

## PRIOR AUTHORIZATION POLICY

**POLICY:** Erythroid Stimulating Agents – Aranesp<sup>®</sup> (darbepoetin alfa injection for intravenous or subcutaneous use – Amgen)

**APPROVAL DATE:** 07/24/2019; selected revision 9/11/2019; selected revision 11/06/2019

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### OVERVIEW

Aranesp is an erythropoiesis-stimulating protein manufactured by recombinant DNA technology that is administered by intravenous (IV) injection or subcutaneous (SC) injection.<sup>1</sup> The agent is also known as an erythropoiesis-stimulating agent (ESA). Aranesp has indications for: 1) the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis; and 2) the treatment of anemia 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 2 additional months of planned chemotherapy. The prescribing information notes that it is not indicated for use in: 1) patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy; 2) in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; 3) in patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion; and 4) as a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia. The prescribing information for Aranesp recommends that therapy should be initiated for adult patients 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 adult patients with CKD not on dialysis, Aranesp should be initiated when Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). 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. Initiate Aranesp for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL. Use the lowest dose of Aranesp to avoid 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.

### 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.<sup>2</sup> The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are  $\geq$  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 failure to adequately respond to ESAs. Iron deficiency can occur following continued ESA use and, therefore, iron supplementation is required in most patients to maintain an optimal response.

ESAs have a role in the management of patients with anemia due to cancer chemotherapy.<sup>3,4</sup> Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) for myelodysplastic syndrome (MDS) [version 2.2019 – October 18, 2018] list Aranesp as having utility anemic, symptomatic patients with MDS if serum erythropoietin levels are  $\leq 500$  mU/mL.<sup>5</sup> 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  $\leq 12.0$  g/dL. Data suggest Aranesp may provide some benefits in MDS.<sup>7-12</sup> The NCCN guidelines for myeloproliferative neoplasms (version 2.2019 – October 29, 2018) address Aranesp and epoetin alfa products as options for treatment with of patients with anemia related to myelofibrosis having a serum erythropoietin level  $\leq 500$  mU/mL.<sup>13</sup> Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

## **Safety**

Aranesp has a Boxed Warning that ESAs increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.<sup>1</sup> For patients with CKD, controlled trials have demonstrated that patients experienced greater risks for death, serious adverse cardiovascular (CV) reactions, and stroke when given ESAs to target a Hb level  $> 11.0$  g/dL. No trial has identified a Hb target level, Aranesp dose, or dosing strategy that negates such risks. Use the lowest Aranesp dose necessary to reduce the need for RBC transfusions. In patients with cancer, ESAs shorten overall survival and/or increase the risk of tumor progression or recurrence in clinical studies involving those with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. The lowest dose to avoid RBC transfusions should be used to avoid risks. Use ESA therapy only for anemia from myelosuppressive chemotherapy. ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. Following the completion of a chemotherapy course, discontinue Aranesp.

## **POLICY STATEMENT**

Prior authorization is recommended for prescription 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. 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. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aranesp as well as the monitoring required for adverse events and long-term efficacy, approval requires Aranesp to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Automation:** None.

## **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Aranesp is recommended in those who meet the following criteria:

### **FDA-Approved Indications**

- 1. Anemia in Patients with Chronic Kidney Disease who are on Dialysis.** Approve for 3 years.
- 2. Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** 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  $\geq 18$  years of age with a hemoglobin  $< 10.0$  g/dL; **OR**
      - b)** The patient is  $< 18$  years of age with a hemoglobin  $\leq 11.0$  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. The patient meets one of the following (a or b):
    - a) The patient is  $\geq 18$  years of age with a hemoglobin  $< 11.5$  g/dL; OR
    - b) The patient is  $< 18$  years of age with a hemoglobin  $\leq 12.0$  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.

**3. Anemia in Patients with Cancer due to Cancer Chemotherapy.** Approve for 6 months 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; AND
  - ii. The patient is currently receiving myelosuppressive chemotherapy; 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  $\leq 12.0$  g/dL; AND
  - ii. The patient is currently receiving myelosuppressive chemotherapy; 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.

**Other Uses with Supportive Evidence**

**4. Anemia Associated with Myelodysplastic Syndrome (MDS).** 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, iii, and iv):
- 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  $\leq 500$  mU/mL; AND
  - ii. Patient is  $\geq 18$  years of age; AND
  - iii. Aranesp is prescribed by, or in consultation with, a hematologist or oncologist; AND
  - iv. 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, iii, and iv):
- i. The patient has a hemoglobin  $\leq 12.0$  g/dL; AND
  - ii. Patient is  $\geq 18$  years of age; AND

- iii. Aranesp is prescribed by, or in consultation with, a hematologist or oncologist; AND
  - iv. 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.
5. **Anemia Associated with Myelofibrosis.** 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, 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  $\leq$  500 mU/mL; AND
  - ii. The agent is prescribed by, or in consultation with, a hematologist or oncologist; 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 and erythropoiesis-stimulating agent (ESA) therapy.** Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
- i. The patient has a hemoglobin  $\leq$  12.0 g/dL; AND
  - ii. The ESA therapy is prescribed by, or in consultation with, a hematologist or oncologist; 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; AND
  - iv. According to the prescriber, the patient has responded to therapy defined as Hb  $\geq$  10 g/dL or an Hb increase of  $\geq$  2 g/dL.

#### 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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.<sup>1</sup> The American Society of Clinical Oncology/American Society of Hematology 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.<sup>3</sup>
2. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers.** Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.<sup>1</sup>
3. **Anemia Associated with Radiotherapy in Cancer.** Aranesp is not indicated for use in patients with cancer who are given only radiation therapy.<sup>1</sup>
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 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

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## OTHER REFERENCES UTILIZED

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