Utilization Review Policy 211B

POLICY: Erythropoiesis-Stimulating Agents – Epoetin Alfa Products Utilization Management Medical Policy

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

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 05/08/2024

COVERAGE CRITERIA FOR: UCare Medicare Plans Only (UCare Medicare, EssentiaCare, Group Plans, MSHO, Connect + Medicare, UCare Your Choice)

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 3.2022 – January 13, 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 ≤ 12.0 g/dL.

- **Myeloproliferative Neoplasms:** The NCCN guidelines (version 2.2022 – April 13, 2022) 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.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of epoetin alfa products in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. All approvals are for the duration documented below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Epogen/Procrit is recommended for request meeting both the preferred product step therapy requirements and indication requirements.

Preferred Product(s): Retacrit, Aranesp
Non-Preferred Products(s): Epogen, Procrit

Step Therapy Requirements:

Authorization for a non-preferred biologic product or biosimilar will be granted if the patient meets any *one* of the items listed below (A, B, C, D or E). Chart notes documenting the issue must be provided at time of request:

A. The patient is *not* considered a new start to the non-preferred product (new start is defined as no use of the requested product in the previous 365 days) OR

B. Allergic reaction to a specific inactive ingredient in all preferred biologic products or biosimilars OR

C. Adverse reaction to a specific inactive ingredient in all preferred biologic products or biosimilars OR

D. Therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure during an adequate trial of all preferred biologic products or biosimilars which allowed sufficient time for a positive treatment outcome documented by medical chart notes OR

E. The patient has a diagnosis not included in the FDA-approved indications of all preferred products, but is included in the FDA-approved indications of the non-preferred product

Please note:

- Factors such as patient or prescriber preference or healthcare facility's or pharmacy's inability or unwillingness to order or stock the preferred product(s) will not be considered
- Common side effects to all products and infusion-related reactions are not considered documented allergic reactions to a preferred product as they would be expected with the innovator and biosimilar products.
- Generally, an adequate trial of a drug is considered to be three months or longer in order to allow time for efficacy to be established

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoetin alfa is recommended in those who meet one of the following criteria.

FDA-Approved Indications

1. **Anemia in Patients with Chronic Kidney Disease (CKD) who are on Dialysis.** Approve for 3 years.

2. **Anemia in Patients with Chronic Kidney Disease (CKD) who are not on Dialysis.**

Criteria. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i and ii):
- **i.** The patient meets one of the following (a or b):
  - **a.** The patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
  - **b.** The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
- **ii.** The patient meets one of the following (a or b):
  - **a.** The patient is currently receiving iron therapy; OR
  - **b.** The patient has adequate iron stores according to the prescriber; OR

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). 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). Approve if the patient meets the following criteria (i and ii):
- **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** The patient meets one of the following (a or b):
  - **a.** The patient is currently receiving iron therapy; OR
  - **b.** The 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. Patients with Anemia and Human Immunodeficiency Virus (HIV) who are Receiving Zidovudine.

Criteria. Approve for 1 year if the patient meets the following criteria (A or B):

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

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). 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). Approve if the patient meets the following criteria (i, ii, and iii):
- **i.** The patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** The patient is currently receiving zidovudine therapy; AND
- **iii.** The patient meets one of the following (a or b):
  - **a)** The patient is currently receiving iron therapy; OR
  - **b)** The patient has adequate iron stores according to the prescriber.

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

A. Patients ≥ 18 years of age. Approve if the dose meets 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. Patients < 18 years of age. Approve if the dose meets 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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4. Anemia in Patients with Cancer due to Cancer Chemotherapy.

Criteria. Approve if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, and iii):
i. The patient has a hemoglobin < 10.0 g/dL (or hematocrit < 30%);[7] 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.

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). 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). Approve for 6 months if the patient meets the following criteria (i, ii and iii):
i. The patient has a hemoglobin ≤ 12.0 g/dL (or hematocrit < 30%);[7] 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 the following dosing regimens (A or B):

A. Patients ≥ 18 years of age. Approve if the dose meets 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. Patients < 18 years of age. Approve if the dose meets 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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5. Reduction of Allogeneic Red Blood Cell (RBC) Transfusions in Patients Undergoing Surgery.

Criteria. Approve for 1 month if the patient meets the following criteria (A, B, C and D):
A) Hemoglobin is ≤ 13.0 g/dL; AND
B) The surgery is elective, nonvascular and noncardiac; AND
C) The patient is not willing or able to donate autologous blood prior to surgery; AND
D) The patient meets one of the following (i or ii):
- **i.** The patient is currently receiving iron therapy; OR
- **ii.** The patient has adequate iron stores according to the prescriber.

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

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

Other Uses with Supportive Evidence

6. Anemia Associated with Myelodysplastic Syndromes (MDS).

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

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). 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). Approve if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The patient has a hemoglobin ≤ 12.0 g/dL; AND
- **iii.** The patient meets one of the following (a or b):
  - **a)** The patient is currently receiving iron therapy; OR
  - **b)** The patient has adequate iron stores according to the prescriber.

Dosing. Approve if the dose meets 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.

7. Anemia Associated with Myelofibrosis.

Criteria. Approve for the duration noted below if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
- **i.** The patient meets one of the following (a or b):
  - **a)** The patient has a hemoglobin < 10.0 g/dL; OR
  - **b)** The patient has a serum erythropoietin level is ≤ 500 mU/mL; AND
- **ii.** The patient meets one of the following (a or b):
  - **a)** The patient is currently receiving iron therapy; OR
  - **b)** The patient has adequate iron stores according to the prescriber; OR

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA) therapy. 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). Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
- **i.** The patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** The patient meets one of the following (a or b):
  - **a)** The patient is currently receiving iron therapy; OR
  - **b)** The patient has adequate iron stores according to the prescriber; AND
- **iii.** The patient has had a response according to the prescriber of Hb ≥ 10 g/dL or an increase of ≥ 2 g/dL.

Dosing. Approve if the dose meets 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Epoetin alfa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. **Anemia Associated with Cancer in Patients not Receiving Cancer Chemotherapy.** Epoetin alfa is not indicated in cancer patients who are not receiving cancer chemotherapy. The American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) guidelines for the use of epoetin alfa and Aranesp in adult patients with cancer recommend that ESAs not be used in treatment of anemia associated with malignancy in those who are not receiving concurrent myelosuppressive chemotherapy.

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

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

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

6. **Non-Anemic Patients (Hemoglobin [Hb] > 13.0 g/dL) prior to Surgery.** Although studies have been done 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.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization criteria. Criteria will be updated as new published data are available.

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 3.2022 – January 13, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 24, 2022.
6. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 2.2022 – April 13, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 24, 2022.
7. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). [Version Number 1, Effective date of version: 7/30/2007. Accessed April 17, 2023].

HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	06/10/2020
Policy revision	**Anemia in a Patient with Chronic Kidney Disease who is <u>not</u> on Dialysis:** Dosing was changed to approve if the doses are equivalent to ≤ 60,000 units total per month.	07/11/2022
UCare Revision	Added "Epogen/Procrit is being prescribed due to a documented Retacrit drug shortage" due to the expected Retacrit supply disruption during Q2-4 2022.	2/14/2022
Policy revision	**Anemia in a Patient with Cancer due to Cancer Chemotherapy:** A non-curative treatment, according to the prescriber was added to the criterion for a patient to be currently receiving myelosuppressive chemotherapy.	10/13/2022
Policy revision	**Anemia in a Patient with Cancer due to Cancer Chemotherapy:** A non-curative treatment, according to the prescriber was added to the criterion for a patient to be currently receiving myelosuppressive chemotherapy.	10/13/2022
Policy revision	**Anemia in a Patient with Chronic Kidney Disease who is <u>not</u> on Dialysis:** For a Patient Currently Receiving an Erythropoiesis-Stimulating Agent, the criterion regarding a patient who is ≥18 years of age, the hemoglobin level was changed from < 11.5 to ≤12.0 g/dL. Since the criterion is now the same as a patient < 18 years of age, the delineation of age was also removed from criteria.	04/17/2023
Selected UCare Revision	Adding Aranesp as a preferred product to the Preferred Product Step Therapy Requirement (For New Starts Only)	03/20/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024

Selected UCare Revision	Removing the option "Epogen or Procrit is being prescribed due to a documented Retacrit drug shortage." In the preferred product step therapy section as the Retacrit manufacturer (Pfizer) has communicated sufficient stock is now available.	12/26/2024
UCare Update	Updated step therapy criteria to require clinical need for non-preferred product over the preferred products including chart note documentation to support the need for a non-preferred product.	05/08/2025