BlueCross BlueShield
Federal Employee Program
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.85.006

Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Hematological Agents	**Original Policy Date:**	December 7, 2011
Subject:	Epoetin alfa	**Page:**	1 of 8

Last Review Date: March 7, 2025

Epoetin alfa

Description

Epogen, Procrit (epoetin alfa), **Retacrit** (epoetin alfa – epbx)

Preferred product: Retacrit
Epogen is neither preferred nor non-preferred

Background
Epogen, Procrit and Retacrit are erythropoiesis-stimulating agents (ESAs) that bind to progenitor stem cells and stimulates the production and differentiation of red blood cells (RBC). Epogen, Procrit and Retacrit stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. Epogen, Procrit and Retacrit increase the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of Epogen, Procrit, or Retacrit being administered. Retacrit is a biosimilar to Epogen. (1-3).

Regulatory Status
FDA-approved indications: Epogen, Procrit and Retacrit are erythropoiesis-stimulating agents (ESA) indicated for: (1-3)

1. Treatment of anemia due to
    a. Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
    b. Zidovudine in HIV-infected patients.
    c. The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
2. Reduction of allogeneic RBC transfusions in patients undergoing elective, non-cardiac, nonvascular surgery

Limitations of Use: (1-3)
Epogen, Procrit and Retacrit have not been shown to improve quality of life, fatigue, or patient wellbeing.
Epogen, Procrit and Retacrit are not indicated for use:

1. In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
2. In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
3. In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion
4. In patients scheduled for surgery who are willing to donate autologous blood.
5. In patients undergoing cardiac or vascular surgery.
6. As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Off-Label Uses: (4-8)

1. Symptomatic anemia in patients with myelodysplastic syndromes (MDS)
2. Anemia in rheumatoid arthritis
3. Anemia due to hepatitis C treatment with ribavirin in combination with either interferon alfa or peginterferon alfa
4. Allogeneic bone marrow transplantation

Epogen, Procrit and Retacrit carry warnings citing the increased risk of myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence (1-3).

Myelodysplastic syndromes (MDS) encompass a series of hematological conditions characterized by chronic cytopenias, including anemia, accompanied by abnormal cellular maturation. As a result, patients with MDS are at risk for symptomatic anemia. At least 80 percent of patients are anemic at the time of diagnosis, while about 50 percent have a hemoglobin level less than 10 g/dL. The use of epoetin alfa for the treatment of symptomatic anemia in patients with MDS is an unlabeled or investigational use according to the FDA. However, their use in MDS is supported by the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) (4-5).

Anemia associated with Hepatitis C therapy is a frequent cause of dose reduction or discontinuation of therapy. Clinical recommendation is to reduce the dosage if anemia

developed. This reduction increases the likelihood of treatment failure. Addition of an ESA agent allows the optimal probability of treatment success (6).

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) provides evidence based clinical guidelines for improving treatment and outcomes in patients with kidney disease. Their recommendations for transferrin saturation, serum ferritin and hemoglobin levels establish a standard of care and are incorporated into this criterion (7). Treatment of anemia associated with rheumatoid arthritis has been shown to reduce disease activity (8).

Several sources, such as the Renal Association, recommend therapy with erythropoietin stimulating agents when the hemoglobin level is less than 11 g/dL in patients not on dialysis (9-11).

Related policies
Aranesp

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Epogen, Procrit, and Retacrit may be considered **medically necessary** if the conditions indicated below are met.

Epogen, Procrit, and Retacrit may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Anemia associated with chronic renal failure
    a. Serum ferritin ≥ 100 ng/ml (labs must have been taken within the last 3 months)

AND ONE of the following:
If patient is NOT on dialysis

a. Initial treatment: Hemoglobin < 11 g/dl***** (labs must have been taken within the last 3 months)
b. Continuing treatment: Hemoglobin ≤ 11 g/dl***** (labs must have been taken within the last 3 months)

If patient is ON dialysis

a. Initial treatment: Hemoglobin < 10 g/dl***** (labs must have been taken within the last 3 months)
b. Continuing treatment: Hemoglobin ≤ 11 g/dl***** (labs must have been taken within the last 3 months)

***** if the hemoglobin level exceeds this level then the prescribing physician must confirm that the dose will be held or reduced until the hemoglobin level returns to the required level.

2. Anemia secondary to chemotherapy
    a. Concomitant myelosuppressive therapy
    b. There is a minimum of two additional months of planned chemotherapy
    c. Prescriber agrees to discontinue use of Epogen/Procrit upon completion of the chemotherapy
    d. Prescriber agrees that transfusions are **NOT** an option for treatment (i.e., end organ failure, CKD, high risk bacterial infections)

3. Anemia secondary to zidovudine-treated Human Immunodeficiency Virus (HIV) patients
    a. Endogenous serum erythropoietin levels ≤ 500 mUnits/mL

4. Anemia in patients scheduled to undergo elective, non-cardiac, nonvascular surgery
    a. Hemoglobin >10 and ≤ 13 g/dl

5. Myelodysplastic syndrome

6. Allogeneic bone marrow transplantation

7. Anemia associated with Hepatitis C (HCV) treatment

8. Anemia associated with rheumatoid arthritis (RA)/ rheumatic disease

AND ALL of the following for **ALL** diagnoses:

a. **NOT** used in combination with another erythropoiesis stimulating agent
b. **Procrit only:** Patient **MUST** have tried the preferred product (Retacrit) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Same as above

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 6 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Epogen, Procrit, and Retacrit are erythropoiesis-stimulating agents (ESAs) that bind to progenitor stem cells and stimulates the production and differentiation of red blood cells (RBC). Epogen, Procrit, and Retacrit stimulate erythropoiesis by the same mechanism as endogenous erythropoietin (1-3).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Epogen, Procrit, and Retacrit while maintaining optimal therapeutic outcomes.

References

1. Epogen [package insert]. Thousand Oaks, CA: Amgen Inc.; April 2024.
2. Procrit [package insert]. Horsham, PA: Janssen Products, LP; April 2024.
3. Retacrit [package insert]. New York: NY: Pfizer Inc.; June 2024.
4. Rizzo JD, Brouwers M, Herley P, et al. American Society of Hematology / American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin

in adult patients with cancer. Blood 2010; 116:4045.
5. NCCN Clinical Practice Guidelines in Oncology® Myelodysplastic Syndromes (Version 3.2023). National Comprehensive Cancer Network, Inc. November 2023. Accessed on January 8, 2024.
6. Eric M Yoshida, Anne Dar Santos, Nilufar Partovi, Jo-Ann E Ford. Erythropoietin and hepatitis C therapy: Useful adjuvant therapy but remember to treat the patient and not just a number Can J Gastroenterol. 2006 Aug; 20(8): 519–520.
7. Kliger, Alan S. et al.KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. American Journal of Kidney Diseases, Volume 62, Issue 5, 849 -859.
8. H R Peeters, M Jongen-Lavrencic, G Vreugdenhil, A J Swaak. Effect of recombinant human erythropoietin on anaemia and disease activity in patients with rheumatoid arthritis and anaemia of chronic disease: a randomised placebo controlled double blind 52 weeks clinical trial. Ann Rheum Dis. 1996 Oct; 55(10): 739–744.
9. Mikhail A, et. al. Clinical Practice Guideline: Anemia of Chronic Kidney Disease. The Renal Association. June 2017.
10. FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. October 8, 2019.
11. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney International Supplements: Volume 2, Issue 4. August 2, 2012.

Policy History

Date	Action
September 2008	FDA labeling revisions with new indications: • Treatment of Anemia of Chronic Renal Failure Patients • Treatment of Anemia in Zidovudine-treated HIV-infected Patients (Epogen and Procrit only) • Treatment of Anemia due to concomitant myelosuppressive chemotherapy- no longer indicated when the anticipated outcome is cure. • Reduction of Allogeneic Blood Transfusion in Surgery patients (Epogen and Procrit only) The August 2008 FDA package insert revisions were two-fold. The first revision was to limit use of any ESA products to patients whom hemoglobin levels are less than 10g/dl. The second revision was to remove the indication for ESA therapy for patients receiving myelosuppressive therapy when the anticipated outcome is cure. Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Individual titration in patients with chronic renal failure should be

	done to achieve and maintain hemoglobin levels between 10 to 12 g/dL. Procrit and Epogen are indicated for the treatment of anemic patients with hemoglobin levels > 10 to ≤ 13 g/dl who are at risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions (1).
October 2008	Allowing PA approval for hemoglobin levels outside the recommended levels if the AP confirms that the dose will be held until hemoglobin levels fall within acceptable range will allow for safe use of the medication while making it available for the patient as soon as clinically appropriate.
September 2011	Separation of Aranesp from the other ESAs' criteria due to differing U.S. Food and Drug administration (FDA) approved indications.
December 2011	Annual review and update
June 2012	Add "or reduced," to "if the hemoglobin level exceeds this level then the prescribing physician must confirm that the dose will be held or reduced until the hemoglobin level returns to the required level."
December 2012	Annual review and update
March 2014	Annual review and update. Removal of TSAT level requirement Modified use with chemotherapy to reflect package insert
December 2015	Annual editorial review and reference update
December 2016	Annual review and reference update Policy code changed from 5.10.06 to 5.85.06
September 2017	Annual editorial review and reference update Addition of requirement to anemia secondary to chemotherapy: Patient's anemia cannot be managed by transfusions Addition of not used in combination with another erythropoiesis stimulating agent
January 2018	Re-worded the requirements for Anemia secondary to chemotherapy: "Patient's anemia cannot be managed by transfusions" changed to "Prescriber agrees that transfusions are NOT an option for treatment (i.e., end organ failure, CKD, high risk bacterial infections) and "Must discontinue use of agent upon completion of the chemotherapy" changed to "Prescriber agrees to discontinue use of Epogen/Procrit upon completion of the chemotherapy"
March 2018	Annual review
June 2018	Addition of Retacrit biosimilar to criteria Change of criteria name to "Epoetin alfa"
September 2018	Annual review and reference update Addition of off-label indications to Retacrit, addition of requirement of endogenous serum erythropoietin level ≤ 500 mUnits/mL to anemia secondary to zidovudine, and removal of anticipated outcome of therapy is not cure of cancer per SME
September 2019	Annual review

December 2019	Annual review and reference update. Addition of requirement to trial preferred product. Changed required hemoglobin level for patients not on dialysis to be < 11 g/dL from < 10 g/dL
September 2020	Annual review and reference update
March 2021	Annual review and reference update
June 2021	Annual review
March 2022	Annual review and reference update
March 2023	Annual review. Changed policy number to 5.85.006
June 2023	Annual review
March 2024	Annual review and reference update
June 2024	Annual review
December 2024	Annual review and reference update
March 2025	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.