

Medicare Advantage Medical Utilization Review Policy

Policy:	Erythropoiesis-Stimulating Agents – Aranesp Utilization Management Medical Policy Aranesp® (darbepoetin alfa intravenous or subcutaneous injection - Amgen)
Date:	07/25/2025
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	All States*
Applicable NCDs, LCDs, and/or LCAs	NCD 110.21

**This policy does not apply to states in jurisdiction J-15 (CGS Administrators, LLC): Kentucky, Ohio. Additional regulation exists for these states necessitating a separate policy.*

**This policy does not apply to states in jurisdiction J-J and J-M (Palmetto GBA): Alabama, Georgia, Tennessee, North Carolina, South Carolina, Virginia, West Virginia. Additional regulation exists for these states necessitating a separate policy.*

**This policy does not apply to states in jurisdictions J-5 and J-8 (Wisconsin Physician Services Insurance Corporation): Iowa, Kansas, Missouri, Nebraska, Indiana, Michigan. Additional regulation exists for these states/territories necessitating a separate policy.*

SUMMARY OF EVIDENCE

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.

Limitations of Use: 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 with ESAs.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.

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 (2025) provide recommendations for the use of ESAs.² Guidelines recommend addressing all correctable causes of anemia (i.e. iron deficiency, malignancy, infection, etc.) before initiating treatment with an ESA or hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI). After all correctable causes of anemia are addressed, KDIGO suggests using ESAs as first-line therapy for treating anemia in patients with CKD rather than HIF-PHIs. Although clinical trials have revealed noninferiority of HIF-PHIs versus ESAs for efficacy as treatment for anemia, some studies suggested a higher risk of major adverse cardiovascular events with HIF-PHIs compared to ESAs in at least some CKD populations. For patients with CKD on dialysis, the guidelines recommend ESA therapy should be initiated when the Hb level is ≤ 9.0 to 10.0 g/dL. For patients with CKD who are not on dialysis, the decision to initiate ESA therapy should be individualized based on many factors (e.g., rate of Hb decline, prior response to iron therapy, transfusion risk, patient symptoms). In adults with anemia and CKD who are being treated with an ESA, ESA therapy should not be used to maintain Hb concentrations above 11.5 g/dL. For pediatric patients with anemia and CKD, the selection of an Hb target for ESA maintenance therapy should be individualized considering potential benefits and harms. 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, ongoing iron supplementation is often required in most patients to maintain an optimal response.

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

- **Hematopoietic Growth Factors:** NCCN guidelines (version 1.2025 – October 11, 2024) indicate Aranesp and epoetin alfa with or without iron supplementation may be warranted for the long-term management of anemia in high-risk patients or in asymptomatic patients with comorbidities receiving myelosuppressive chemotherapy where cure is not anticipated.³
- **Myelodysplastic Syndrome (MDS):** NCCN guidelines (version 2.2025 – January 17, 2025) list Aranesp and epoetin alfa products as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.⁴ 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 1.2025 – February 21, 2025) 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.⁵ Iron stores should be adequate. The guidelines also advise that ESAs are generally less effective for the management of transfusion-dependent anemia.

ANALYSIS OF EVIDENCE

The information provided in the summary of evidence is supported by labeled indications, CMS-approved compendia, published clinical literature, clinical practice guidelines, and/or applicable National Coverage

Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs). Refer to the Sources of Information section of this policy for additional information.

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 Sources of Information 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 Sources of Information 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.

Indications with a ^ below are referenced in both the corresponding Standard Medical Utilization Management Internal Policy AND applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications may be internally developed and/or referenced in applicable NCDs, LCDs, and/or LCAs. For these indications, internally developed coverage criteria is denoted throughout the policy in the following manner: 1) IC-L (internal criteria supported by the labeled indication), 2) IC-COMP (internal criteria supported by CMS-approved compendia), 3) IC-ISGP (internal criteria intended to interpret or supplement general provisions outlined in applicable NCDs, LCDs, and/or LCAs), or 4) IC-EC (internal criteria intended to expand coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs). For these indications, coverage criteria that is NOT denoted with one of the above indicators is referenced in applicable NCDs, LCDs, and/or LCAs. Additional information supporting the rationale for determination of internal coverage criteria can be found via the Sources of Information section.

Indications with a @ below are referenced in the corresponding Standard Medical Utilization Management Internal Policy, but are NOT directly referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs). Coverage criteria for these indications is internally developed. These indications and their respective coverage criteria represent expanded coverage beyond the coverage outlined in applicable NCDs, LCDs, and/or LCAs.

Indications with a # below are supported and referenced in applicable National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and/or Local Coverage Articles (LCAs), but are NOT directly referenced in the corresponding Standard Medical Utilization Management Internal Policy. Coverage criteria for these indications is referenced in applicable NCDs, LCDs, and/or LCAs.

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
 - 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 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 $< 30\%$); AND
- ii. Patient meets BOTH of the following (a and b):
 - a. Patient is currently receiving myelosuppressive chemotherapy; ^{IC-ISGP} AND
 - b. According to the prescriber, myelosuppressive chemotherapy is considered non-curative; ^{IC-ISGP} AND

- iii. Patient meets one of the following (a or b):
 - a. Patient is currently receiving iron therapy; ^{IC-ISGP} OR
 - b. Patient has adequate iron stores according to the prescriber. ^{IC-ISGP}
- 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 $< 30\%$); ^{IC-ISGP} AND
 - ii. Patient meets BOTH of the following (a and b):
 - a. Patient is currently receiving myelosuppressive chemotherapy; ^{IC-ISGP} AND
 - b. According to the prescriber, myelosuppressive chemotherapy is considered non-curative; ^{IC-ISGP} AND
 - iii. Patient meets one of the following (a or b):
 - a. Patient is currently receiving iron therapy; ^{IC-ISGP} OR
 - b. Patient has adequate iron stores according to the prescriber. ^{IC-ISGP}

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
 - 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.

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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aranesp is not recommended in the following situations:

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.

SOURCES OF INFORMATION

1. Aranesp® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; May 2024.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (2025). Public Review Draft; November 2024. Accessed on: June 17, 2025. Available at: <https://kdigo.org/guidelines/anemia-in-ckd/>
3. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 1.2025 – October 11, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on July 7, 2025.
4. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2025 – January 17, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on July 7, 2025.
5. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 1.2025 – February 21, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on July 7, 2025.
6. 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. Revision date: 10/2024. Accessed July 25, 2025].

HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy.	9/11/2019
Select revision	Reviewed and revised original policy created 09/11/2019 in accordance with NCD 110.21.	11/6/2019
Select revision	Non-clinical update to policy to add the statement “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 <u>not</u> necessarily mean that the applicable condition or diagnosis is excluded from coverage.”	1/30/2020
Select revision	Added the following to the Policy Statement “ <u>Note</u> : 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.”	04/03/2020
Policy revision	*Removed the following conditions from conditions not recommended for coverage – “6. Any Anemia in Cancer or Cancer Treatment Patients Due to Any of the Following: Folate Deficiency, B-12 Deficiency, Iron Deficiency, Hemolysis, Bleeding, or Bone Marrow Fibrosis, 7. Prophylactic Use to	05/05/2020

	Prevent Chemotherapy-Induced Anemia, 8. Prophylactic Use to Reduce Tumor Hypoxia, 9. Patients with Erythropoietin-Type Resistance Due to Neutralizing Antibodies, 10. Anemia Due to Cancer Treatment if Patient Has Uncontrolled Hypertension" * Anemia in Patients with Cancer due to Cancer Chemotherapy – changed initial therapy approval duration to 6 months; removed specific language requiring patient's Hgb or Hct level be immediately prior to initiation of therapy; removed requirement that the chemotherapy be used for solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia; for patients currently receiving ESA – changed Hgb requirement to ≤ 12.0 g/dL (previously was less than 10 g/dL); for patients currently receiving ESA – removed requirement that patient has experienced a hemoglobin rise of 1 g/dL or more (or a hematocrit rise of 3% or more) compared to pretreatment baseline after 8 weeks of treatment	
Policy revision	Anemia in Patients with Cancer due to Cancer Chemotherapy – added requirement that patient meet one of the following Patient is currently receiving iron therapy; OR Patient has adequate iron stores according to the prescriber.	10/13/2020
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
Non-clinical Update	Added Note: <i>*This policy does not apply to states in jurisdiction J-J and J-M (Palmetto GBA): Alabama, Georgia, Tennessee, North Carolina, South Carolina, Virginia, West Virginia. Additional regulation exists for these states necessitating a separate policy.</i>	11/20/2023
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.	01/06/2025
Policy revision	No criteria changes. Formatting and notation updates.	03/10/2025
Policy review	No criteria changes. Based on review of commercial policy annual review.	07/25/2025