POLICY:  Erythropoiesis-Stimulating Agents – Aranesp Utilization Management Medical Policy
• Aranesp® (darbepoetin alfa intravenous or subcutaneous injection – Amgen)

REVIEW DATE:  07/20/2022; selected revision 09/28/2022, 03/22/2023

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.

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.¹ 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.

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 several 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. 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. 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 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 indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 one of the following criteria:

FDA-Approved Indications

1. **Anemia in a Patient with Chronic Kidney Disease who is on Dialysis.** Approve for 3 years.

2. **Anemia in a Patient with Chronic Kidney Disease who is 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. Patient meets one of the following (a or b):
       - a) Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
       - b) Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
     - ii. 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; OR
   - **B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent.** Approve if the patient meets the following criteria (i and ii):
     - 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).
     - i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - ii. 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) Patient is ≥ 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) Patient is < 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 a Patient 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. Patient has a hemoglobin < 10.0 g/dL; 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; OR
   - **B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent.** Approve if the patient meets the following criteria (i, ii, and iii):
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).

i. Patient has a hemoglobin \( \leq 12.0 \text{ g/dL} \); AND

ii. Patient meets BOTH of the following (\text{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 (\text{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 (\text{A or B)}:

\text{A) Patient is \geq 18 years of age.} Approve if the dose meets the following (\text{i and ii)}:

\begin{enumerate}
  \item Each dose is \leq 500 mcg; AND
  \item Each dose is given no more frequently than once every week; OR
\end{enumerate}

\text{B) Patient is < 18 years of age.} Approve if the dose meets the following (\text{i and ii)}:

\begin{enumerate}
  \item Each dose is \leq 2.25 mcg/kg; AND
  \item Each dose is given no more frequently than once every week.
\end{enumerate}

**Other Uses with Supportive Evidence**

4. **Anemia Associated with Myelodysplastic Syndrome.** Approve for 1 year if the patient meets the following criteria (\text{A or B)}:

\text{A) Initial Therapy.} Approve if the patient meets the following criteria (\text{i, ii, iii, and iv)}:

\begin{enumerate}
  \item Patient is \geq 18 years of age; AND
  \item Patient meets one of the following (\text{a or b)}:
    \begin{enumerate}
      \item Patient has a hemoglobin < 10.0 g/dL; OR
      \item Patient has a serum erythropoietin level \leq 500 mU/mL; AND
    \end{enumerate}
  \item Patient meets one of the following (\text{a or b)}:
    \begin{enumerate}
      \item Patient is currently receiving iron therapy; OR
      \item Patient has adequate iron stores according to the prescriber; AND
    \end{enumerate}
  \item The medication is prescribed by or in consultation with a hematologist or oncologist.
\end{enumerate}

\text{B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent.} Approve if the patient meets the following criteria (\text{i, ii, iii, and iv)}:

\begin{enumerate}
  \item Patient is \geq 18 years of age; AND
  \item Patient has a hemoglobin \leq 12.0 g/dL; AND
  \item Patient meets one of the following (\text{a or b)}:
    \begin{enumerate}
      \item Patient is currently receiving iron therapy; OR
      \item Patient has adequate iron stores according to the prescriber; AND
    \end{enumerate}
  \item The medication is prescribed by or in consultation with a hematologist or oncologist.
\end{enumerate}

**Dosing.** Approve if the dose meets the following (\text{A and B)}:

\text{A) Each dose is \leq 500 mcg; AND}

\text{B) Each dose is given no more frequently than once every 2 weeks.}
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. Patient meets one of the following (a or b):
      a) Patient has a hemoglobin < 10.0 g/dL; OR
      b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
   
   ii. 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; AND
   
   iii. The medication is prescribed by or in consultation with a hematologist or oncologist.

B) **Patient is Currently Receiving an Erythropoiesis-Stimulating Agent.** Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):

   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).

   i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
   
   ii. 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; AND
   
   iii. According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL; AND
   
   iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

**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 a Patient not Receiving Myelosuppressive Cancer Chemotherapy.** Aranesp is not indicated in patients with cancer who are not receiving cancer chemotherapy.\(^1\)

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.\(^1\)

3. **Anemia Associated with Radiotherapy in Cancer.** Aranesp is not indicated for use in patients with cancer who are given only radiation therapy.\(^1\)

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**

**HISTORY**

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Review Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Revision</td>
<td>No criteria changes.</td>
<td>07/21/2021</td>
</tr>
<tr>
<td>Annual Revision</td>
<td>No criteria changes.</td>
<td>07/20/2022</td>
</tr>
<tr>
<td>Selected Revision</td>
<td><strong>Anemia in a Patient with Cancer due to Cancer Chemotherapy:</strong> A non-curative treatment, according to the prescriber was added to the criterion for a patient to be currently receiving myelosuppressive chemotherapy.</td>
<td>09/28/2022</td>
</tr>
<tr>
<td>Selected Revision</td>
<td><strong>Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis:</strong> 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 &lt; 11.5 to ≤ 12.0 g/dL. Since the criterion is now the same as a patient &lt; 18 years of age, the delineation of age was also removed from criteria.</td>
<td>03/22/2023</td>
</tr>
</tbody>
</table>