Medicare Advantage Medical Utilization Review Policy

Policy:	**Erythropoiesis-Stimulating Agents – Aranesp Utilization Management Medical Policy** • Aranesp® (darbepoetin alfa intravenous or subcutaneous injection – Amgen)
Date:	01/08/2025
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	CGS J15 – Ohio, Kentucky

OVERVIEW

Aranesp, an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis.
- **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.

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.[1] Aranesp is not indicated for the following uses:

- 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 anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

The iron status should be evaluated in all patients before and during treatment.[1] Therapy should be initiated for **adults with CKD on dialysis** when the hemoglobin (Hb) level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the Aranesp dose. For **adults with CKD who are not on dialysis**, consider initiating Aranesp only when 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 level exceeds 10.0 g/dL, reduce or interrupt the Aranesp dose and use the lowest dose sufficient to reduce the need for RBC transfusions. For **pediatric patients with CKD**, initiate Aranesp when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of Aranesp. Initiate Aranesp for **patients on cancer** chemotherapy only if the Hb is < 10.0 g/dL and if there is a minimum of two additional months of planned chemotherapy. Use the lowest dose of Aranesp to avoid RBC transfusions.

Dosing Information

Doses of Aranesp are titrated based on Hb 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.[2] 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.

Aranesp 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.[3] 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.[4] Iron stores should be adequate. The guidelines also advise that ESAs are generally less effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Aranesp 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 provided for the duration noted 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 Aranesp 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 a hematocrit < 30%);[6] OR
  - **b.** The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL (or a hematocrit < 30%);[6] 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 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 ≤ 0.45 mcg/kg; AND
- ii. Each dose is given no more frequently than once every 4 weeks; OR

B. Patients < 18 years of age. Approve if the dose meets the following (i and ii):
- i. Each dose is ≤ 0.75 mcg/kg; AND
- ii. Each dose is given no more frequently than once every 2 weeks.

3. 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%);[5-6] 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.** 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.

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%);[5-6] 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.** 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):
- **a.** Each dose is ≤ 500 mcg; AND
- **b.** Each dose is given no more frequently than once every week; OR

B) Patients < 18 years of age. Approve if the dose meets the following (i and ii):
- **a.** Each dose is ≤ 2.25 mcg/kg; AND
- **b.** Each dose is given no more frequently than once every week.

Other Uses with Supportive Evidence

4. Anemia Associated with Myelodysplastic Syndrome (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.** The patient meets one of the following (a or b):
  - **a.** The patient has a hemoglobin < 10.0 g/dL (or hematocrit < 30%);[6] OR
  - **b.** The patient has a serum erythropoietin level is ≤ 500 mU/mL; AND
- **ii.** Patient is ≥ 18 years of age; 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.** Patient is ≥ 18 years of age; 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 ≤ 500 mcg; AND
B. Each dose is given no more frequently than once every 2 weeks.

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5. 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 and 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, iii, and iv):
- **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.** According to the prescriber, the patient has responded to therapy defined as Hb ≥ 10 g/dL or a Hb increase of ≥ 2 g/dL.

Dosing. Approve if the dose meets the following (A and B):
A. Each dose is ≤ 500 mcg; AND
B. Each dose is given no more frequently than once every 2 weeks.

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6. Patients with Anemia and Human Immunodeficiency Virus (HIV) who are Receiving Zidovudine (and/or Other Nucleoside Reverse Transcriptase Inhibitors (NRTI) Used in Treatment of HIV/Acquired Immunodeficiency Syndrome [AIDS]).[6]

Criteria.[6] 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 has a hemoglobin < 10.0 g/dL (or a hematocrit < 30%); AND
- **ii.** The patient is currently receiving zidovudine therapy and/or other nucleoside reverse transcriptase inhibitors (NRTI) used in treatment of HIV/AIDS; 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.

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/or other nucleoside reverse transcriptase inhibitors (NRTI) used in treatment of HIV/AIDS; 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 ≤ 500 mcg; AND
- **ii.** Each dose is given no more frequently than once every week; OR

B) Patients < 18 years of age. Approve if the dose meets the following (i and ii):
- **i.** Each dose is ≤ 2.25 mcg/kg; AND
- **ii.** Each dose is given no more frequently than once every week.

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7. Anemia of Chronic Disease.[6]

Criteria.[6] Approve if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
- **i.** The patient has a hemoglobin < 10.0 g/dL (or a hematocrit < 30%); AND
- **ii.** The patient's anemia is secondary to one of the following chronic diseases: rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease or ulcerative colitis), or hepatitis C and undergoing treatment; 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.

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's anemia is secondary to one of the following chronic diseases: rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease or ulcerative colitis), or hepatitis C and undergoing treatment; AND

iii. The patient meets one of the following (i or ii):

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 ≤ 500 mcg; AND

ii. Each dose is given no more frequently than once every week; OR

B) Patients < 18 years of age. Approve if the dose meets the following (i and ii):

i. Each dose is ≤ 2.25 mcg/kg; AND

ii. Each dose is given no more frequently than once every week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Aranesp 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 Myelosuppressive Cancer Chemotherapy.** Aranesp is not indicated in patients with cancer 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 Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML), or other Myeloid Cancers.** Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.

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

4. **To Enhance Athletic Performance.** Aranesp 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 Aranesp is not appropriate in these types of situations.

6. 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. Aranesp® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2024.
2. 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.
3. 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.
4. 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.
5. 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 July 25, 2024].
6. Centers for Medicare and Medicaid Services. CGS Administrators, LLC. Local Coverage Determination (LCD): Erythropoiesis Stimulating Agents (ESA) (L34356) [Original effective date: 10/01/2015; Revision effective date: 03/07/2024]. Accessed on January 8, 2025.
7. Centers for Medicare and Medicaid Services. CGS Administrators, LLC. Local Coverage Article (LCA): Billing and Coding: Erythropoiesis Stimulating Agents (ESA) (A56462) [Original effective date: 10/3/2019; Revision effective date: 10/1/2024]. Accessed on January 8, 2025.

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 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.	04/19/2023
Policy review	No criteria changes (based on review of LCD/LCA revision surveillance)	03/21/2024
Policy review	No criteria changes Based on review of commercial policy annual revision	07/25/2024
Policy review	No criteria changes. Review based on NCD surveillance review.	01/08/2025