Clinical Policy: Epoetin Alfa (Epogen, Procrit), Epoetin Alfa-epbx (Retacrit)

Reference Number: ERX.SPA.88
Effective Date: 10.01.16
Last Review Date: 05.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Epoetin alfa (Epogen®, Procrit®) and its biosimilar, epoetin alfa-epbx (Retacrit™), are erythropoiesis-stimulating agents (ESAs).

FDA Approved Indication(s)

Epogen, Procrit, and Retacrit are indicated for:

- Treatment of anemia due to:
  - Chronic kidney disease (CKD) in patients on dialysis and not on dialysis
  - Zidovudine in human immunodeficiency virus (HIV)-infected patients
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery

Limitation(s) of use:

- Epogen, Procrit, and Retacrit have not been shown to improve quality of life, fatigue, or patient well-being.
- Epogen, Procrit, and Retacrit are not indicated for use:
  - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy
  - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
  - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion
  - In patients scheduled for surgery who are willing to donate autologous blood
  - In patients undergoing cardiac or vascular surgery
  - As a substitute for RBC transfusions in patients who require immediate correction of anemia

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Epogen, Procrit, and Retacrit are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Anemia Due to Chronic Kidney Disease (must meet all)**:**

1. Diagnosis of anemia of CKD (dialysis and non-dialysis members);
2. Prescribed by or in consultation with a hematologist or nephrologist;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
4. Pretreatment hemoglobin level < 10 g/dL;

5. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

B. Anemia Due to Zidovudine in HIV-infected Patients (must meet all)**:**
1. Diagnosis of zidovudine-induced anemia;
2. Prescribed by or in consultation with a hematologist or HIV specialist;
3. Member is HIV-positive;
4. Dose of zidovudine is ≤ 4,200 mg/week;
5. Endogenous serum erythropoietin levels ≤ 500 mUnits/mL;
6. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
7. Pretreatment hemoglobin level < 10 g/dL;
8. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

C. Anemia due to Chemotherapy in Patients with Cancer (must meet all)**:**
1. Request is for use in solid or non-myeloid malignancies in members receiving myelosuppressive chemotherapy without curative intent;
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age ≥ 5 years;
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
5. Pretreatment hemoglobin < 10 g/dL;
6. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*).

Approval duration: 6 months or until the completion of chemotherapy course (whichever is less) (*see Appendix D for dose rounding guidelines*)

D. Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery (must meet all)**:**
1. Member is at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery;
2. Perioperative hemoglobin > 10 to ≤ 13 g/dL;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
4. Member is unwilling or unable to donate autologous blood pre-operatively;
5. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed one of the following (a or b):
   a. 300 Units/kg administered daily for a total of 15 doses (*see Appendix D for dose rounding guidelines*);
   b. 600 Units/kg for a total of 4 doses (*see Appendix D for dose rounding guidelines*).

Approval duration: 15 days (for 300 units/kg daily) OR 21 days (for 600 units/kg in 4 doses)

E. Anemia Associated with Myelodysplastic Syndromes (off-label) (must meet all)**:**
1. Diagnosis of anemia from myelodysplastic syndrome (MDS);
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age ≥ 18 years;
4. Current (within the last 3 months) serum erythropoietin (EPO) ≤ 500 mU/mL;

5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
6. Pretreatment hemoglobin < 10 g/dL;
7. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*).

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

F. Myelofibrosis-Associated Anemia (off-label) (must meet all)**:**
1. Diagnosis of anemia associated with myelofibrosis;
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age ≥ 18 years;
4. Current (within the last 3 months) serum EPO < 500 mU/mL;
5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
6. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*).

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

G. Other diagnoses/indications (must meet all)**:**
1. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*).
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Anemia Due to Chronic Kidney Disease (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

B. Anemia Due to Zidovudine in HIV-infected Patients (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
3. Current hemoglobin level ≤ 12 g/dL;
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

C. Anemia Due to Chemotherapy in Patients with Cancer (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
3. Continuation of ESA therapy is concurrent with myelosuppressive chemotherapy;
4. If member has received ≥ 8 weeks of ESA therapy, member meets both of the following (a and b):
   a. Documented response to therapy as evidenced by a rise in hemoglobin levels > 1 g/dL;
   b. No RBC transfusions are required;
5. Current hemoglobin < 10 g/dL;
6. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months or until the completion of chemotherapy course, whichever is less (*see Appendix D for dose rounding guidelines*)

D. Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery
1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

E. Anemia Associated with Myelodysplastic Syndrome (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
3. If member has received ≥ 12 weeks of ESA therapy, member meets one of the following (a or b):
   a. Documented response to therapy as evidenced by a rise in hemoglobin levels > 1.5 g/dL;
   b. Decrease of RBC transfusions requirement;
4. Current hemoglobin ≤ 12 g/dL;
5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

F. Myelofibrosis-Associated Anemia (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy (examples may include, but are not limited to: for transfusion-independent members, a ≥ 2 g/dL increase in hemoglobin with a baseline hemoglobin < 10 g/dL; or for previously transfusion-dependent members, transitioning to become transfusion-independent);
3. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months (*see Appendix D for dose rounding guidelines*)

G. Other diagnoses/indications (must meet all)**:**
1. Member meets one of the following (a or b):
   a. If Epogen is requested, failure of Retacrit, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
2. Member meets one of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy. **Approval duration: Duration of request or 6 months (whichever is less)**; or
   b. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CKD: chronic kidney disease
ESA: erythropoiesis-stimulating agent
FDA: Food and Drug Administration
HIV: human immunodeficiency virus
RBC: red blood cell

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with erythropoietin protein drugs
  - Allergic reactions
  - Use of the multiple-dose vials containing benzyl alcohol in neonates, infants, pregnant women, and lactating women
- Boxed warning(s): ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence

Appendix D: Dose Rounding Guidelines

Weight-based Dose Range	Vial Quantity Recommendation
≤ 2,099.99 units	1 vial of 2,000 units
2,100 units-3,149.99 units	1 vial of 3,000 units
3,150 units-4,199.99 units	1 vial of 4,000 units
4,200 units-6,299.99 units	1 vial of 4,000 units and 1 vial of 2,000 units
6,300 units-7,349.99 units	1 vial of 4,000 units and 1 vial of 3,000 units
7,350 units-8,399.99 units	2 vials of 4,000 units
8,400 units-10,499 units	1 vial of 10,000 units
10,500 units-12,599.99 units	1 vial of 2,000 units and 1 vial of 10,000 units
12,600 units-13,649.99 units	1 vial of 3,000 units and 1 vial of 10,000 units
13,650 units-14,699.99 units	1 vial of 4,000 units and 1 vial of 10,000 units
14,700 units-16,799.99 units	1 vial of 2,000 units, 1 vial of 4,000 units and 1 vial of 10,000 units
16,800 units-17,849.99 units	1 vial of 3,000 units, 1 vial of 4,000 units and 1 vial of 10,000 units
17,849 units-18,899.99 units	2 vials of 4,000 units and 1 vial of 10,000 units

Weight-based Dose Range	Vial Quantity Recommendation
18,900 units-20,999 units	2 vials of 10,000 units

Appendix E: States with Regulations against Redirections in Certain Oncology Settings

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial requests only** For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Anemia due to CKD	Initial dose: 50 to 100 units/kg 3 times weekly (adults) intravenously (IV) or subcutaneously (SC) and 50 units/kg 3 times weekly (children on dialysis) IV or SC. Individualize maintenance dose. IV route recommended for patients on hemodialysis.	Varies depending on indication and frequency of administration
Anemia due to zidovudine in HIV-infected patients	100 units/kg IV or SC 3 times weekly	
Anemia due to chemotherapy	40,000 units SC weekly *or* 150 units/kg SC 3 times weekly (adults) until completion of a chemotherapy course; 600 units/kg IV weekly (children ≥ 5 years) until completion of a chemotherapy course	
Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery	300 units/kg per day SC daily for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery *or* 600 units/kg SC weekly in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery	
Anemia associated with MDS†	40,000-60,000 units SC one to two times weekly	
Anemia associated with myelofibrosis†	In a clinical trial, patients initially received erythropoietin 10,000 units SC 3 days per week. Erythropoietin was increased to 20,000 units 3 days per week if a response was not obtained after 2 months and erythropoietin was discontinued in patients who did not experience a response at 3 months.	

† *Off-label indication*

VI. Product Availability

Drug Name	Availability
Epoetin alfa (Epogen)	• Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, and 10,000 units/mL • Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL
Epoetin alfa (Procrit)	• Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL • Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL
Epoetin alfa-epbx (Retacrit)	• Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, 40,000 units/mL • Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL

VII. References

1. Epogen Prescribing Information. Thousand Oaks, CA: Amgen Inc.; July 2018. Available at http://www.epogen.com/. Accessed February 17, 2022.
2. Procrit Prescribing Information. Thousand Oaks, CA: Amgen Inc.; July 2018. Available at http://www.procrit.com/. Accessed February 17, 2022.
3. Bohlius J, Bohlke K, Castelli R, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update: Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents. 2019 May 20; J Clin Oncol 37(15):1336-1351. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.18.02142.
4. Mancino P, Falasca K, Ucciferri C, Pizzigallo E, Vecchiet J. Use of Hematopoietic Growth Factor in the Management of Hematological Side Effects Associated to Antiviral Treatment for Hcv Hepatitis. Mediterranean Journal of Hematology and Infectious Diseases. 2010;2(1):e2010003. doi:10.4084/MJHID.2010.003.
5. Afdhal NH, Dieterich DT, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology. 2004 May;126(5):1302-11.
6. Epoetin alfa. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed February 17, 2022.
7. Myelodysplastic Syndromes (Version 3.2022). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 17, 2022.
8. Myeloproliferative Neoplasms (Version 2.2021). In National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 17, 2022.
9. Hematopoietic Growth Factors (Version 1.2022). In National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 17, 2022.
10. Epoetin Alfa Drug Monograph. Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 17, 2022..
11. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 17, 2022.
12. Retacrit Prescribing Information. Lake Forest, IL: Hospira, Inc., August 2020. Available at https://www.pfizerpro.com/product/retacrit/hcp. Accessed February 17, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2018 annual review: All Indications: removed criteria that are under the purview of the prescriber-"Member does not require immediate correction of anemia", and "Other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) have been corrected or excluded"; removed safety requirements related to contraindications per safety guidance endorsed by Medical Affairs; modified initial/continued approval duration to 6 months (except surgery); Anemia due to CKD:	01.10.18	05.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
removed requirement related to dosage reduction per hemoglobin level on re-auth since it is not a hard stop to discontinue and specialist is involved in care.; Anemia due to zidovudine: removed age requirement-published literature has reported use in pediatric patients per PI; Anemia due to chemotherapy: removed criteria that are under the purview of the prescriber-"Member has non-myeloid malignancy", a minimum of 2 additional months of planned chemotherapy, chemotherapy is being given as palliative treatment, and anemia cannot be managed by transfusion; removed "member is receiving concomitant myelosuppressive chemotherapy" since chemo is already included as part of the diagnosis; Reduction of RBC transfusion in surgery patients: removed age requirement-literature available for pediatric dosing (Micromedex); Anemia associated with MDS: added specialist requirement; clarified that the lab for serum EPO should be current (within the past 3 months); added requirement for positive response to therapy on re-auth; Added NCCN compendial/recommended use (category 2A): MF-associated anemia; References reviewed and updated.		
Newly FDA-approved biosimilar added: Retacrit; removed myelofibrosis-associated anemia, anemia due to myelodysplastic syndrome, anemia secondary to combination ribavirin and interferon-alfa therapy in patients infected with hepatitis C virus off label uses since DrugDex IIb not covered; references reviewed and updated.	06.26.18	08.18
2Q 2019 annual review: added NCCN compendium supported uses for myelofibrosis-associated anemia and anemia due to myelodysplastic syndrome; references reviewed and updated	01.30.19	05.19
2Q 2020 annual review: for anemia with chemotherapy, modified diagnosis requirement to confirm request is for use in solid or non-myeloid malignancies in members receiving myelosuppressive chemotherapy without curative intent consistent with NCCN and ASCO recommendations; added appendix D: dose rounding guidelines; added reference to appendix D within criteria; modified re-direction for Epogen requests from Procrit to Retacrit per formulary status and previously approved clinical guidance; references reviewed and updated.	02.13.20	05.20
RT4: added new multiple-dose vial formulation for Retacrit and updated Appendix C with benzyl alcohol-related contraindication.	07.08.20	
2Q 2021 annual review: added existing Epogen redirection to Retacrit to apply for continued authorization; for MDS and MF associated anemia added for continued therapy hemoglobin or transfusion response criteria per NCCN; added allowance for bypassing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings references reviewed and updated.	02.23.21	05.21
Added Nevada and Ohio to Appendix E.	08.03.21	
2Q 2022 annual review: added to the other diagnoses/indications criteria set in Section I and II requirement for Epogen redirection to Retacrit unless state regulations do not allow step therapy in certain oncology settings; references reviewed and updated.	02.17.22	05.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of

physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.