**OVERVIEW:** Erythropoiesis stimulating agents (ESA) are utilized for treatment of anemia (low red blood cells) resulting from chronic kidney failure, chemotherapy, certain treatments for human immunodeficiency virus (HIV) and to reduce the need for blood transfusions during and after certain major surgeries. These medications stimulate bone marrow production of red blood cells (erythropoiesis) by a similar mechanism as endogenous erythropoietin, thus treating anemia.

Darbepoetin alfa (Aranesp, Amgen Inc., Thousand Oaks, CA) is an erythropoiesis-stimulating protein produced by recombinant DNA technology. It is a 37,000 dalton 165-amino acid protein that contains 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin only contains three chains. The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone.

In 2018, the U.S. Food and Drug Administration (FDA) approved Hospira’s Retacrit™ (epoetin alfa-epbx), a biosimilar to Epogen® (Amgen) and Procrit® (Janssen). Retacrit is approved for treating anemia caused by chronic kidney disease, chemotherapy, or the use of zidovudine in patients with HIV infection. It is also approved to reduce the chance that a red blood cell transfusion will be needed in patients undergoing elective, noncardiac, nonvascular surgery. These are the same indications as Epogen and Procrit. The dose of Retacrit varies depending on the indication.

**Boxed Warning**

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. 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 hemoglobin (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. Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to use and/or dispense Aranesp to those with cancer. 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.

Epoetin alfa (Epogen/Procrit, Amgen Inc.) is a 30,400 dalton 165-amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology. Produced by mammalian cells into which the human erythropoietin gene has been introduced, the product contains the identical amino acid sequence of isolated natural erythropoietin.
**Boxed Warning**
Epogen/Procrit 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. 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 hemoglobin (Hb) level > 11.0 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that negates such risks. Use the lowest Epogen/Procrit dose necessary to reduce the need for RBC transfusions. For use in cancer, ESAs shorten overall survival and/or increase the risk of tumor progression or recurrence in clinical studies involving patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Prescribers and hospitals are required to enroll and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen/Procrit to those with cancer. Use the lowest dose needed to avoid RBC transfusions. Use ESAs only for anemia due to myelosuppressive chemotherapy. ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. Discontinue ESAs after the completion of a chemotherapy course. In surgery patients, deep vein thrombosis (DVT) prophylaxis is recommended due to the increased risk of DVT.

**POLICY STATEMENT**
Prior authorization is recommended for prescription benefit coverage of Aranesp and Epogen/Procrit/Retacrit. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**
Coverage of Erythropoiesis Stimulating Agents is recommended in those who meet the following criteria:

**Food and Drug Administration (FDA)-Approved Indications**

1. **Darbepoetin alfa:** The Company consider darbepoetin alfa medically necessary providing that at least one of the following medical criteria is met:

   - Chronic kidney disease (CKD), receiving dialysis and all the following:
     1. For initial therapy, hemoglobin (Hb) is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children; OR For patients currently receiving Aranesp or Retacrit/Epogen®/Procrit® (epoetin alfa injection), Hb is ≤ 12.0 g/dL for adults or children OR for patients currently receiving Mircera® (methoxy polyethylene glycol-epoetin beta injection), Hb is ≤ 11.5 g/dL for adults; OR
     2. For continuation therapy, if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol for dose reduction and withholding doses if subsequent Hb values exceed 12g/dL.
   3. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron
therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%; AND
4. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

Initial Approval/Extended Approval.

a) Initial Approval. Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.

b) Extended Approval. Extended approval is at 6-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol for dose reduction and withholding doses if subsequent Hb values exceed 12g/dL.

• Chronic kidney disease†, not receiving dialysis and all the following:

1. For initial therapy hemoglobin (Hb) is < 10.0 g/dL in adults and ≤ 11.0 g/dL for children; OR
   For patients currently receiving Aranesp or Epogen/Procrit/Retacrit, Hb is ≤ 12.0 g/dL for adults or children OR for patients currently receiving Mircera Hb is ≤ 11.5 g/dL for adults; OR
2. For continuation therapy, if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol for dose reduction and withholding doses if subsequent Hb values exceed 12g/dL.
3. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
4. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

Initial Approval/Extended Approval.

a) Initial Approval. Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.

b) Extended Approval. Extended approval is at 6-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol
for dose reduction and withholding doses if subsequent Hb values exceed 12g/dL.

- Cancer chemotherapy-induced anemia and **all** of the following:

  1. Hb <10 g/dL for initial; OR Hb is ≤ 12.0 g/dL for patients currently receiving Aranesp or Epogen/Procrit/Retacrit; AND
  2. Concomitant myelosuppressive chemotherapy (e.g., fluorouracil, capecitabine) and upon initiation, ≥2 months of chemotherapy is planned; AND
  3. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum tranferrin saturation is < 20%); AND
  4. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**

  a) **Initial Approval.** Initial approval is for 4 months if Hb is < 10 g/dL.
  b) **Extended Approval.** Approval can be given at 4-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. If the patient does not have a response, discontinue Aranesp. Discontinue Aranesp following completion of a cancer chemotherapy course.

- Myelodysplastic syndrome (MDS) and **all** of the following:

  1. Age ≥18; AND
  2. Hb <10 g/dL; OR serum erythropoietin level ≤500 mU/mL; OR Hb is ≤ 12.0 g/dL for patients currently receiving Aranesp or Epogen/Procrit/Retacrit; AND
  3. Aranesp is prescribed by, or in consultation with, a hematologist or oncologist; AND
  4. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum tranferrin saturation is < 20%); AND
  5. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**

  a) **Initial Approval.** Initial approval is for 6 months if Hb is ≤ 10 g/dL OR the serum erythropoietin level is ≤ 500 mU/mL.
  b) **Extended Approval.** Approve at additional 6-month intervals if a response is achieved (increase in Hb or a decrease in transfusions) and Hb is ≤ 12.0 g/dL. For patients not responding, despite dose titrations and/or concomitant use of granulocyte colony stimulating factor (G-CSF) (e.g., Neupogen® [filgrastim injection]) during the first 6 months, discontinue Aranesp and evaluate and treat for other causes of anemia.
II.  **Epoetin alfa:** The Company consider epoetin alfa medically necessary providing that *at least one* of the following medical criteria is met:

- Chronic kidney disease (CKD), receiving dialysis and *all* the following:
  1. For initial therapy, hemoglobin (Hb) is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children; OR For patients currently receiving Epogen/Procrit/Retacrit or Aranesp® (darbepoetin alfa injection), Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children OR for patients currently receiving Mircera® (methoxy polyethylene glycol-epoetin beta injection), Hb is ≤ 11.5 g/dL for adults; AND; AND
  2. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
  3. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**
- **Initial Approval.** Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.
- **Extended Approval.** Extended approval is at 6-month intervals if the Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Epogen/Procrit/Retacrit and evaluate and treat for other causes of anemia.

- Chronic kidney disease, not receiving dialysis and *all* the following:
  1. For initial therapy hemoglobin (Hb) is < 10.0 g/dL in adults and ≤ 11.0 g/dL for children; OR For patients currently receiving Aranesp or Epogen/Procrit/Retacrit, Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children OR for patients currently receiving Mircera Hb is ≤ 11.5 g/dL for adults; AND
  2. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
  3. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**
- **Initial Approval.** Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.
- **Extended Approval.** Extended approval is at 6-month intervals if the Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding
discontinue Epogen/Procrit/Retacrit and evaluate and treat for other causes of anemia.

- Cancer chemotherapy-induced anemia and all of the following:
  1. Hemoglobin <10 g/dL; and
  2. Concomitant myelosuppressive chemotherapy (e.g., fluorouracil, capecitabine) and upon initiation, >2 months of chemotherapy is planned; and
  3. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**

  a) *Initial Approval*. Initial approval is for 4 months if Hb is < 10.0 g/dL.
  b) *Extended Approval*. Approval can be given at 4-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. If the patient does not have a response, discontinue Epogen/Procrit/Retacrit. Discontinue Epogen/Procrit/Retacrit following completion of a chemotherapy course.

- Myelodysplastic syndrome (MDS) and all of the following:
  1. Age ≥ 18; and
  2. Hb <10 g/dL; OR serum erythropoietin level ≤ 500 mU/mL; OR Hb is ≤ 12.0 g/dL for patients currently receiving Aranesp or Epogen/Procrit/Retacrit; AND
  3. Epogen/Procrit/Retacrit is prescribed by, or in consultation with, a hematologist or oncologist; AND
  4. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
  5. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

**Initial Approval/Extended Approval.**

  a) *Initial Approval*. Initial approval is for 6 months if Hb is ≤ 10 g/dL OR the serum erythropoietin level is ≤ 500 mU/mL.
  b) *Extended Approval*. Approve at additional 6-months intervals if a response is achieved (increase in Hb or a decrease in transfusions) and Hb is ≤ 12.0 g/dL. For patients not responding, despite dose titrations and/or concomitant use of G-CSF (e.g., Neupogen® [filgrastim injection]) during the first 6 months, discontinue Epogen/Procrit/Retacrit and evaluate and treat for other causes of anemia.

- Human immunodeficiency virus and all of the following
1. Concomitant zidovudine treatment; AND
2. Hb is ≤ 10.0 g/dL for initial therapy; OR endogenous erythropoietin levels are ≤ 500 mUnits/mL for initial therapy; OR Hb is ≤ 12.0 g/dL for patients currently receiving Epogen/Procrit; AND
3. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
4. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.

Initial Approval/Extended Approval.
   a) Initial Approval. Initial approval is for 4 months.
   b) Extended Approval. Approval can be given at 4-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. If no response is achieved, discontinue therapy and evaluate for other causes of anemia. If the patient does not have a response, discontinue Epogen/Procrit/Retacrit. Discontinue Epogen/Procrit/Retacrit when the patient stops zidovudine therapy.

• Elective, non-cardiac, non-vascular surgery to reduce the need for allogeneic red blood cell (RBC) transfusions and all of the following:
   1. Hb ≤ 13 g/dL; and
   2. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate; AND
   3. Unwilling or unable to donate autologous blood prior to surgery; AND
   4. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%).

Initial Approval/Extended Approval. Approve for one month.

During of Therapy in Patients Undergoing Surgery (to Reduce Allogeneic RBC Transfusions). Approve for use before surgery for up to one month.

• Human immunodeficiency virus (HIV) and all of the following:
   1. Concomitant zidovudine treatment; AND
   2. Hb is ≤ 10.0 g/dL for initial therapy; OR endogenous erythropoietin levels are ≤ 500 mUnits/mL for initial therapy; OR Hb is ≤ 12.0 g/dL for patients currently receiving Epogen/Procrit/Retacrit; AND
   3. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Epogen/Procrit/Retacrit prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%); AND
   4. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate.
Initial Approval/Extended Approval.

a) Initial Approval. Initial approval is for 4 months. 

b) Extended Approval. Approve at additional 4-month intervals if the patient has a response to therapy and Hb is ≤ 12.0 g/dL. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. If the patient does not have a response, discontinue Epogen//Retacrit.

Note: Erythropoiesis stimulating agents are not recommended for use with myelosuppressive chemotherapy with curative intent (e.g., cancers for which there is therapy with curative intent: early stage breast cancer, Hodgkin lymphoma, non-Hodgkin’s lymphoma, testicular cancer, early stage non-small cell lung cancer).

†Chronic kidney disease is defined as either kidney damage (i.e., pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or glomerular filtration rate (GFR) <60 mL/min/1.73 m² ≥3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Aranesp, Epogen, Retacrit and Procrit have 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, Epogen, Retacrit and Procrit are 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 Epogen/Procrit/Retacrit 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, Epogen, Retacrit and Procrit are indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.

3. Anemia Associated with Radiotherapy in Cancer. Aranesp, Epogen, Retacrit and Procrit are not indicated for use in cancer patients who are given only radiation therapy.

4. To Enhance Athletic Performance. Aranesp, Epogen, Retacrit and Procrit are 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, Epogen, Retacrit or Procrit is not appropriate in these types of situations.

6. Non-Anemic Patients (Hemoglobin [Hb] > 13.0 g/dL) prior to Surgery. Although studies have been done that involved non-anemic patients undergoing various surgeries receiving Epogen/Procrit/Retacrit preoperatively and sometimes postoperatively to prevent transfusions or subsequent anemia, the overall benefit of this therapy in those with relatively normal preoperative Hb level is questionable. Epogen/Procrit/Retacrit did not statistically significantly decrease the number
of patients who underwent transfusions in a double-blind, placebo-controlled trial involving patients (n = 218) scheduled to undergo elective orthopedic hip or knee surgery whose pretreatment Hb was > 13.0 g/dL but ≤ 15.0 g/dL. In another small study patients undergoing total hip replacement surgery with normal preoperative Hb levels (most patients had a baseline Hb > 13.0 g/dL) did not have improved Hb levels or a reduction in allogeneic blood transfusions with Epogen/Procrit/Retacrit use.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES


