Clinical Policy: Epoetin Alfa (Epogen, Procrit), Epoetin Alfa-epbx (Retacrit)
Reference Number: ERX.SPA.88
Effective Date: 10.01.16
Last Review Date: 11.18

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Epoetin alfa (Epogen®, Procrit®) and its biosimilar, epoetin alfa-epbx (Retacrit™), are erythropoiesis-stimulating agents (ESAs).

FDA Approved Indication(s)
Epogen, Procrit, and Retacrit are indicated for:
- Treatment of anemia due to:
  - Chronic kidney disease (CKD) in patients on dialysis and not on dialysis
  - Zidovudine in human immunodeficiency virus (HIV)-infected patients
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery

Limitation(s) of use:
- Epogen, Procrit, and Retacrit have not been shown to improve quality of life, fatigue, or patient well-being.
- Epogen, Procrit, and Retacrit are 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
  - In patients scheduled for surgery who are willing to donate autologous blood
  - In patients undergoing cardiac or vascular surgery
  - As a substitute for RBC transfusions in patients who require immediate correction of anemia

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Epogen, Procrit, and Retacrit are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Anemia Due to Chronic Kidney Disease (must meet all):
      1. Diagnosis of anemia of CKD (dialysis and non-dialysis members);
      2. Prescribed by or in consultation with a hematologist or nephrologist;
      3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
      4. Pretreatment hemoglobin level < 10 g/dL;
      5. If Epogen is requested, failure of Procrit unless contraindicated or clinically significant adverse effects are experienced.
   Approval duration: 6 months
   
   B. Anemia Due to Zidovudine in HIV-infected Patients (must meet all):
      1. Diagnosis of zidovudine-induced anemia;
2. Prescribed by or in consultation with a hematologist or HIV specialist;
3. Member is HIV-positive;
4. Dose of zidovudine is ≤ 4,200 mg/week;
5. Endogenous serum erythropoietin levels ≤ 500 mUnits/mL;
6. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
7. Pretreatment hemoglobin level < 10 g/dL;
8. If Epogen is requested, failure of Procrit unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 6 months

C. Anemia due to Chemotherapy in Patients with Cancer (must meet all):
1. Diagnosis of anemia due to chemotherapy;
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age ≥ 5 years;
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
5. Pretreatment hemoglobin < 10 g/dL;
6. If Epogen is requested, failure of Procrit unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 6 months or until the completion of chemotherapy course (whichever is less)

D. Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery (must meet all):
1. Member is at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery;
2. Perioperative hemoglobin > 10 to ≤ 13 g/dL;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%;
4. Member is unwilling or unable to donate autologous blood pre-operatively;
5. If Epogen is requested, failure of Procrit unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 15 days (for 300 units/kg daily) OR 21 days (for 600 units/kg in 4 doses)

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
A. Anemia Due to Chronic Kidney Disease (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months

B. Anemia Due to Zidovudine in HIV-infected Patients (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Current hemoglobin level ≤ 12 g/dL;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months
C. Anemia Due to Chemotherapy in Patients with Cancer (must meet all):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   2. Continuation of ESA therapy is concurrent with myelosuppressive chemotherapy;
   3. If member has received ≥ 8 weeks of ESA therapy, member meets both of the following (a and b):
      a. Member is responding positively to therapy as evidenced by rise in hemoglobin levels > 1 g/dL;
      b. No RBC transfusions are required;
   4. Current hemoglobin < 10 g/dL;
   5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level ≥ 100 mcg/L or serum transferrin saturation ≥ 20%.

Approval duration: 6 months or until the completion of chemotherapy course, whichever is less

D. Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery (must meet all):
   1. Re-authorization is not permitted. Members must meet the initial approval criteria.
   2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   CKD: chronic kidney disease
   ESA: erythropoiesis-stimulating agent
   FDA: Food and Drug Administration
   HIV: human immunodeficiency virus
   RBC: red blood cell

   Appendix B: Therapeutic Alternatives
   Not applicable

   Appendix C: Contraindications/Boxed Warnings
   • Boxed warning: ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence
   • Retacrit is contraindicated in:
     o Uncontrolled hypertension
     o Pure red cell aplasia (PRCA) that begins after treatment with Retacrit or other erythropoietin protein drugs

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia due to CKD</td>
<td>Initial dose: 50 to 100 units/kg 3 times weekly (adults) intravenously (IV) or subcutaneously (SC) and 50 units/kg 3 times weekly (children on dialysis)</td>
<td>Varies depending on indication and</td>
</tr>
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</table>
### Indication

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<thead>
<tr>
<th>Indication</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Anemia due to zidovudine in HIV-infected patients</td>
<td>IV or SC. Individualize maintenance dose. IV route recommended for patients on hemodialysis.</td>
<td>frequency of administration</td>
</tr>
<tr>
<td>Anemia due to chemotherapy</td>
<td>100 units/kg IV or SC 3 times weekly</td>
<td></td>
</tr>
<tr>
<td>Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery</td>
<td>300 units/kg per day SC daily for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery or 600 units/kg SC weekly in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery</td>
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</tbody>
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*Off-label indication*

### VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
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</table>
| Epoetin alfa (Epogen)      | • Single-dose vial: 2000, 3000, 4000, and 10,000 units/mL  
• Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL |
| Epoetin alfa (Procrit)     | • Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 units/mL  
• Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL |
| Epoetin alfa-epbx (Retacrit)| • Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, 40,000 units/mL |

### VII. References

10. Oncologic Drugs Advisory Committee. FDA briefing document: Epoetin Hospira, a proposed biosimilar to Epogen/Procrit (epoetin alfa) (BLA 125545). Published May 18, 2017. Available at

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from USS.SPMN.13 Erythropoiesis Stimulating Agents and converted to new template. Removed all safety criteria and requests for documentation. Added requirement for adequate iron stores and exclusion of all other causes of anemia. -Anemia due to chemo: added requirement for current Hgb &lt; 10 g/dL per CMS policy. -Anemia of CKD: added Hgb requirement for pediatric patients and modified criteria to allow for continued therapy after 12 weeks. -Anemia due to MDS: removed approval for members with Hgb &gt; 12 g/dL. -Anemia due to HCV treatment: added duration of ribavirin treatment (whichever is less) to initial approval duration. -Zidovudine-induced anemia: removed dose adjustment criteria and simplified specific Hgb levels to Hgb ≤ 12 g/dL.</td>
<td>08.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Converted to new template. Initial: added age restriction to all indications except CKD; indicated that iron lab should be current (within the last 3 months). For anemia due to chemo-added requirement that anemia cannot be managed by transfusion. Re-auth: for CKD, modified requirement related to current hemoglobin level to allow dose reduction per PI.</td>
<td>07.17</td>
<td>08.17</td>
</tr>
<tr>
<td>2Q 2018 annual review: All Indications: removed criteria that are under the purview of the prescriber-“Member does not require immediate correction of anemia”, and “Other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) have been corrected or excluded”; removed safety requirements related to contraindications per safety guidance endorsed by Medical Affairs; modified initial/continued approval duration to 6 months (except surgery); Anemia due to CKD: removed requirement related to dosage reduction per hemoglobin level on re-auth since it is not a hard stop to discontinue and specialist is involved in care.; Anemia due to zidovudine: removed age requirement-published literature has reported use in pediatric patients per PI; Anemia due to chemotherapy: removed criteria that are under the purview of the prescriber-“Member has non-myeloid malignancy”, a minimum of 2 additional months of planned chemotherapy, chemotherapy is being given as palliative treatment, and anemia cannot be managed by transfusion; removed “member is receiving concomitant myelosuppressive chemotherapy” since chemo is already included as part of the diagnosis; Reduction of RBC transfusion in surgery patients: removed age requirement-literature available for pediatric dosing (Micromedex); Anemia associated with MDS: added specialist requirement; clarified that the lab for serum EPO should be current (within the past 3 months); added requirement for positive response to therapy on re-auth; Added NCCN compendial/recommended use (category 2A): MF-associated anemia; References reviewed and updated.</td>
<td>01.10.18</td>
<td>05.18</td>
</tr>
<tr>
<td>Newly FDA-approved biosimilar added: Retacrit; removed myelofibrosis-associated anemia, anemia due to myelodysplastic syndrome, anemia secondary to combination ribavirin and interferon-alfa therapy in patients</td>
<td>06.26.18</td>
<td>08.18</td>
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<tr>
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<td>infected with hepatitis C virus off label uses since DrugDex IIb not covered; references reviewed and updated.</td>
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**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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