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 18, 2017
Next Review Date: January 2018

Related policies:
CP# 13.02.01 Kidney transplants

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s 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 Prestige Health Choice 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. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of erythropoietin listed below to be clinically proven and, therefore, medically necessary when the following criteria are met:

- The member is enrolled in an end-stage renal disease (ESRD) program.
- The hemoglobin (Hgb) is <12 g/dL or hematocrit (Hct) is <36 percent.
- Patient is being treated at a dialysis center.
- Completion and documentation of laboratory tests to ensure no other treatable cause of anemia. The history and studies required are listed here.

All of the necessary lab work (listed below) is documented on the prior authorization (PA) form or submitted with request:
- 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.
- History of Epogen® usage.

Limitations:

- Chemotherapy-associated anemia.
- Anemia of chronic kidney disease.
- Epogen®.
Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

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.

The use of erythropoietin for indications other than ESRD is not addressed in this policy.

Alternative covered services:

Investigation into other causes of anemia, physician office visits and lab studies. Please see the Summary of Clinical Evidence table (pages 3 – 5).

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 been suggested. Erythropoietin is produced by recombinant DNA technology in cell culture and therapeutic uses include treating the anemias of chronic kidney disease and cancer treatments.

Searches

Prestige Health Choice 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 14, 2016. Search term was “erythropoietin.”

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

Erythropoietin-stimulating agents (ESAs) 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 use.

Evidence does not support routine use of ESAs in stroke or in preterm infants.

Further research is needed regarding the impact of dosing and overall exposure on adverse events.

**Policy updates:**

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).

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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</table>
| Coronado (2015) | **Key points:**  
  • 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:**  
  • Longer-acting ESA 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 ESA in peritoneal and pediatric dialysis patients and to compare different longer-acting ESA (such as darbepoetin). |
| Bath (Cochrane, 2013) | **Key points:**  
  • Randomized controlled trials (RCTs), September 2012.  
  • 11 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) | **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.  
  • ESAs with great caution, if at all, in patients with active malignancy. |
| UK National Institute for Clinical Excellence | **Key points:**  
  • Published literature, – 2009. |
| (NICE) (2011) Anemia in chronic kidney disease | • ESAs should not be initiated in iron deficiency without first managing the deficiency.  
• Iron-replete patients: individualized discussion/balancing of ESA risk vs. benefit, followed by agreed interval for therapy assessment. |
| --- | --- |
| Buckley (2013) Clinical and cost effectiveness of an institutional erythropoietin utilization management program | **Key points:**  
• Pre-/post-implementation analysis of 795 patients (chronic kidney disease, HIV/AIDS, cancer) at one institution (2010 – 2011).  
• 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 (AHRQ, 2013) Epoetin and darbepoetin for anemia in cancer patients | **Key points:**  
• 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) Economic evaluation: nurse-vs. physician-driven anemia management protocols in hemodialysis | **Key points:**  
• 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 (Cochrane, 2012) Early erythropoietin for preventing red cell transfusion in preterm and/or low birth weight infants | **Key points:**  
• RCTs, May 2012.  
• 27 trials (2,293 preterm infants).  
• Early EPO reduced risk for red cell transfusions but reductions are small and of limited 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 ESAs 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 g/L.  
• Red cell transfusions also an option.  
• No studies in anemic myeloma, non-Hodgkin’s lymphoma or chronic lymphocytic leukemia in absence of anemia. |
| Lambin (Cochrane, 2009) Erythropoietin as adjuvant treatment for head and neck cancer | **Key points:**  
• RCTs, – 2009; radiation, with/without erythropoietin.  
• Five trials (1,397 patients).  
• Significantly worse survival with epoetin than radiation alone. |
<table>
<thead>
<tr>
<th><strong>Hayes (2008)</strong></th>
<th>Erythropoietin should not be administered to head and neck cancer patients outside a research setting.</th>
</tr>
</thead>
</table>
| **Cody (Cochrane, 2005)** | **Key points:**  
  - Two recent studies: breast or advanced cervical cancer patients receiving ESAs: shorter survival or more rapid tumor growth. |

**References**

**Professional society guidelines:**


**Peer-reviewed references:**


Cody JD, Daly C, Campbell MR, Khan I, et al. Recombinant human erythropoietin for chronic renal


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**

LCD # L34165: ERYTHROPOIETIN Stimulating Agents (ESA). Noridian Healthcare Solutions: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34165&ver=6&CovSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=erythropoietin&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAACAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34165&ver=6&CovSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=erythropoietin&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAACAAAAAA%3d%3d&). Accessed November 14, 2016.


LCD # L34255: Drugs and Biologicals: ERYTHROPOIETIN Analogues. Cahaba Government Benefit Administrators: [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34255&ver=6&CovSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=erythropoietin&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAACAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34255&ver=6&CovSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=erythropoietin&KeyWordLookUp=Title&KeyWordSearchType=And&list_type=ncd&bc=gAAAAACAAAAAA%3d%3d&).
**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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<th>CPT Code</th>
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<tr>
<td>D63.1</td>
<td>Anemia in chronic kidney disease</td>
<td></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>
<td></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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<tr>
<td>N18.6</td>
<td>End stage renal disease</td>
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<tr>
<th>HCPCS Code</th>
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<tbody>
<tr>
<td>J0882</td>
<td>Injection, darbepoetin alfa (ESRD on dialysis)</td>
<td></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 formulary criteria**

**Prior authorization criteria:**

EPOGEN® (epoetin alfa): 2,000 units/mL; 3,000 units/mL; 4,000 units/mL; 10,000 units/mL; 20,000 units/mL; 40,000 units/mL.

**Prior authorization criteria for approval: Administration of Epogen® in ESRD patients treated at dialysis centers:**

- Patient is being treated at a dialysis center.
- The necessary lab work (listed below) is documented on the PA form or submitted with request:
  - 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.
- History of Epogen® usage.

If all the above criteria are not met, the request is referred to a medical director for medical necessity review. If all the above conditions are met, the patient is placed into one of the following categories based on diagnosis:

- Epogen® treatment naïve with normal iron status (Section A).
- Epogen® treatment naïve with iron deficiency (Section B).
- Receiving Epogen® treatment with normal iron status (Section C).
- Receiving Epogen® treatment with iron deficiency (Section D).

**Section A: Epogen® treatment naïve with normal iron status (TSAT > 20 percent and Ferritin > 100 ng/mL):**

- The patient has a hemoglobin < 10 g/dL and/or hematocrit < 33 percent.
- Epogen® dosing is being initiated at 100 units/kg three times a week (TIW) or less.

If all the above conditions are met, the request will be approved with a three-month duration; if all the above criteria are not met, the request is referred to a medical director for medical necessity review.

**Section B: Epogen® treatment naïve with iron deficiency (TSAT < 20 percent and Ferritin < 100 ng/mL):**

- The patient has a hemoglobin < 10 g/dL and/or hematocrit <33 percent.
- The patient is in the process of receiving iron supplementation (i.e., 25 – 125 mg IV once weekly or >200 mg elemental iron orally daily).
- The patient’s Epogen® dose is less than or equal to 100 units/kg TIW.

If all the above conditions are met, the request will be approved with a two-month duration to allow follow-up on outcome of iron supplementation; if all the above criteria are not met, 50,000 units of Epogen® per month will be authorized and the request is referred to a medical director for medical necessity review.

**Section C: Existing therapy with Epogen® with normal iron status (TSAT > 20 percent and Ferritin > 100 ng/mL):**

- The patient has a hemoglobin < 12 g/dL and/or hematocrit < 36 percent.
- The patient’s hematocrit increased more than 8 percent in the past month, or Hgb increased by more than 1 g/dL in a two-week period, after starting the current dose, and the Epogen® dose has been reduced by at least 25 percent compared to the last course of therapy, and therapy was withheld for one to two weeks.
- If the patient’s Hgb/Hct is below target range after receiving therapy for at least four weeks and the dose is the same as last month or was increased by no more than 25 percent of the previous dose.
- If the patient’s current Epogen® dose was started less than eight weeks ago and their hematocrit has increased by less than 4 percent over the past two weeks or less than 8 percent over the last four weeks, and the ordered dose of Epogen® is the same as last month or less.
• If the patient’s hemoglobin is in target range (10 – 12 g/dL) and the ordered dose is either reduced or the same dose as the previous month.
• The ordered dose is not an increase in dosage that is within four weeks of last dosage change or start of therapy, with a medical reason provided for an early increase.
• If the patient’s hemoglobin exceeds 12 g/dL despite dose reduction, the Epogen® dose was withheld until hemoglobin dropped to 12 g/dL or less and the ordered Epogen® dose was reduced by 25 percent.
• If the dose is greater than 300 units/kg TIW, then documentation (within the past two months) of iron maximum supplementation, documentation of patients TSAT >20 percent and ferritin >100 ng/mL (within the past two months) was submitted from a hematologist recommending the current dose if all reversible causes for Epogen® resistance have been ruled out.

If all the above conditions are met, the request will be approved with a three-month duration; if all the above criteria are not met, the request is referred to a medical director for medical necessity review.

Section D: Existing therapy on Epogen® with iron deficiency (TSAT < 20 percent and Ferritin < 100 ng/mL):
• The patient has a hemoglobin < 12 g/dL and/or hematocrit < 36 percent.
• The patient is currently receiving iron supplementation (i.e., 25 – 125 mg IV once weekly or > 200 mg elemental iron orally daily).
• The ordered dose is an increase in dosage within one month’s time of last dosage change or start of therapy, and a medical reason was provided for an early increase.
• The Epogen® dose is less than or equal to 100 units/kg TIW.

If all the above conditions are met, the request will be approved with a two-month duration to allow follow-up on outcome of iron supplementation; if all the above criteria are not met, the request is referred to a medical director for medical necessity review.

FDA indication:
• Treatment of anemia of chronic renal failure patients.
• Treatment of anemia in zidovudine-treated HIV-infected patients.
• Treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown reduction in the need for RBC transfusion in patients with metastatic, nonmyeloid malignancies receiving chemotherapy for a minimum of two months.
  – Epogen® is not indicated for use in patients receiving hormonal agents, therapeutic biologic products or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
  – Epogen® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of Epogen® on progression-free and overall survival.
  – Epogen® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding.
  – Procrit® use has been demonstrated in controlled clinical trials to improve
symptoms of anemia, quality of life, fatigue or patient well-being.

- Treatment of anemic patients (Hgb > 10 to < 13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogenic blood transfusion.

**Dosage and administration:**

**CKD patients:**

<table>
<thead>
<tr>
<th>General Therapeutic Guidelines in CKD Patients for Epoetin Alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting dose</strong>&lt;br&gt;(Initiate Epogen® treatment when the hemoglobin level is less than 10 g/dL)</td>
</tr>
<tr>
<td><strong>Maximum dose — (with normal iron stores)</strong>&lt;br&gt;Intravenous administration</td>
</tr>
<tr>
<td>****Doses greater than maximum doses require hematologist consultation and recommendation.</td>
</tr>
<tr>
<td><strong>Reduce dose by 25% when:</strong></td>
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<tr>
<td><strong>Dose should be temporarily withheld when:</strong></td>
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<tr>
<td><strong>Increase dose up to 25% of previous dose if:</strong></td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
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<tr>
<td><strong>Suggested target hemoglobin</strong></td>
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</tbody>
</table>

*Dose adjustment should not be made more frequently than once a month, unless clinically indicated.*

**References**


Revision/review date: 8/2013
Associated policy: Prior Authorization of Medications 236.200

**NOTE:** Physician review must override criteria when, in his or her professional judgment, the requested item is medically necessary.