Clinical Policy Title: Erythropoietin for end-stage renal disease

Clinical Policy Number: 00.02.07

Effective Date: June 1, 2015
Initial Review Date: February 19, 2014
Most Recent Review Date: January 11, 2018
Next Review Date: January 2019

Policy contains:
- Chemotherapy-associated anemia.
- Anemia of chronic kidney disease.

Related policies:

CP# 13.02.01 Kidney transplantation

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of erythropoietin for end-stage renal disease (ESRD) to be clinically proven and, therefore, medically necessary when the following criteria are met (Coronado, 2015; Hahn, 2014; UK National Institute for Clinical Excellence [NICE] 2011):

- The member is enrolled in an ESRD program at a dialysis center.
- The initial hemoglobin (Hgb) on treatment-naïve presentation is <10 gm/dL or hematocrit (Hct) is <33 percent or Hgb <12 g/dL or Hct is <36 percent if member has been under treatment previously.
- Patient has been evaluated for iron-deficiency anemia, folate-deficiency, and vitamin B12 deficiency and is being treated concurrently as indicated.
- Patient has completed laboratory tests including but not limited to:
  - Hemoglobin — last three months’ results (to determine rolling Hgb).
  - Hematocrit — last three months’ results (to determine rolling Hct).
  - Serum ferritin — within past two months.
  - Transferrin saturation — within past two months.
  - Serum iron — within past two months.
Total iron binding capacity (TIBC) — within past two months.
Vitamin B12 and folate levels — within past two months.

Limitations:

Coverage of specific pharmaceuticals and/or treatments is subject to prior authorization by plan criteria. Prior authorization criteria for the pharmaceuticals listed in this coverage policy are set forth in Appendix A.

Alternative covered services:

Routine patient evaluation and management by a network health care provider

Background

Erythropoietin (epoetin or EPO) is a hormone that controls red blood cell (RBC) production. Epoetin is produced by the kidneys and acts by stimulating red cell progenitors in the bone marrow. Additional roles include vasoconstriction-dependent hypertension, angiogenesis simulation, smooth muscle cell proliferation, iron absorption and neuronal protection in hypoxic conditions such as stroke. Roles in memory and depression have also been suggested.

Synthetic epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®) are produced by recombinant deoxyribonucleic acid (DNA) technology in cell culture. Therapeutic uses include treating the anemias of chronic kidney disease and anemia secondary to cancer chemotherapy.

Searches

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on November 15, 2017. Searched terms were: “erythropoietin,” and "end-stage renal disease."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• Guidelines based on systematic reviews.
• Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Attempts to define the optimum timing for initiation and dosing of erythropoietin have been a mixed bag. Two Cochrane reviews found a paucity of evidence to support either early versus delayed EPO administration for ESRD (Coronado 2015) or to endorse longer intervals of administration except in the setting of conventional adult renal hemodialysis (Hahn 2014).

Erythropoietin-stimulating agents for chemotherapy-associated anemia (except for head and neck cancer) increase surrogate outcome indicators such as hemoglobin, but serious adverse events (thromboembolism) and shortened survival are also associated with its use. Evidence does not support routine use of erythropoietin-stimulating agents in stroke or in preterm infants.

Policy updates:

None.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, methods, recommendations</th>
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<tbody>
<tr>
<td>Coronado (2015)</td>
<td>Key points:</td>
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| Early versus delayed erythropoietin for the anaemia of end-stage kidney disease. | • Systematic literature search to assess the benefits and harms of early versus delayed EPO for the anemia of ESRD yielded 1910 records, of which 1376 were excluded following title and abstract assessment.  
  • The authors assessed 158 full text records and identified 18 studies (66 records) of interest.  
  • None of the records, however, matched the inclusion criteria for the topic review.  
  • The authors therefore found no evidence to assess the benefits and harms of early versus delayed EPO for the anemia of ESRD. |
| Hahn (2014)       | Key points:                       |
| Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients. | • Longer-acting erythropoiesis-stimulating agents administered at one- to four-week intervals are non-inferior to recombinant human EPO given one to three times/week in terms of achieving hemoglobin targets.  
  • There are no significant differences in adverse events in hemodialysis patients attributable to either agent.  
  • Additional trials are required to evaluate different frequencies of erythropoiesis-stimulating agents in peritoneal and pediatric dialysis patients and to compare different longer-acting erythropoiesis-stimulating agents (such as darbepoetin). |
<table>
<thead>
<tr>
<th>Citation</th>
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<tr>
<td><strong>Bath (2013)</strong></td>
<td><strong>Key points:</strong></td>
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| Colony stimulating factors (CSFs) for stroke | • Randomized controlled trials (RCTs), September 2012.  
• Eleven trials (1,275 subjects with acute or subacute ischemic or hemorrhagic stroke).  
• Significant increase in death by end of trial and no significant (NS) increase in serious adverse events.  
• Increase in red cell counts but no impact on platelets, white cells or infarct volume.  
• Insufficient evidence for any CSFs in stroke. |
| **Kidney Disease: Improving Global Outcomes (KDIGO) (2012)**  
**Anemia in chronic kidney disease: ESA initiation** | **Key points:**                   |
|                                               | • Address all correctable causes of anemia (iron deficiency, inflammation) first.  
• Balance potential benefits against risks (stroke, vascular access loss and hypertension) for the individual.  
• Erythropoiesis-stimulating agents should be used with great caution, if at all, in patients with active malignancy. |
| **UK National Institute for Clinical Excellence (NICE) (2011)**  
**Anemia in chronic kidney disease** | **Key points:**                   |
|                                               | • Published literature, – 2009.  
• Erythropoiesis-stimulating agents should not be initiated in iron deficiency without first managing the deficiency.  
• Iron-replete patients: individualized discussion/balancing of risk versus benefit, followed by agreed interval for therapy assessment. |
| **Buckley (2013)**                           | **Key points:**                   |
• Proportion of patients for whom epoetin was prescribed was significantly lower (by 45%) and more appropriate (25%; largely in non-specific anemia) post-implementation.  
• Annual cost savings of $198,352 ($16,529/month). |
| **Grant (2013)**                             | **Key points:**                   |
| Epoetin and darbepoetin for anemia in cancer patients | • Results consistent with 2006 review: reduced need for transfusions but increased risk of thromboembolism.  
• Fatigue scores better but still less than minimally important clinical difference.  
• Increased mortality.  
• Further research needed: Could dosing practices and overall exposure influence harms? |
| **Saunders (2013)**                          | **Key points:**                   |
| Economic evaluation: nurse- vs. physician-driven anemia management protocols in hemodialysis | • Retrospective case-control.  
• All subjects reached target hemoglobin levels.  
• Use and costs for iron higher in physician group; use and cost for EPO higher in nurse group.  
• Further research (direct rather than surrogate outcomes) required. |
| **Ohlsson (2012)**                           | **Key points:**                   |
| Early erythropoietin for preventing red cell | • Twenty-seven trials (2,293 preterm infants).  
• Early EPO reduced risk for red cell transfusions but reductions are small and of limited |
<table>
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| transfusion in preterm and/or low birth weight infants | clinical importance.  
  - Increased risk for retinopathy of prematurity.  
  - No evidence for neuro-protective role.  
  - EPO not recommended for routine use in preterm infants.  
  - Other Cochrane reviews in progress: preterm, term and late-term infants. |

**Dutch Institute for Healthcare Improvement (2011)**  
**Blood transfusion guideline**  
**Key points:**  
- Use of erythropoiesis-stimulating agents in patients with anemia due to cancer: Only for chemotherapy-induced anemia with the aim of reducing need for transfusion.  
- Effects on mortality and survival of cancer patients: Discuss dangers (thrombosis, decreased survival) and benefits (fewer transfusions) with patients. EPO for indications in cancer patients other than therapy-induced anemia is not recommended.

**Shehata (2010)**  
**Cancer Care Ontario**  
**Erythropoietic agents for anemia in cancer patients.**  
**Key points:**  
- Recommended as treatment option for patients with chemotherapy-associated anemia and hemoglobin <100 gL.  
- Red cell transfusions also an option.  
- No studies in anemic myeloma, non-Hodgkin’s lymphoma or chronic lymphocytic leukemia in absence of anemia.

**Lambin (2009)**  
**Erythropoietin as adjuvant treatment for head and neck cancer**  
**Key points:**  
- Radiation, with/without erythropoietin.  
- Five trials (1,397 patients).  
- Significantly worse survival with epoetin than radiation alone.  
- Erythropoietin should not be administered to head and neck cancer patients outside a research setting.

**Hayes (2008)**  
**FDA news: risks of erythropoietin-stimulating agents (ESAs)**  
**Key points:**  
- Two recent studies: breast or advanced cervical cancer patients receiving erythropoiesis-stimulating agents shorter survival or more rapid tumor growth.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


CMS National Coverage Determinations (NCDs):
No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):


Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Anemia in chronic kidney disease</td>
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<tr>
<td>I12.0</td>
<td>Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease</td>
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<tr>
<td>I13.2</td>
<td>Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease</td>
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<td>N18.6</td>
<td>End stage renal disease</td>
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<tbody>
<tr>
<td>J0882</td>
<td>Injection, darbepoetin alfa (ESRD on dialysis)</td>
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<tr>
<td>J0886</td>
<td>Injection, epoetin alfa, 1,000 units (for ESRD on dialysis)</td>
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Appendix A

PerformRx
Prior Authorization Group: Erythropoiesis-Stimulating Agents
Drug(s): Darbepoetin Alfa-Polysorbate 80 (Aranesp®), Epoetin Alfa (Procrit®)

- ARANESP® is preferred agent for Chronic Kidney Disease and for patients receiving chemotherapy that are 18 years of age or older.
- Procrit requires documentation (consistent with pharmacy claims data, OR for new members to the health plan consistent with medical chart history) of adequate trials and/or has a documented medical reason (e.g. intolerance or hypersensitivity) for not utilizing ARANESP when appropriate

Covered Uses: Medically accepted indications are defined using the following sources: the U.S. Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or national treatment/standard of care guidelines.

For all cases if criteria is met, the request will be approved for up to 1 month if the patient is deficient in iron, B12 or folate, and up to 3 months for all other requests. If the criteria is not met, the request is referred to a Medical Director/clinical reviewer for medical necessity review.

Criteria:
All lab results must be submitted within 30 days of the request.

- Hemoglobin, hematocrit, serum ferritin level (normal is greater than 100ng/ml), transferrin saturation (TSAT) (normal is greater than 20 percent), vitamin B12 level, folate level, and erythropoietin level (for HIV related anemia)

1. Initial approval for anemia of pre-dialysis chronic kidney disease or anemia due to chemotherapy:

- Hemoglobin less than 10g/dl OR if the member is new to the health plan and was receiving therapy at the previous health plan the member has a documented (submitted lab result dated within 30 days of request) hemoglobin <12 g/dL.
- If the member has low B12 levels, folate levels or is iron deficient, the patient is either receiving appropriate supplementation or member is beginning therapy to correct deficiency.
- The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.
- If the request is for Procrit®, the provider submitted a documented medical reason (i.e., intolerance) why they are unable to use Aranesp for patients that are 18 or older.

Reauthorization:

- If the member has been receiving therapy and their hemoglobin is less than 12 g/dL and one of the following apply (if applicable):
  o The ordered dose is reduced by 25 percent of previous dose if the rate of Hgb increase was greater than 1g/dL over a two-week period.
  o The ordered dose is increased from the previous dose if the patients Hgb improved less than 1g/dL over a four–to-six-week period and iron stores were adequate.
  o An increase in dose does not occur more than once per month (by 25 percent).
If the member is iron deficient, the member is in the process of receiving either oral or IV iron supplementation. The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

If the request is for Procrit®, the provider submitted a documented medical reason (i.e., intolerance) why they are unable to use Aranesp for patients that are 18 or older.

2. Initial approval for anemia due to Zidovudine-treated HIV infected patients:
   - Hemoglobin less than 11g/dl OR if the member is new to the health plan and was receiving therapy at the previous health plan the member has a documented (submitted lab result dated within 30 days of request) hemoglobin <12 g/dL.
   - Patient has been receiving a highly active antiretroviral therapy (HAART) regimen for the past 35 days.
   - Documentation, within 30 days of the request, that the patient has an erythropoietin level < 500 units/mL.
   - If the member has low B12 levels, folate levels or is iron deficient, the patient is either receiving appropriate supplementation or member is beginning therapy to correct deficiency.
   - The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

Reauthorization:
   - If the member has been receiving therapy and their hemoglobin is less than 12 g/dL and one of the following apply (if applicable):
     - The ordered dose is reduced by 25 percent of previous dose if the rate of Hgb increase was greater than 1g/dL over a two week period OR the Hgb is increasing and approaching 12 g/dL.
     - The ordered dose is increased from the previous dose if the patients Hgb improved less than 1g/dL over a four-to-six-week period and iron stores were adequate.
     - An increase in dose does not occur more than once per month.
     - If the member is iron deficient, the member is in the process of receiving either oral or IV iron supplementation. The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

3. Initial approval for anemia due to ribavirin-induced nemia:
   - Hemoglobin less than 10g/dl OR if the member is new to the health plan and was receiving therapy at the previous health plan the member has a documented (submitted lab result dated within 30 days of request) hemoglobin <12 g/dL.
   - Patient is currently receiving ribavirin therapy.
   - If the member has low B12 levels, folate levels or is iron deficient, the patient is either receiving appropriate supplementation or member is beginning therapy to correct deficiency.
   - The medication is being recommended and/or prescribed at an appropriate dose for indication, as recommended in compendia or standard of care guidelines.
Reauthorization:

- If the member has been receiving therapy and their hemoglobin is less than 12 g/dL and one of the following apply (if applicable):
  - The ordered dose is reduced by 25% of previous dose if the rate of Hgb increase was greater than 1g/dL over a two-week period OR the Hgb is increasing and approaching 12 g/dL.
  - The ordered dose is increased from the previous dose if the patients Hgb improved less than 1g/dL over a four-to-six-week period and iron stores were adequate.
  - An increase in dose does not occur more than once per month.
  - If the member is iron deficient, the member is in the process of receiving either oral or IV iron supplementation. The member is currently receiving ribavirin therapy, and documentation submitted indicates a dosage reduction of ribavirin but the member still became anemic.
  - The medication is being recommended and/or prescribed at an appropriate dose for indication, as recommended in compendia or standard of care guidelines.

4. Initial approval for allogenic blood transfusion surgery patients:

- Hemoglobin less than 13g/dl and greater than 10g/dl.
- The patient has normal iron stores and is, or will be, receiving adequate iron supplementation.
- The patient is scheduled for an elective, non-cardiac, nonvascular surgery.
- The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

5. Initial approval for anemia due to Other Medically Acceptable Indications:

- Hemoglobin less than 11g/dl OR if the member is new to the health plan and was receiving therapy at the previous health plan the member has a documented (submitted lab result dated within 30 days of request) hemoglobin <12 g/dL.
- If the member has low B12 levels, folate levels or is iron deficient, the patient is either receiving appropriate supplementation or member is beginning therapy to correct deficiency.
- The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

Reauthorization:

- If the member has been receiving therapy and their hemoglobin is less than 12 g/dL and one of the following apply (if applicable):
  - The ordered dose is reduced by 25 percent of previous dose if the rate of Hgb increase was greater than 1g/dL over a two-week period OR the Hgb is increasing and approaching 12 g/dL.
  - The ordered dose is increased from the previous dose if the patients Hgb improved less than 1g/dL over a four-to-six-week period and iron stores were adequate.
  - An increase in dose does not occur more than once per month.
• If the member is iron deficient, the member is in the process of receiving either oral or IV iron supplementation.
• The medication is being recommended and/or prescribed at an FDA appropriate dose for indication.

Review date: April 2017.