# NON-FORMULARY Clinical Guideline
Erythropoiesis-Stimulating Agents
Epogen® (epoetin alfa), Procrit® (epoetin alfa), Aranesp® (darbepoetin alfa)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Epogen and Procrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment of Anemia of Chronic Renal Failure Patients: including patients on dialysis and patients not receiving dialysis.</td>
<td></td>
</tr>
<tr>
<td>• Treatment of zidovudine-induced anemia in HIV-infected patients with circulating endogenous erythropoietin concentrations &lt; 500 mUnits/ml who are receiving a dose of zidovudine &lt;= 4200 mg/week</td>
<td></td>
</tr>
<tr>
<td>• Treatment of Anemia in Cancer Patients: in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.</td>
<td></td>
</tr>
<tr>
<td>• Reduction of Allogeneic Blood Transfusion in Surgery Patients: in patients (hemoglobin &gt; 10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.</td>
<td></td>
</tr>
<tr>
<td>• Off Label use†</td>
<td></td>
</tr>
<tr>
<td>➢ Anemia of prematurity, in combination with iron supplementation</td>
<td></td>
</tr>
<tr>
<td>➢ Anemia associated with myelodysplastic syndrome (MDS)</td>
<td></td>
</tr>
<tr>
<td>➢ Anemia due to pegylated interferon and ribavirin treatment for hepatitis C</td>
<td></td>
</tr>
</tbody>
</table>

| Aranesp | |
| • Treatment of Anemia of Chronic Renal Failure Patients: including patients on dialysis (ESRD) and patients not on dialysis. | |
| • Treatment of Anemia in Cancer Patients on Chemotherapy: in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. | |

| Dosage Forms | |
| • Epogen: 2000 units/mL, 3000 units/mL, 4000 units/mL, 10,000 units/mL, 20,000 units/mL, 40,000 units/mL in single-dose vials | |
| • Procrit: 2000 units/mL, 3000 units/mL, 4000 units/mL, 10,000 units/mL, 20,000 units/mL, 40,000 units/mL with all dosage strengths in single-dose vials | |
| • Aranesp: 25 mcg/1 mL, 40 mcg/1 mL, 60 mcg/1 mL, 100 mcg/1 mL, 150 mcg/0.75 mL, 200 mcg/1 mL, 300 mcg/1 mL, 500 mcg/1 mL in polysorbate or albumin solution. Available as single-dose vials or pre-filled syringes | |

| Dosage | |
| Refer to product information | |

| Dosage for Off-label Use: |
Anemia of prematurity, in combination with iron supplementation:
- 25—100 units/kg SC three times weekly. Alternative regimens include 100 units/kg SC 5 times per week or 200 units/kg SC every other day for 10 days

Anemia associated with myelodysplastic syndrome (MDS)
- Epoetin doses of 40,000-60,000 IU 2-3 times per week have been used
- When used in combination with G-CSF, increased response rate is seen

Anemia due to pegylated interferon and ribavirin treatment for hepatitis C
- Epoetin doses of 40,00-60,000 units per week have been used

Authorization Guidelines
Prior authorization personnel will review the request for prior authorization and apply the clinical guidelines to assess the medical necessity of the request for a prescription for Epogen, Procrit, or Aranesp. If the guidelines are met, the reviewer will prior authorize the prescription. If the guidelines are not met, the prior authorization request will be referred to a physician reviewer for a medical necessity determination. Such a request for prior authorization will be approved when, in the professional judgment of the physician reviewer, the services are medically necessary to meet the medical needs of the recipient.

For patients who meet all of the following:
- Does not have uncontrolled hypertension
- No known hypersensitivity to mammalian cell-derived products
- No known hypersensitivity to albumin (human)
- If prescribed Epogen or Procrit:
  Supporting medical records for all indications. Note: Target Hb 10-11 g/dl
  - Diagnosis with underlying cause of anemia documented
  - Hemoglobin
    - New starts: Hb below 10 g/dl within the last 2 weeks
    - Maintenance treatment:
      - For CKD on dialysis: Hb ≤11 g/dl within the last 2 weeks
      - For CKD not on dialysis: Hb ≤10 g/dl within the last 2
  - Iron Studies showing member has adequate iron stores to support erythropoiesis
    - Serum ferritin of at least 100 ng/ml, and
    - Transferrin saturation (iron saturation) of at least 20%

Additional documentation required for specific indications:
- Treatment of Anemia in HIV-infected Patients receiving zidovudine ≤4200 mg/week: Endogenous erythropoietin levels ≤ 500 mUnits/mL
- Treatment of Anemia in Cancer Patients currently receiving chemotherapy for
at least 2 months:
- Documentation of non-myeloid malignancy (e.g., solid tumor, multiple myeloma, lymphomas)
- Concurrent chemotherapy regimen

- **Reduction of Allogeneic Blood Transfusion in Non-Cardiac, Non-Vascular Surgery Surgery Patients:** documented hemoglobin > 10 to ≤ 11 g/dL

**Off label use**
- **Anemia of prematurity, in combination with iron supplementation**
  - member has either a birth weight of less than 1500 grams, OR
  - a gestational age of less than 33 weeks
- **Anemia associated with myelodysplastic syndrome (MDS)**
  - Recent erythropoietin level <500 mU/ml
- **Anemia due to pegylated interferon and ribavirin treatment for hepatitis C**
  - Recent (within 2 weeks) Hb <10 g/dl, AND, one of the following:
    - Member is at <12 weeks of treatment
    - Member is at >12 weeks of treatment and was unresponsive to a 200mg/day ribavirin dosage reduction for at least 2 weeks
    - At any time during treatment if member has any of the following:
      - Symptomatic anemia, OR
      - Cirrhosis, OR
      - liver transplant, OR
      - HIV co-infection, OR
      - Advanced age with stage 3 fibrosis

**Other indications**
- With appropriate clinical literature to support safety and efficacy (Note: Not currently recommended for treatment of anemia due to Castleman's disease, aplastic anemia, sickle cell disease or Gaucher’s disease)

- If prescribed **Aranesp** - authorize after trial and failure of Procrit or Epogen OR documented intolerance to Procrit and Epogen

†Off-label use based on peer-reviewed clinical studies

**Prior Authorization Requirements**

<table>
<thead>
<tr>
<th>Initial Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction of Allogenic Blood Transfusion in Surgery Patients:</strong> 21 days of therapy per surgery</td>
</tr>
<tr>
<td><strong>Anemia of prematurity, in combination with iron supplementation:</strong> 6 weeks</td>
</tr>
<tr>
<td><strong>2 months for all other indications</strong></td>
</tr>
</tbody>
</table>

**Renewal**
• **Anemia of prematurity, in combination with iron supplementation:** No renewal
• **3 months for all other indications**
• **Need recent (within 2 weeks) H/H demonstrating improvement in Hb, with Hb <11 g/dl**

### References


### Primary Reference Policy

7600.12 Non-Formulary Management

### Additional information
Dosage Conversion Information:

Aranesp (Darbepoetin alfa) differs from Epogen/Procrit (epoetin alfa) by the addition of 2 carbohydrate chains, resulting in different dosing regimens. The manufacturers have suggested a conversion ratio of epoetin alfa to darbepoetin alfa of 400:1 at a minimum, and no greater than 254:1. The US Federal Government has performed its own review and has determined the following ratio for use in Medicare payments: 260 units of epoetin alfa to 1 mcg darbepoetin alfa (260:1).

Aetna considers erythropoiesis stimulating agents experimental and investigational for all other indications, including the following conditions, because its use in these situations is not supported by the peer reviewed medical literature (not an all-inclusive list):

1. Anemia due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, or bone marrow fibrosis.
2. Anemia due to bleeding (other than indications I.F. (high-risk surgery) and I.I. (special circumstance members) above).
3. Anemia associated with the treatment of acute and chronic myelogenous leukemia (AML, CML) or erythroid cancers.
5. Anemia associated only with radiotherapy.
6. Prophylactic use to prevent anticancer chemotherapy-induced anemia.
7. Prophylactic use to prevent tumor hypoxia.
8. Anemia in persons with erythropoietin-type resistance due to neutralizing antibodies.
10. Members who require immediate correction of severe anemia;
11. Anemia in Gaucher's disease;
12. Anemia in Castleman's disease;
13. Anemia in paroxysmal nocturnal hemoglobinuria (PNH);
14. Sickle cell anemia;
15. Sepsis-associated anemia;
16. Cerebral hypoxia/ischemia;
17. Cognitive decline in persons with schizophrenia;
18. Stroke (except for I.E above);
19. Aplastic anemia;
20. Cardiogenic shock-associated anemia;
21. Postural tachycardia syndrome;
22. Hemolytic anemia;
23. Myelofibrosis;

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted the CMS to review its coverage of erythropoietin analog therapy. CMS (2007) determined that erythropoietin analog therapy is not reasonable and necessary for the following clinical conditions, either because of a deleterious effect of erythropoietin analogs on the underlying disease or because the underlying disease increases their risk of adverse effects related to erythropoietin analog use. These conditions
include:

- Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
- The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;
- The anemia of cancer not related to cancer treatment;
- Any anemia associated only with radiotherapy;
- Prophylactic use to prevent chemotherapy-induced anemia;
- Prophylactic use to reduce tumor hypoxia;
- Patients with erythropoietin-type resistance due to neutralizing antibodies; and
- Anemia due to cancer treatment if patients have uncontrolled hypertension

2010 FDA Safety Announcement

The FDA is requiring all drugs called Erythropoiesis-Stimulating Agents (ESAs) to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs. FDA required Amgen, the manufacturer of these products, to develop a risk management program because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.

As part of the REMS, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs. In addition to the Medication Guide, Amgen was required to develop the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program for healthcare professionals who prescribe ESAs to patients with cancer.

Under the ESA APPRISE Oncology program, Amgen will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer. Amgen is also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program.

The goals of the REMS for the ESAs are:

- To support informed decisions between patients and their healthcare professionals who are considering treatment with an ESA by educating them on the risks of ESAs.
- To mitigate the risk of decreased survival and/or poorer tumor outcomes in patients with cancer by implementing the part of the REMS called the ESA APPRISE Oncology Program.

Additional Information for Healthcare Professionals and Hospitals: ESA use in cancer

Healthcare Professionals

The ESA APPRISE Oncology program requires that all healthcare professionals who prescribe ESAs
for patients with cancer do the following:

- Complete a training module that covers the use of ESAs. Completion of the training module is required for enrollment in the ESA APPRISE Oncology program.

- Sign the patient/healthcare professional acknowledgement form prior to the patient receiving an ESA. The acknowledgement form attests that the healthcare professional and patient have discussed the risks of using an ESA.

- Re-enroll in the ESA APPRISE Oncology program every three years.

Healthcare professionals not enrolled in the ESA APPRISE Oncology program will not be able to prescribe ESAs for use in patients with cancer.

As part of the enrollment in the ESA APPRISE Oncology program, healthcare professionals must attest to their understanding of the following:

- That ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancer.

- To decrease the risks of ESAs, the lowest dose needed should be used to avoid red blood cell transfusion.

- ESAs should be discontinued following completion of a chemotherapy course of treatment.

- Aranesp® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy, based on studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, non-myeloid malignancies.

- Epogen®/Procrit® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy, based on studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months.

- ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.

- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.

- ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

Additional Information for Healthcare Professionals: non-cancer use of ESAs

- Healthcare professionals who prescribe ESAs for anemia not caused by cancer chemotherapy are required to provide a copy of the Medication Guide to each patient or their representative when an ESA is dispensed.

- Healthcare professionals who use ESAs only for non-cancer uses are not required to enroll in the ESA APPRISE Oncology program.

Evaluation and Monitoring of the APPRISE Oncology Program
<table>
<thead>
<tr>
<th>Amgen will be responsible for ensuring compliance with the program:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amgen will conduct real-time monitoring of prescribing and purchases in private-practice settings and clinic audits.</td>
</tr>
<tr>
<td>• Hospitals in the program will be audited to ensure compliance with the ESA APPRISE Oncology Program.</td>
</tr>
<tr>
<td>• Failure to comply will result in a suspension of access to ESAs.</td>
</tr>
</tbody>
</table>