproliferative neoplasms (Primary MF, Post-PV MF, Post-ET MF)	Hemoglobin is 11 g/dL or less (or hematocrit 33% or less)
Anemia associated with RA treatment	**BOTH** of the following: 1. Hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Member is prescribed concomitant therapy for the treatment of RA that is known to cause anemia (e.g., methotrexate)
Anemia associated with Hepatitis C management	**BOTH** of the following: 1. Hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Member is receiving concomitant therapy with ribavirin and **EITHER** of the following a. Interferon-alfa b. Peg-interferon alfa
Methoxy polyethylene glycol-epoetin beta (Mircera)	
Anemia due to CKD	**ONE** of the following: 1. On dialysis: hemoglobin is 11 g/dL or less (or hematocrit 33% or less) 2. Not on dialysis: hemoglobin is 10 g/dL or less (or hematocrit 30% or less) 3. Less than 18 years of age: hemoglobin is 12 g/dL or less (or hematocrit 36% or less)
†Hemoglobin level should be current (i.e., within last 30 days) ESA, erythropoiesis stimulating agent; CKD, chronic kidney disease; MDS, myelodysplastic syndrome; MF, myelofibrosis: Post-PV MF, post polycythemia vera myelofibrosis; Post-ET MF, post essential thrombocythemia myelofibrosis; RA, rheumatoid arthritis	

*Note: May be used temporarily as rescue therapy or prior to transitioning to daprodustat for anemia of CKD

Approval duration for continuation: 6 months

Erythropoietin, darbepoetin, and methoxy polyethylene glycol-epoetin beta are considered **experimental or investigational** for the following indications because these conditions are not supported by the peer reviewed medical literature (not an all-inclusive list):

1. Anemia in Gaucher's disease
2. Anemia in Castleman's disease
3. Sickle cell anemia
4. Sepsis-associated anemia

5. Anemia of cancer not related to cancer treatment
6. Any anemia associated only with radiotherapy.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Iron status should be evaluated in all persons before and during ESA treatment and iron repletion should be maintained. Prior to therapy initiation, other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) should be corrected. Additionally, ESAs should not be initiated in persons with a hemoglobin of 10 g/dL or greater.

The FDA-approved indications and initial recommended doses for erythropoiesis stimulating agents (ESAs) are listed in Table 3. When initiating therapy for persons with CKD, hemoglobin levels should be monitored at least weekly until stable and then monthly thereafter. Both epoetin alfa products and darbepoetin alfa are indicated for treatment of anemia due to the effects of concomitant myelosuppressive therapy. Initiation should only occur in persons with hemoglobin less than 10 g/dL and if there is a minimum of two additional months of planned chemotherapy.

TABLE 3:

FDA-approved Indications and Recommended Dosing	
Indication	**Recommended Dosing**
Epoetin alfa (i.e., Procrit and Epogen) and epoetin alfa-epbx [Retacrit]	
Anemia due to CKD¶	• Initial: 50-100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (pediatrics) • Maintenance: individualize dose
Anemia due to Zidovudine in HIV-Infected persons	100 Units/kg 3 times weekly
Anemia due to effects of concomitant myelosuppressive chemotherapy‡	• Adults: 40,000 Units weekly or 150 Units/kg 3 times weekly • Children (5 years or older): 600 Unit/kg weekly
To reduce allogeneic RBC transfusions in persons undergoing elective, non-cardiac, non-vascular surgery	**EITHER** of the following • 300 Units/kg/day for 15 days total (10 days before surgery, day of surgery, and for 4 days after surgery • 600 Units/kg weekly (administered as 4 doses on 21, 14, and 7 days before surgery and on the day of surgery.

Darbepoetin alfa (Aranesp)	
CKD on dialysis	• 0.45 mcg/kg IV* or SQ weekly OR • 0.75 mcg/kg IV* or SQ every 2 weeks
CKD not on dialysis	• 0.45 mcg/kg IV or SQ every 4 weeks
CKD in pediatrics	• 0.45 mcg/kg IV* or SQ weekly OR • 0.75 mcg/kg IV* or SQ every 2 weeks
Anemia due to effects of concomitant myelosuppressive chemotherapy‡	• 2.25 mcg/kg SQ weekly • 500 mcg SQ every 3 weeks
Methoxy polyethylene glycol-epoetin beta (Mircera)	
CKD on dialysis	• 0.6 mcg/kg IV* or SQ every 2 weeks. • Once Hgb is stabilized, the dose may be administered once monthly at a dose twice that of the every-two-week dose
CKD not on dialysis	• 1.2 mcg/kg SQ every month. • Alternatively, a starting dose of 0.6 mcg/kg may be administered IV or SQ once every 2 weeks.
Pediatric patients 5 to 17 years of age on hemodialysis (converting from another ESA)	• Dosed once every 4 weeks IV based on total weekly epoetin alfa or darbepoetin alfa (see prescribing information)
¶ On dialysis and not on dialysis; ‡ a minimum of two additional months of chemotherapy should be planned; * IV recommended in persons on hemodialysis; CKD, chronic kidney disease; HIV, human immunodeficiency virus; RBC, red blood cell; IV, intravenous; SQ, subcutaneous	

Dose Adjustments

A. **Anemia due to CKD**

*****All ESAs:** Continued administration should be based on the individual's response to therapy (e.g., hemoglobin levels). The dose should not be increased more frequently than once every 4 weeks for persons with CKD. Avoid frequent dose adjustments

1. Rapid hemoglobin rise: if hemoglobin rises more than 1 g/dL in a 2-week period, reduce the dose by 25% or more as needed to reduce rapid responses.
2. Inadequate responses: if hemoglobin does not rise by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%. Of note, for persons who do not respond adequately over a 12 week period, further dose escalation is unlikely to improve response and may increase risks.
3. Dose interruption
    a. Anemia of CKD on dialysis: If hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose.

b. Anemia of CKD not on dialysis: If hemoglobin level approaches or exceeds 10 g/dL, reduce or interrupt the dose.

B. **Anemia due to concomitant myelosuppressive chemotherapy**

1. **Epoetin alfa (Procrit and Epogen)**

a. Dose Reduction: reduce by 25% if **EITHER** of the following:

- Hemoglobin rises more than 1 g/dL in any 2 week period
- Hemoglobin rises to a level need to avoid RBC transfusion

b. Dose Interruption: withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose of 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

c. Dose Increase: after initial 4 weeks of therapy, if hemoglobin increases by less than 1 g/dL **AND** remains below 10 g/dL, increase dose to:

- 300 Units/kg three times per week OR 60,000 Units weekly in adults
- 900 Units/kg (max 60,000 units) weekly in children
- If no response as measure by hemoglobin levels or if RBC transfusions are still required after 8 weeks, discontinue epoetin alfa.

2. **Darbepoetin alfa (Aranesp):** Table 3 provides the recommended dose adjustments

Table 4:

Darbepoetin alfa Recommended Dose Adjustments for Treatment of Anemia Due to Concomitant Myelosuppressive Chemotherapy		
Dose Adjustment	**Weekly Schedule**	**Every 3 Week Schedule**
Either of the following: • If hemoglobin increases greater than 1 g/dL in any 2-week period • If hemoglobin reaches a level needed to avoid RBC transfusion	Reduce dose by 40%	Reduce dose by 40%
If hemoglobin exceeds a level needed to avoid RBC transfusion	• Withhold dose until hemoglobin approaches a level where RBC transfusions may be required • Reinitiate at a dose 40% below the previous dose	• Withhold dose until hemoglobin approaches a level where RBC transfusions may be required • Reinitiate at a dose 40% below the previous dose
If hemoglobin increases by less than 1 g/dL and remains below 10 g/dL after 6 weeks of therapy	Increase dose to 4.5 mcg/kg/week	No dose adjustment
• If there is no response as measured by hemoglobin levels or if RBC transfusions	Discontinue	Discontinue

are still required after 8 weeks of therapy • Following completion of a chemotherapy course		

Anemia due to zidovudine treatment in HIV infected persons: Epoetin alfa and Epoetin alfa-epbx

- **Dose increase:** if hemoglobin does not increase after 8 weeks of therapy, increase dose by approximately 50-100 Units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 Units/kg
- **Dose interruption:** hold therapy if hemoglobin exceeds 12 g/dL. Resume at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.
- **Discontinuation:** discontinue if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 3 weeks.

Drug Availability:

- **Epoetin alfa (Epogen and Procrit):** supplied as single-dose and multi-dose vials
  1. **Single-dose vials:** 2000-, 3000-, 4000-, 10,000, and 40,000 Units/mL
  2. **Multi-dose vials (contain benzyl alcohol):** 20,000 Units/2 mL and 20,000 Units/mL
- **Epoetin alfa-epbx [Retacrit]: supplied as single-dose and multi-dose vials**
  1. **Single-dose vials:** 2000-, 3000-, 4000-, 10,000, and 40,000 Units/mL
- **Darbepoetin alfa (Aranesp):** supplied as single-dose vials and single-dose pre-filled syringes
  1. **Single-dose vials**: 25-, 40-, 60-, 100-, 200-, 300-, and 500 mcg/mL; 150 mcg/0.75 mL
  2. **Single-dose pre-filled syringes:** 10 mcg/0.4 mL, 25 mcg/0.42 mL, 40 mcg/0.4 mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, and 500 mcg/1 mL
- **Methoxy polyethylene glycol-epoetin beta (Mircera):** supplied as single-use prefilled syringes.
  1. 30 mcg/0.3 mL, 50 mcg/0.3 mL, 75 mcg/0.3 mL, 100 mcg/0.3 mL, 150 mcg/0.3 mL, 200 mcg/0.3 mL

PRECAUTIONS:

Boxed Warning (all ESAs)

ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

- **Chronic Kidney Disease**
  - In controlled trials, subjects 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 ESA dose sufficient to reduce the need for RBC transfusions

- **Cancer**
  - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of subjects with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
  - Use the lowest dose to avoid RBC transfusions.
  - Use ESAs only for anemia from myelosuppressive chemotherapy.
  - ESAs are not indicated for persons receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
  - Discontinue ESA therapy following the completion of a chemotherapy course.
- **Peri-surgery**
  - Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended

Contraindications

- **All ESAs**
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with epoetin or other erythropoietin protein drugs
  - Serious allergic reactions to the specified ESA
- **Epoetin alfa (Epogen and Procrit)**
  - Use of the multi-dose vials in neonates, infants, pregnant women, and nursing mothers

Precautions/Warnings

- **All ESAs**
  - Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in persons with coexistent cardiovascular disease and stroke.
  - Increased mortality and/or increased risk of tumor progression or recurrence in persons with cancer.
  - Hypertension: Control hypertension prior to initiating and during treatment with erythropoietin.
  - Seizures: erythropoietin increases the risk for seizures in persons with CKD. Increase monitoring of these individuals for changes in seizure frequency or premonitory symptoms
  - PRCA: If severe anemia and low reticulocyte count develop during erythropoiesis treatment, withhold erythropoiesis and evaluate for PRCA
  - Discontinue if serious allergic reaction or severe cutaneous reaction occurs
- **Retacrit**
  - Contains phenylalanine

BILLING/CODING INFORMATION:

HCPCS Coding:

J0881	Injection, darbepoetin alfa, 1 microgram (Non-ESRD use)
J0882	Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
J0885	Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887	Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888	Injection, epoetin beta, 1 microgram, (for non-ESRD use)
J3591	Unclassified drug or biological used for esrd on dialysis
Q4081	Injection, epoetin alfa, 100 Units (for ESRD on dialysis)
Q5105	Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for esrd on dialysis), 100 units
Q5106	Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for non-esrd use), 1000 units

ICD-10 Diagnosis Codes That Support Medical Necessity:

B18.2	Chronic viral hepatitis C
B19.20	Unspecified viral hepatitis C without hepatic coma
B20	Human immunodeficiency virus [HIV] disease
C00.0 – C00.9	Malignant neoplasm of lip
C01	Malignant neoplasm of base of tongue
C02.0 – C02.9	Malignant neoplasm of other and unspecified parts of tongue
C03.0 – C03.9	Malignant neoplasm of gum
C04.0 – C04.9	Malignant neoplasm of floor of mouth
C05.0 – C05.9	Malignant neoplasm of palate
C06.0 – C06.9	Malignant neoplasm of other and unspecified parts of mouth
C07	Malignant neoplasm of parotid gland
C08.0 – C08.9	Malignant neoplasm of other and unspecified major salivary glands
C09.0 – C09.9	Malignant neoplasm of tonsil
C10.0 – C10.9	Malignant neoplasm of oropharynx
C11.0 – C11.9	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of pyriform sinus
C13.0 – C13.9	Malignant neoplasm of hypopharynx
C14.0 – C14.8	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0 – C17.9	Malignant neoplasm of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0 – C21.8	Malignant neoplasm of anus and anal canal
C22.0 – C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C23	Malignant neoplasm of gallbladder
C24.0 – C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C25.0 – C25.9	Malignant neoplasm of pancreas
C26.0 – C26.9	Malignant neoplasm of other and ill-defined digestive organs
C30.0 – C30.1	Malignant neoplasm of nasal cavity and middle ear
C31.0 – C31.9	Malignant neoplasm of accessory sinuses
C32.0 – C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00 – C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus

C38.0 – C38.8	Malignant neoplasm of heart, mediastinum and pleura
C39.0 – C39.9	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40.0 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0 – C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.0 – C43.9	Malignant melanoma of skin
C44.0 – C44.9	Other malignant neoplasm of skin
C45.0 – C45.9	Mesothelioma
C46.0 – C46.9	Kaposi's sarcoma
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C49.A0 -- C49.A9	Gastrointestinal stromal tumor
C50.0 – C50.929	Malignant neoplasm of breast
C51.0 – C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56.0 – C56.9	Malignant neoplasm of ovary
C57.0 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C60.0 – C60.9	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C62.00 – C62.92	Malignant neoplasm of testes
C63.0 – C63.9	Malignant neoplasm of other and unspecified male genital organs
C64.0 – C68.9	Malignant neoplasm of urinary tract
C69.0 – C69.92	Malignant neoplasm of eye and adnexa
C70.0 – C70.9	Malignant neoplasm of meninges
C71.0 – C71.9	Malignant neoplasm of brain
C72.0 – C72.9	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73	Malignant neoplasm of thyroid gland
C74.00 – C74.92	Malignant neoplasm of adrenal gland
C75.0 – C75.9	Malignant neoplasm of other endocrine glands and related structures
C76.0 – C76.8	Malignant neoplasm of other and ill-defined sites
C77.0 – C77.9	Secondary and unspecified malignant neoplasm of lymph nodes
C78.00 – C78.89	Secondary malignant neoplasm of respiratory and digestive organs
C79.00 – C79.9	Secondary malignant neoplasm of other and unspecified sites
C80.0 – C80.2	Malignant neoplasm without specification of site
C81.00 – C81.99	Hodgkin lymphoma
C82.00 – C82.99	Follicular lymphoma
C83.00 – C83.99	Non-follicular lymphoma
C84.00 – C84.99	Mature T/NK-cell lymphomas
C85.10 – C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C86.0 – C86.6	Other specified types of T/NK-cell lymphoma
C88.0 – C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas
C90.00 – C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.00 – C91.92	Lymphoid leukemia
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C93.10	Chronic myelomonocytic leukemia, not having achieved remission
C94.0 – C94.82	Other leukemias of specified cell type

C96.0 – C96.9	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
D00.0 – D00.2	Carcinoma in situ of oral cavity, esophagus and stomach
D01.0 – D01.9	Carcinoma in situ of other and unspecified digestive organs
D02.0 – D02.4	Carcinoma in situ of middle ear and respiratory system
D03.0 – D03.9	Melanoma in situ
D04.0 – D04.9	Carcinoma in situ of skin
D05.0 – D05.99	Carcinoma in situ of breast
D06.0 – D06.9	Carcinoma in situ of cervix uteri
D07.0 – D07.69	Carcinoma in situ of other and unspecified genital organs
D09.0 – D09.9	Carcinoma in situ of other and unspecified sites
D37.0 – D37.9	Neoplasm of uncertain behavior or oral cavity and digestive organs
D38.0 – D38.6	Neoplasm of uncertain behavior of middle ear and respiratory and intrathoracic organs
D39.0 – D39.9	Neoplasm of uncertain behavior of female genital organs
D40.0 – D40.9	Neoplasm of uncertain behavior of male genital organs
D41.0 – D41.9	Neoplasm of uncertain behavior of urinary organs
D42.0 – D42.9	Neoplasm of uncertain behavior of meninges
D43.0 – D43.9	Neoplasm of uncertain behavior of brain and central nervous system
D44.0 – D44.9	Neoplasm of uncertain behavior of endocrine glands
D45	Polycythemia vera
D46.0 – D46.9	Myelodysplastic syndromes
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del (5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes
D47.0 – D47.9	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D48.0 – D48.9	Neoplasm of uncertain behavior of other and unspecified sites
D49.0 – D49.9	Neoplasms of unspecified behavior
D50.9	Iron deficiency anemia, unspecified
D61.01 – D61.9	Other aplastic anemias and other bone marrow failure syndromes
D63.0	Anemia in neoplastic disease
D63.1	Anemia in chronic kidney disease
D63.8	Anemia in other chronic diseases classified elsewhere
D64.2	Secondary sideroblastic anemia due to drugs and toxins
D64.81	Anemia due to antineoplastic chemotherapy
D64.9	Anemia, unspecified
D75.81	Myelofibrosis
I12.0 – I12.9	Hypertensive chronic kidney disease
I13.0 – I13.2	Hypertensive heart and chronic kidney disease without heart failure
M05.40 – M06.9	Rheumatoid arthritis
N18.1 – N18.9	Chronic kidney disease
P61.2	Anemia of prematurity
Q85.00	Neurofibromatosis, unspecified
Q85.01	Neurofibromatosis, type 1
Q85.02	Neurofibromatosis, type 2
T37.5X5A – T37.5X5S	Adverse effect of antiviral drugs
T39.4X5A – T39.4X5S	Adverse effect of antirheumatics, not elsewhere classified
T45.1X5A – T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

Z41.8	Encounter for other procedures for purposes other than remedying health state
Z51.11	Encounter for antineoplastic chemotherapy
Z51.89	Encounter for other specified aftercare

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products: Medical necessity is determined using any applicable NCD or LCD and then Step therapy Requirements for Medicare Outpatient (Part B) Medications outlined in Policy (09-J3000-39). The following National Coverage Determination (NCD) and Local Coverage Determination (LCD) located at www.fcso.com were reviewed on the last guideline revised date: Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions, (110.21), Erythropoiesis Stimulating Agents, (L34633)

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

AZT: a drug used in the treatment of Human Immunodeficiency Virus (HIV).

Chronic Renal Failure (CRF): the Glomerular Filtration Rate (GFR) is less than 20 to 25% of normal. The kidneys cannot regulate volume and solute composition and patients develop edema, metabolic acidosis and hypocalcemia.

Creatinine: an end product of metabolism, found in muscle and blood, excreted in the urine; increased quantities are found in advanced stages of renal disease.

Erythroid: pertaining to any of the cells in the developmental series ending in erythrocytes.

Erythropoietin: a protein naturally made in the kidneys, which acts on the bone marrow to stimulate the body's production of red blood cells.

ESRD: end-stage renal disease (kidney failure).

Hematocrit: a method for determining the volume of packed red blood cells in a blood specimen.

Hemoglobin: a method for measuring the oxygen carrying capacity of the red blood cells.

Hepatitis C: a form of viral hepatitis previously referred to as non-B hepatitis. It is the most common form of blood transfusion acquired hepatitis. Risk factors include recent blood transfusion, IV drug abuse, and occupational exposure to blood products. Sexual transmission is considered rare.

Myelodysplasia: The bone marrow is not effective in producing enough red blood cells, as well as other cells, resulting in anemia.

Myelodysplastic syndrome (MDS): a bone marrow disorder that is marked especially by an abnormal reduction in one or more types of circulating blood cells due to defective growth and maturation of blood-forming cells in the bone marrow and that sometimes progresses to acute myelogenous leukemia.

Non-myeloid malignancy: a cancer of the body that is not associated with cancer of the white blood cells in the bone marrow, spleen or blood.

Renal failure: kidney failure, often requiring dialysis.

Zidovudine: AZT.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

06/15/00	New Medical Coverage Guideline.
08/29/02	Reviewed with no revisions.
01/01/04	Annual HCPCS coding update.
04/01/05	Reviewed and revised: Anemia of CRF on dialysis Hgb 10 g/dl or Hct 30%, Anemia of CRF not on dialysis Hgb 11 g/dl or Hct 33%, and added continuation of coverage statement.
01/01/06	HCPCS update deleted expired code Q4055, added new code J0886.
07/15/06	Reviewed with no revisions.
10/15/06	Revised by updating ICD-9 code.
01/01/07	HCPCS update, added Q4081. MCG revised to include Medicare Part D as program exception.
08/15/07	Reviewed: Reformatted guideline, added note regarding how to proceed once HCT and HGB reach 12 and 36, renamed guideline to include Non-ESRD indications, maintain current coverage and limitations, updated dosing guidelines, added Non-ESRD code J0885, reformatted ICD-9 codes to be consistent with LCD 5984, and updated references.
03/15/08	Review and revision; consisting of renaming guideline to include darbepoetin, updated coverage criteria, updated coding, reformatted, updated references and links.
04/15/08	Revision; consisting of updating a “NOTE” for clarification and updating dosing and administration section to be consistent with coverage criteria.
09/15/08	Revision; consisting of revising boxed warning.
03/15/09	Review and revision; consisting of adding maximum doses and updating references.
06/15/09	Revision consisting of removing coverage for anemia from previous chemo in past 12 months.
10/15/09	Revision; consisting of clarifying dosages and updating coding.
01/15/10	Revision; consisting of updating codes.
04/15/10	Revision; consisting of updating codes.
05/15/10	Review and revision; consisting of clarifying position statement and updating references.
10/01/10	Revision; consisting of updating codes.
11/15/10	Revision; consisting of updating codes.
02/01/11	Revision; consisting of updating codes.
02/15/11	Revision; consisting of adding ICD-10 codes, and adding note regarding age of laboratory values.
05/15/11	Review and revision to guideline; consisting of updating references.
06/15/11	Revision to guideline; consisting of modifying coverage criteria for CRF.
08/15/11	Revision to guideline; consisting of modifying position statement and updating precautions, updates of ICD-10 codes.
01/15/12	Revision to guideline; consisting of updating dosage and administration.
05/15/12	Review and revision to guideline; consisting of updating position statement and references.
07/01/12	Revision to guideline, consisting of adding new agent and update coding.
01/01/13	Annual HCPCS Update: added HCPCS code J0890 and removed code Q2047
02/15/13	Revision to guideline; consisting of updating coding.
06/15/13	Review and revision to guideline; consisting of revising and reformatting the position statement; revising and reformatting dosage/administration and precautions sections; updating references, coding, and program exceptions
10/15/13	Revision to guideline; consisting of clarifying language for treatment of chemotherapy induced anemia.
05/15/14	Review and revision to guideline; consisting of reformatting position statement and updating references.

10/01/14	Revision to guideline; consisting of adding HCPCS codes Q9972 and Q9973.
01/01/15	Revision to guideline; consisting of annual coding update.
05/15/15	Review and revision to guideline; consisting of updating description, position statement, dosage/administration, and references.
10/01/15	Revision to guideline consisting of coding updates and update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
12/15/15	Revision to guideline consisting of update to the position statement.
01/01/16	Annual HCPCS coding update: deleted code J0886.
05/15/16	Review and revision to guideline; consisting of updating the position statement, dosing, coding, and references.
10/01/16	Update to ICD-10 codes.
05/15/17	Review and revision to guideline; consisting of updating the position statement, coding, and references.
06/15/17	Review and revision to guideline; consisting of updating the position statement and references.
09/15/17	Revision to guideline consisting of update to the position statement.
05/15/18	Review and revision to guideline; consisting of updating the position statement and references.
07/15/18	Revision to guideline consisting of updating the position statement, dosing, coding and references.
11/15/18	Revision to guideline consisting of updating the description and position statement.
01/01/19	Revision: HCPCS code updates. Added J3591.
05/15/19	Review and revision to guideline; consisting of updating position statement, dosing and references.
07/15/19	Update to Program Exceptions.
01/01/20	Revision: HCPCS code updates. Revised descriptions for Q5105 and Q5106.
05/15/20	Revision to guideline consisting of updating the position statement and references.
05/15/21	Review and revision to guideline consisting of updating the position statement and references.
08/15/21	Revision to guideline consisting of updating the position statement and references.
07/15/22	Review and revision to guideline consisting of updating the position statement, drug availability, and references.
10/15/23	Review and revision to guideline consisting of updating the position statement for myelodysplastic syndromes and updated LCD.
08/15/24	Review and revision to guideline consisting of updating the position statement not to permit use in combination with daprodustat or vadadustat.
07/15/25	Review and revision to guideline; consisting of including Epogen as one of the preferred agents with Procrit and Retacrit.
07/15/25	Revision to remove comparative effectiveness statement. Clarified the note for use of preferred agents.