Effective Date.....**11/15/2023**
Next Review Date.....**11/15/2024**
Coverage Policy Number.....**IP0296**

Epoetin Alfa Products

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Related Coverage Resources

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. 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.

Overview

This policy supports medical necessity review for the following **Epoetin Alfa Products:**

- **Epogen®** (epoetin alfa intravenous or subcutaneous injection)
- **Procrit®** (epoetin alfa intravenous or subcutaneous injection)
- **Retacrit®** (epoetin alfa-epbx intravenous or subcutaneous injection)

Medical Necessity Criteria

Epoetin Alfa Products are considered medically necessary when ONE of the following is met (1, 2, 3, 4, 5, 6, 7, or 8):

1. **Anemia in an Individual with Chronic Kidney Disease who is on Dialysis.**

2. **Anemia in an Individual with Chronic Kidney Disease who is not on Dialysis.** Individual meets **ALL** of the following criteria (A, B, and C):

A. Individual meets **ONE** of the following (i or ii):
   i. Individual is 18 years of age or older with a hemoglobin less than 10.0 g/dL
   ii. Individual is less than 18 years of age with a hemoglobin less than or equal to 11.0 g/dL
B. Individual meets **ONE** of the following (i or ii):
   i. Individual is currently receiving iron therapy
   ii. Individual has adequate iron stores according to the prescriber
C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Dosing for Chronic Kidney Disease who is not on Dialysis; the maximum dose is 60,000 units per month.

3. **Anemia in an Individual with Cancer due to Cancer Chemotherapy.** Individual meets **ALL** the following criteria (A, B, C, and D):
   A. Individual has a hemoglobin less than10.0 g/dL
   B. Individual is currently receiving myelosuppressive chemotherapy and the anticipated outcome is not cure
   C. Individual meets **ONE** of the following (i or ii):
      i. Individual is currently receiving iron therapy
      ii. Individual has adequate iron stores according to the prescriber
   D. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

   Dosing for Anemia in an Individual with Cancer due to Cancer Chemotherapy; ONE of the following dosing regimens (A or B):
   A) Individual is 18 years of age or older; the maximum dose is 300 units/kg given 3 times a week
   B) Individual is less than 18 years of age; the dose is less than or equal to 900 units/kg or maximum of 60,000 units given once weekly

4. **Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine.** Individual meets **ALL** of the following criteria (A, B, and C):
   A. Individual meets **ONE** of the following (i or ii):
      i. Individual has a hemoglobin less than 10.0 g/dL
      ii. Individual has serum erythropoietin level less than or equal to 500 mU/mL
   B. Individual meets **ONE** of the following (i or ii):
      i. Individual is currently receiving iron therapy
      ii. Individual has adequate iron stores according to the prescriber
   C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Dosing for Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine; ONE of the following dosing regimens (A or B):
A) Individual is 18 years of age or older; the maximum dose is 300 units/kg given 3 times a week
B) Individual is less than 18 years of age; the maximum dose is 400 units/kg given 3 times per week

5. **Reduction of Allogeneic Red Blood Cell Transfusions in an Individual Undergoing Surgery.** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
   A. Hemoglobin is less than or equal to13.0 g/dL
   B. The surgery is elective, non-vascular and non-cardiac
   C. Individual is not willing or able to donate autologous blood prior to surgery
   D. Individual meets **ONE** of the following (i or ii):
      i. Individual is currently receiving iron therapy
      ii. Individual has adequate iron stores according to the prescriber
   E. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Dosing for Reduction of Allogeneic Red Blood Cell Transfusions in an Individual Undergoing Surgery meets ONE of the following (A or B):

A) The maximum dose is 300 units/kg per day for 15 doses
B) The maximum dose is 600 units/kg per day for 4 doses

6. **Anemia Associated with Myelodysplastic Syndrome.** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Individual is 18 years of age or older
    B. Individual meets **ONE** of the following (i or ii):
        i. Individual has a hemoglobin less than 10.0 g/dL
        ii. Individual has a serum erythropoietin level less than or equal to 500 mU/mL
    C. Individual meets **ONE** of the following (i or ii):
        i. Individual is currently receiving iron therapy
        ii. Individual has adequate iron stores according to the prescriber
    D. The medication is prescribed by or in consultation with a hematologist or oncologist
    E. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Dosing for Anemia Associated with Myelodysplastic Syndrome, the maximum dose is 60,000 units given 2 times per week

7. **Anemia Associated with Myelofibrosis.** Individual meets **ALL** of the following criteria (A, B, C, and D):
    A. Individual meets **ONE** of the following (i or ii):
        i. Individual has a hemoglobin less than 10.0 g/dL
        ii. Individual has a serum erythropoietin level less than or equal to 500 mU/mL
    B. Individual meets **ONE** of the following (i or ii):
        i. Individual is currently receiving iron therapy
        ii. Individual has adequate iron stores according to the prescriber
    C. The medication is prescribed by or in consultation with a hematologist or oncologist
    D. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Dosing for Anemia Associated with Myelofibrosis; the maximum dose is 60,000 units given 2 times per week

8. **Anemia associated with Hepatitis C Treatment.** Individual meets **ALL** of the following criteria (A, B, and C):
    A. Pretreatment Hgb less than 10.0 g/dL
    B. Individual is currently receiving ribavirin in combination with either interferon alfa or peginterferon alfa
    C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below [Individual and Family Plans **ONLY**]

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Individual and Family Plan Non-Covered Products and Covered Alternative(s):

Non-Covered Product	Criteria
Epogen (epoetin alfa)	There is documentation the individual is intolerant to Procrit [may require prior authorization]

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.

Reauthorization Criteria

Epoetin Alfa Products are considered medically necessary for continued use when initial criteria are met AND **ONE** of the following is met (1, 2, 3, 4, 5, 6, 7, or 8):

1. **Anemia in an Individual with Chronic Kidney Disease who is on Dialysis.** Individual meets the following criteria:
    A. Documentation of beneficial response

2. **Anemia in an Individual with Chronic Kidney Disease who is not on Dialysis.** Individual meets the following criteria:
    A. Individual meets **ONE** of the following (i or ii):
        i. Individual is 18 years of age or older with a hemoglobin less than 11.5 g/dL
        ii. Individual is less than 18 years of age with a hemoglobin less than or equal to 12.0 g/dL

3. **Anemia in an Individual with Cancer due to Cancer Chemotherapy.** Individual meets the following criteria:
    A. Individual has a hemoglobin less than or equal to 12.0 g/dL

4. **Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine.** Individual meets the following criteria:
    A. Individual has a hemoglobin less than or equal to 12.0 g/dL

5. **Reduction of Allogeneic Red Blood Cell Transfusions in an Individual Undergoing Surgery.**
    Not applicable for continuation beyond initial approval duration.

6. **Anemia Associated with Myelodysplastic Syndrome.** Individual meets the following criteria:
    A. Individual has a hemoglobin less than or equal to 12.0 g/dL

7. **Anemia Associated with Myelofibrosis.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual has a hemoglobin less than or equal to 12.0 g/dL
    B. According to the prescriber, individual has responded to therapy defined as hemoglobin greater than or equal to 10 g/dL or a hemoglobin increase of greater than or equal to 2 g/dL

8. **Anemia associated with Hepatitis C Treatment.** Individual meets the following criteria:
    A. Hemoglobin is less than or equal to 12.0 g/dL

Authorization Duration

Initial approval duration:

- **Anemia in an Individual with Chronic Kidney Disease who is on Dialysis:** Up to 3 years.
- **Anemia in an Individual with Chronic Kidney Disease who is not on Dialysis:** Up to 12 months.
- **Anemia in an Individual with Cancer due to Cancer Chemotherapy:** Up to 6 months.
- **Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine:** Up to 12 months.
- **Reduction of Allogeneic Red Blood Cell Transfusions in an Individual Undergoing Surgery:** Up to 1 month.
- **Anemia Associated with Myelodysplastic Syndrome:** Up to 12 months.
- **Anemia Associated with Myelofibrosis:** Up to **3** months.
- **Anemia associated with Hepatitis C Treatment:** Up to 6 months.

Reauthorization approval duration:

- **Anemia in an Individual with Chronic Kidney Disease who is on Dialysis:** Up to 3 years.

- **Anemia in an Individual with Chronic Kidney Disease who is not on Dialysis:** Up to 12 months.
- **Anemia in an Individual with Cancer due to Cancer Chemotherapy:** Up to 6 months.
- **Anemia in an Individual with Human Immunodeficiency Virus who is Receiving Zidovudine:** Up to 12 months.
- **Reduction of Allogeneic Red Blood Cell Transfusions in an Individual Undergoing Surgery:** Not applicable for continuation beyond initial approval duration.
- **Anemia Associated with Myelodysplastic Syndrome:** Up to 12 months.
- **Anemia Associated with Myelofibrosis:** Up to 12 months.
- **Anemia associated with Hepatitis C Treatment:** Up to 6 months.

Conditions Not Covered

Epoetin Alfa Products are considered not medically necessary for the following:

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

Epoetin Alfa Products are considered experimental, investigational, or unproven for **ANY** other use including the following (this list may not be all inclusive):

1. **Anemia Associated with Cancer in an Individual not Receiving Myelosuppressive Cancer Chemotherapy.** Epoetin alfa is not indicated in individuals 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 individuals with cancer who are given only radiation therapy.[1-3]

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

5. **Non-Anemic Individuals (Hemoglobin greater than 13.0 g/dL) Prior to Surgery.** Although studies have been done that involved non-anemic individuals 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.

6. **Anemia of Prematurity.** Epoetin alfa combined with iron supplementation has shown to increase hematocrit during the first several weeks of life and reduce transfusion requirements.[7] Although it appears that Epoetin alfa may be beneficial for this condition, it is not routinely recommended.

7. **Use in Individuals Receiving Myelosuppressive Chemotherapy with a Curative Intent.** Erythropoiesis-stimulating agents (ESAs) are not indicated for use in individuals with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.[1-3]

Coding / Billing Information

Note: 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

Background

OVERVIEW

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.*

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.

Therapy should be initiated for patients 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.[1-3] For adults with CKD who are not on dialysis, epoetin alfa should be initiated when the Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). 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. 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. 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. Hb can be increased to (or near) a concentration of 12.0 g/dL at which time the dose of epoetin alfa should be titrated to maintain that level.

Dosing Information

Doses 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 1.2023 – September 12, 2022) 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 1.2023 – May 19, 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 not effective for the management of transfusion-dependent anemia.

References

1. Procrit® intravenous or subcutaneous injection [prescribing information]. Horsham, PA: Janssen; May 2020.
2. Epogen® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; July 2018.
3. Retacrit® subcutaneous or intravenous injection [prescribing information]. New York, NY and Lake Forest, IL: Pfizer and Hospira; June 2021.
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 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 25, 2023.
6. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 25, 2023.

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