Reference number(s)
1982-A

Standard Medicare Part B Management Aranesp

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Aranesp	darbepoetin alfa

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Treatment of Anemia due to:

- Chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.
- The effects of concomitant myelosuppressive chemotherapy in patients with non-myeloid malignancies, 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.
- Aranesp is not indicated for use:
  - 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 the anemia can be managed by transfusion.
  - As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Note: Use in members on dialysis is covered under the Medicare Part B dialysis benefit and is excluded from coverage under this policy.

Compendial Uses

- Treatment of anemia due to myelodysplastic syndrome[2,3,6,9-10]
- Prophylaxis of anemia of prematurity[3,14]
- Anemia in patients who will not/cannot receive blood transfusions[5,12-13]
- Myelofibrosis-associated anemia[2,7-8]
- Cancer patients who are undergoing palliative treatment[2,5,8,11]

Nationally Covered Indication[8]

Centers for Medicare and Medicaid Services guidelines provide coverage for Aranesp for anemia secondary to myelosuppressive chemotherapy based on the criteria in Exclusions, Coverage Criteria, and Continuation of Therapy sections.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

The following exclusions criteria apply to members requesting use for anemia due to concomitant myelosuppressive chemotherapy:

- The anemia is due to folate, B-12, or iron deficiency.
- The anemia is due to hemolysis, bleeding, or bone marrow fibrosis.
- The anemia is due to treatment for acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), or erythroid cancers.
- The anemia of cancer is not related to cancer treatment.
- The anemia is due to treatment with radiotherapy only.
- Prophylactic use to prevent chemotherapy-induced anemia.
- Prophylactic use to reduce tumor hypoxia.
- Use in members with erythropoietin-type resistance due to neutralizing antibodies.
- Members with uncontrolled hypertension.

Coverage Criteria

Note: Requirements regarding hemoglobin level exclude values due to a recent transfusion.

Anemia Due to Chronic Kidney Disease[1,4]

Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in members not receiving dialysis with pretreatment hemoglobin less than 10 grams per deciliter (g/dL) or hematocrit less than 30%.

Anemia Due to Concomitant Myelosuppressive Chemotherapy[1,5,8]

Authorization of 8 weeks may be granted for the treatment of anemia due to concomitant chemotherapy in members when all of the following criteria are met:

- The member is receiving chemotherapy for a solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia.
- The hemoglobin level immediately prior to initiation or maintenance of therapy is less than 10 g/dL or the hematocrit is less than 30%.
- The starting dose is not greater than an average of 2.25 micrograms per kilogram (mcg/kg) per week.

Anemia Due to Myelodysplastic Syndrome[2,3,6,9-11]

Authorization of 12 weeks may be granted for the treatment of anemia due to myelodysplastic syndrome in members with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

Prophylaxis of Anemia of Prematurity[3,14]

Authorization of 12 weeks may be granted for the prophylaxis of anemia of prematurity in members less than 1 year of age.

Anemia in Members Who Will Not/Cannot Receive Blood Transfusions[4,5,12-13]

Authorization of 12 weeks may be granted for treatment of anemia in members who will not/cannot receive blood transfusions (e.g., religious beliefs) whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

Myelofibrosis-associated anemia[2,7,8]

Authorization of 12 weeks may be granted for the treatment of myelofibrosis-associated anemia when both of the following criteria are met:

- The member has a hemoglobin level less than 10 g/dL or hematocrit less than 30%.
- The member has an erythropoietin (EPO) level less than 500 milliunits per milliliter (mU/mL).

Anemia Due to Cancer[2,5]

Authorization of 12 weeks may be granted for treatment of anemia in members who have cancer and are undergoing palliative treatment.

Continuation of Therapy

Note: Requirements regarding current hemoglobin level exclude values due to a recent transfusion.

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 weeks may be granted for treatment of anemia due to concomitant myelosuppressive chemotherapy when all of the following criteria are met:

- The member is currently receiving therapy with Aranesp.
- The member does not have any exclusions listed in the Exclusions section.
- The member has experienced at least a 1 g/dL increase in hemoglobin or a 3% increase in hematocrit.
- The member's hemoglobin remains below 11 g/dL or the prescriber will hold or reduce the dose of Aranesp to maintain a hemoglobin level sufficient to avoid transfusion.
- Treatment will not extend beyond 8 weeks following the final dose of myelosuppressive chemotherapy given in the member's current chemotherapy regimen.

Authorization of 12 weeks may be granted for all other indications when all of the following criteria are met:

- The member is currently receiving therapy with Aranesp.
- The member is receiving Aranesp for an indication listed in the Coverage Criteria section.
- Aranesp has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Aranesp.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia for Chronic Kidney Disease
- Management of cancer-associated anemia with erythropoiesis-stimulating agents: American Society of Clinical Oncology (ASCO)/American Society of Hematology Clinical Practice Guideline Update
- NCCN guideline: Myelodysplastic syndromes
- NCCN guideline: Myeloproliferative neoplasms
- NCCN guideline: Hematopoietic growth factors
- Medicare National Coverage Determinations (NCD) Manual

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aranesp are covered in addition to the following:

- Treatment of anemia due to myelodysplastic syndrome
- Prophylaxis of anemia in prematurity
- Anemia in patients who will not/cannot receive blood transfusions
- Myelofibrosis-associated anemia

- Cancer patients who are undergoing palliative treatment

Explanation of Rationale

Support for FDA-approved indications (anemia due to chronic kidney disease, anemia due to chemotherapy in members with cancer) can be found in the manufacturer's prescribing information.

Support for using darbepoetin alfa to treat anemia due to myelodysplastic syndrome can be found in the National Comprehensive Cancer Network's (NCCN) guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndrome supports the use of darbepoetin alfa for the treatment of symptomatic anemia associated with lower risk (IPSS low/intermediate-1) disease with del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7). Darbepoetin alfa can also be used for the treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an SF3B1 mutation), with serum erythropoietin (EPO) $\leq$ 500 mU/mL as either a single agent, or in combination with either lenalidomide or granulocyte-colony stimulating factor (G-CSF) following no response or erythroid response followed by loss of response to an erythropoiesis-stimulating agent (ESA) alone. Finally, darbepoetin alfa can be used as treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts $\geq$ 15% (or ring sideroblasts $\geq$ 5% with an SF3B1 mutation), with serum EPO $\leq$ 500 mU/mL as a single agent or in combination with a G-CSF.

In a single-arm study (N=206), treatment with darbepoetin alfa produced favorable erythroid responses in patients with anemia due to low-risk myelodysplastic syndromes. At week 13 and over the course of the study, 17% and 28% of ESA-naive patients and 35% and 42% of prior ESA-treated patients required a red blood cell (RBC) transfusion. A major and minor erythroid response rate occurred in 49% and 22% of ESA-naive patients and in 26% and 18% in ESA-experienced patients at week 13, and at the end of the study at 53 or 55 weeks the major and minor response rates were 59% and 15% of ESA-naive patients and 34% and 16% in ESA-experienced patients (Gabrilove et al., (2008)).

The American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) Clinical Practice Guideline Update titled "Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents" (2019) state that some evidence supports the use of darbepoetin alfa in patients with anemia associated with lower-risk myelodysplastic syndrome.

Support for using darbepoetin alfa for prophylaxis against anemia of prematurity can be found in a study by Ohls et al. (2013). Erythropoiesis-stimulating agents (ESA; darbepoetin alfa and erythropoietin) reduced the need for blood transfusions compared with placebo in preterm infants (mean birth weight, 946 g; mean gestation, 27.7 weeks) at 4 high-altitude institutions using a restrictive transfusion protocol in a randomized trial (n=102). Infants received either darbepoetin 10 mcg/kg subcutaneously (subQ) once weekly, erythropoietin 400 units/kg subQ 3 times weekly, or placebo until the completion of 35 weeks' gestation. The mean number of transfusions/subjects was lower in the ESA groups compared with the placebo group (1.2 in both darbepoetin alfa and erythropoietin vs 2.4 in placebo). However, there was no significant difference in the number of transfusion-free patients in the ESA groups when compared with placebo. Absolute reticulocyte count and hematocrit were significantly higher and donor exposure was lower in the ESA groups compared with the placebo group. There was no difference between the ESA and placebo groups in mortality and preterm morbidity.

Support for using darbepoetin alfa to treat anemia in patients who will not/cannot receive blood transfusions can be found in a review article by Lawson and Ralph (2015). Recombinant erythropoietin is the most frequently used

erythropoiesis-stimulating agent (ESA). It was first used in the treatment of anemia secondary to end-stage renal disease. Recombinant erythropoietin acts by stimulating the following: (i) proliferation and differentiation of erythroid precursors to increase immature erythrocyte production; (ii) release of erythrocytes from bone marrow; and (iii) hemoglobin (Hb) production. It may also protect cells by inhibiting various protein kinase cascades while increasing stem cell recruitment into damaged areas and has platelet-activating effects. The effects of recombinant erythropoietins are partly governed by ferritin, transferrin, iron, vitamin B12, and folic acid concentrations. Before surgery, it is important to check which recombinant erythropoietin preparation is being used because some do contain trace amounts of human albumin, which may conflict with the beliefs of some Jehovah's Witnesses. The response appears to be dose dependent, with an increase in reticulocyte count being seen within 10 days and new erythropoiesis within 1–6 weeks.

Four Jehovah's Witness patients who either exhibited preoperative anemia or developed postoperative anemia refractory to endogenous erythropoietin were discharged from the hospital in good condition after treatment with recombinant human erythropoietin (EPO) 50 to 280 Units per kilogram body weight daily. The fifth patient, who exhibited no signs of systemic inflammation following emergency hemicolectomy, was also treated with intravenous iron, but not with erythropoietin. No predictor of response was identified in this series; therefore, use of erythropoietin in this patient subgroup would be based strictly on humanitarian grounds (Wolff et al., 1997).

The National Comprehensive Cancer Network’s guildeline for hematopoietic growth factors supports the use of darbepoeitin alfa to treat anemia in cancer patients who refuse blood transfusions.

Support for using darbepoetin alfa to treat myelofibrosis-associated anemia can be found in the National Comprehensive Cancer Network’s guideline for myeloproliferative neoplasms. The NCCN Guideline supports the use darbepoetin alfa for the management of myelofibrosis-associated anemia with serum erythropoietin less than 500 mU/mL.

Support for using darbepoetin alfa to treat anemia in patients who have cancer and are undergoing palliative treatment can be found in the National Comprehensive Cancer Network’s guideline for hematopoietic growth factors.

Use in cancer and related neoplastic conditions is covered according to the conditions outlined in the National Coverage Determination Manual section 110.21 (Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions).

References

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