Drug Coverage Policy

Effective Date.....10/15/2024
Coverage Policy Number.....IP0296
Policy Title.....Epoetin Alfa Products

Erythropoiesis-Stimulating Agents – Epoetin Alfa Products

- Epogen® (epoetin alfa intravenous or subcutaneous injection – Amgen)
- Procrit® (epoetin alfa intravenous or subcutaneous injection – Janssen)
- Retacrit® (epoetin alfa-epbx intravenous or subcutaneous injection – Pfizer)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Epoetin alfa (Epogen, Procrit, Retacrit), an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1-3]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusions.

- **Anemia due to chemotherapy in patients with cancer**, in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- **Anemia due to zidovudine**, in patients with human immunodeficiency virus (HIV) infection.
- **Reduction of allogeneic RBC transfusions**, in patients with perioperative hemoglobin (Hb) > 10.0 to ≤ 13.0 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

Retacrit is a biosimilar to Epogen/Procrit.[3] Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.[1-3] Epoetin alfa is not indicated for the following uses:

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

The iron status should be evaluated in all patients before and during treatment with epoetin alfa.[1-3] Therapy should be initiated for **adults with CKD on dialysis** when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of epoetin alfa. For **adults with CKD who are not on dialysis**, consider initiating epoetin alfa only when the Hb is < 10.0 g/dL and other considerations apply (e.g., rate of Hb decline indicates patient is likely to need RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal). If the Hb exceeds 10.0 g/dL, reduce or interrupt the epoetin alfa dose and use the lowest dose sufficient to reduce the need for RBC transfusions. For **pediatric patients with CKD**, initiate epoetin alfa when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of epoetin alfa. Initiate epoetin alfa for **patients on cancer chemotherapy** only if the Hb is < 10.0 g/dL. Use the lowest dose of epoetin alfa necessary to avoid RBC transfusions. Epoetin alfa is indicated for the treatment of **anemia due to zidovudine** given at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mU/mL. It is recommended to withhold epoetin alfa if Hb exceeds 12.0 g/dL. Data show that epoetin alfa elevated or maintained Hb and/or hematocrit and decreased transfusions in anemic patients (Hb < 10.0 g/dL) who were receiving zidovudine. Patients with baseline endogenous serum erythropoietin levels ≤ 500 mU/mL derived greater benefit with epoetin alfa (e.g., achievement of higher hematocrit, reduction in transfusion requirements) compared with those having levels greater than this threshold.

Dosing Information

Doses of epoetin alfa are titrated based on hemoglobin values. Refer to the prescribing information regarding increasing, reducing, interrupting, or conversion dosing. Use the lowest dose sufficient to reduce the need for RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[4] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized

based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

Epoetin alfa is recommended in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Myelodysplastic Syndrome (MDS):** NCCN guidelines (version 2.2024 – May 22, 2024) list Aranesp and epoetin alfa products as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[5] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb range of 10 to 12.0 g/dL but not to exceed 12.0 g/dL.
- **Myeloproliferative Neoplasms:** The NCCN guidelines (version 1.2024 – December 21, 2023) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level < 500 mU/mL.[6] Iron stores should be adequate. The guidelines also advise that ESAs are generally less effective for the management of transfusion-dependent anemia.

Medical Necessity Criteria

Epoetin alfa is considered medically necessary when ONE of the following is met:

FDA-Approved Indications

1. **Anemia in a Patient with Chronic Kidney Disease who is on Dialysis.** Approve for 3 years.

2. **Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i, ii and iii):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iii.** Preferred product criteria is met for the product(s) as listed in the below table(s)
   - **B)** Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets BOTH of the following (i and ii):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).

i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
ii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber.

Dosing. Approve if the doses are equivalent to ≤ 60,000 units total per month.

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3. Anemia in a Patient with Cancer due to Cancer Chemotherapy. Approve for 6 months if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii and iv):
i. Patient has a hemoglobin < 10.0 g/dL; AND
ii. Patient meets BOTH of the following (a and b):
a) Patient is currently receiving myelosuppressive chemotherapy; AND
b) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
iii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber; AND
iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets ALL of the following (i, ii, and iii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
ii. Patient meets BOTH of the following (a and b):
a) Patient is currently receiving myelosuppressive chemotherapy; AND
b) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
iii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Patient is ≥ 18 years of age. Approve if the dose meets BOTH of the following (i and ii):
i. Each dose is ≤ 300 Units/kg; AND
ii. Each dose is given no more frequently than 3 times a week; OR

B) Patient is < 18 years of age. Approve if the dose meets ALL of the following (i, ii, and iii):
i. Each dose is ≤ 900 Units/kg; AND
ii. Each dose is ≤ 60,000 Units (Maximum Dose); AND
iii. Each dose is given no more frequently than once weekly.

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4. Anemia in a Patient with Human Immunodeficiency Virus who is Receiving Zidovudine. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
i. Patient meets ONE of the following (a or b):
a) Patient has a hemoglobin < 10.0 g/dL; OR
b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
ii. Patient is currently receiving zidovudine therapy; AND
iii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
c) Patient has adequate iron stores according to the prescriber; AND

iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets ALL of the following (i, ii, and iii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or darbepoetin alfa product (e.g., Aranesp).
- **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** Patient is currently receiving zidovudine therapy; AND
- **iii.** Patient meets ONE of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Patient is ≥ 18 years of age. Approve if the dose meets BOTH of the following (i and ii):
- **i.** Each dose is ≤ 300 Units/kg; AND
- **ii.** Each dose is given no more frequently than 3 times per week; OR

B) Patient is < 18 years of age. Approve if the dose meets BOTH of the following (i and ii):
- **i.** Each dose is ≤ 400 Units/kg; AND
- **ii.** Each dose is given no more frequently than 3 times per week.

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5. Reduction of Allogeneic Red Blood Cell Transfusions in a Patient Undergoing Surgery. Approve for 1 month if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Hemoglobin is ≤ 13.0 g/dL; AND
- **B)** The surgery is elective, nonvascular, and noncardiac; AND
- **C)** Patient is not willing or able to donate autologous blood prior to surgery; AND
- **D)** Patient meets ONE of the following (i or ii):
  - **i.** Patient is currently receiving iron therapy; OR
  - **ii.** Patient has adequate iron stores according to the prescriber; AND
- **E)** Preferred product criteria is met for the product(s) as listed in the below table(s)

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Approve if the dose meets BOTH of the following (i and ii):
- **i.** Each dose is ≤ 300 Units/kg per day; AND
- **ii.** The total amount of doses is ≤ 15 doses; OR

B) Approve if the dose meets BOTH of the following (i and ii):
- **i.** Each dose is ≤ 600 Units/kg per day; AND
- **ii.** The total amount of doses is ≤ 4 doses.

Other Uses with Supportive Evidence

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6. Anemia Associated with Myelodysplastic Syndrome. Approve for 1 year if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv and v):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following (a or b):
    - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
    - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
  - **iii.** Patient meets ONE of the following (a or b):
    - **a)** Patient is currently receiving iron therapy; OR
    - **b)** Patient has adequate iron stores according to the prescriber; AND

iv. The medication is prescribed by or in consultation with a hematologist or oncologist; AND
v. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
i. Patient is ≥ 18 years of age; AND
ii. Patient has a hemoglobin ≤ 12.0 g/dL; AND
iii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber; AND
iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

Dosing. Approve if the dose meets BOTH of the following (A and B):
A) Each dose is ≤ 60,000 Units; AND
B) Each dose is given no more frequently than 2 times a week.

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7. Anemia Associated with Myelofibrosis. Approve for the duration noted below if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii and iv):
i. Patient meets ONE of the following (a or b):
a) Patient has a hemoglobin < 10.0 g/dL; OR
b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
ii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber; AND
iii. The medication is prescribed by or in consultation with a hematologist or oncologist; AND
iv. Preferred product criteria is met for the product(s) as listed in the below table(s)

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
ii. Patient meets ONE of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber; AND
iii. According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL; AND
iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

Dosing. Approve if the dose meets BOTH of the following (A and B):
A) Each dose is ≤ 60,000 Units; AND
B) Each dose is given no more frequently than once every 2 weeks.

Individual and Family Plans:

Product	Criteria
Epogen (epoetin alfa)	Patient meets **BOTH** of the following criteria (1 and 2): 1. Patient has tried Procrit [may require prior authorization]

Product	Criteria
	2. Patient cannot continue to use Procrit due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] which, according to the prescriber, would result in a significant allergy or serious adverse reaction

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Anemia Associated with Cancer in a Patient not Receiving Myelosuppressive Cancer Chemotherapy.** Epoetin alfa is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1-3]

2. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML), or other Myeloid Cancers.** Epoetin alfa is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1-3]

3. **Anemia Associated with Radiotherapy in Cancer.** Epoetin alfa is not indicated for use in patients with cancer who are given only radiation therapy.[1-3]

4. **To Enhance Athletic Performance.** Epoetin alfa is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. **Anemia due to Acute Blood Loss.** Use of epoetin alfa is not appropriate in these types of situations.

6. **Non-Anemic Patient (Hemoglobin > 13.0 g/dL) Prior to Surgery.** Although studies have been conducted that involved non-anemic patients undergoing various surgeries receiving epoetin alfa preoperatively and sometimes postoperatively to prevent transfusions or subsequent anemia, the overall benefit of this therapy in those with relatively normal preoperative Hb level is questionable.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0885	Injection, epoetin alfa, (for non-ESRD use), 1000 units
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

References

1. Procrit® intravenous or subcutaneous injection [prescribing information]. Horsham, PA: Janssen; May 2024.
2. Epogen® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2024.
3. Retacrit® subcutaneous or intravenous injection [prescribing information]. Lake Forest, IL: Pfizer; June 2024.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012; 2(Suppl):279-335.
5. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2024 – May 22, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 8, 2024.
6. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 1.2024 – December 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 8, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** title from "Epoetin Alfa Products" to "Erythropoiesis-Stimulating Agents – Epoetin Alfa Products" **Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria **Anemia in an Individual with Cancer due to Cancer Chemotherapy.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria **Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria	10/15/2024

	Added "Patient is currently receiving zidovudine therapy" **Anemia Associated with Myelodysplastic Syndrome.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria **Anemia Associated with Myelofibrosis.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria **Anemia associated with Hepatitis C Treatment.** **Added** "Patient is Currently Receiving an Erythropoiesis-Stimulating Agent" criteria **Preferred Product Criteria Table.** Updated "There is documentation the individual is intolerant to Procrit [may require prior authorization]" to "Patients meets BOTH of the following: (1) Patient has tried Procrit [may require prior authorization], (2) Patient cannot continue to use Procrit due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] which, according to the prescriber, would result in a significant allergy or serious adverse reaction **Conditions Not Covered.** **Removed** "Anemia of Prematurity, Use in Individuals Receiving Myelosuppressive Chemotherapy with a Curative Intent" **Removed** "not medically necessary" language	

The policy effective date is in force until updated or retired.