Clinical Policy Title: Erythropoietin-stimulating agents for chronic kidney disease

Clinical Policy Number: CCP.1088

Effective Date: June 1, 2015
Initial Review Date: February 19, 2014
Most Recent Review Date: January 8, 2019
Next Review Date: January 2020

Related policies:

CCP.1211 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-stimulating agents for treating anemia associated with chronic kidney disease\(^1\) to be clinically proven and, therefore, medically necessary to reduce the need for red blood cell transfusion when all of the following criteria are met (Kidney Disease: Improving Global Outcomes, 2012a; U.S. Food and Drug Administration, 2011, 2017a, 2017b, 2018):

- Member has adequate iron stores (e.g., serum ferritin > 100 µg/L or serum transferrin saturation > 20 percent).
- All other correctable causes of anemia (e.g., vitamin deficiency, metabolic or chronic

\(^1\) Defined as abnormalities of kidney structure or function (glomerular filtration rate < 60 mL/min/1.73 m\(^2\)) present for more than three months (Kidney Disease: Improving Global Outcomes, 2012b).
inflammatory conditions, or bleeding) have been addressed and are treated concurrently as indicated.

- Clinical indications, in accordance with U.S. Food and Drug Administration product labelling or guideline-directed care:
  - For members on dialysis, initiate therapy when hemoglobin < 10 g/dL. Continue therapy if hemoglobin < 11 g/dL.
  - For members not on dialysis, initiate or continue therapy when hemoglobin < 10 g/dL, the rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion, and the goal is to reduce the risk of alloimmunization and/or other red blood cell transfusion-related risks.
  - Pediatric patients ages 1 month or older regardless of dialysis status, initiate therapy when hemoglobin < 10 g/dL, or continue therapy to maintain target hemoglobin threshold from 11.0 g/dL to 12.0 g/dL.
  - For maintenance therapy, higher target hemoglobin thresholds may be chosen if the improvements to quality of life outweigh the increased cardiovascular risks associated with maintaining higher target thresholds.

For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.

**Limitations:**

Erythropoietin-stimulating agent therapy administered on the same day as dialysis is considered an integral part of the dialysis. It is not eligible as a separate and distinct service.


- In pediatric members less than one month old, as its safety and effectiveness has not been established in this population.
- In members with anemia due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, or bone marrow fibrosis.
- For immediate correction of severe anemia.


- Uncontrolled hypertension.
- Pure red cell aplasia that begins after treatment or other erythropoietin protein drugs.
- History of serious allergic reactions, including anaphylaxis, to components of erythropoietin-stimulating agents (e.g., known hypersensitivity to human albumin).
- Conditions that decrease therapeutic effectiveness (e.g., hemoglobinopathies, bone marrow failure, known erythropoietin-type resistance).
• Conditions where the risks associated with erythropoietin-stimulating agents may outweigh the benefits (e.g., previous or current malignancy, previous stroke).

Multiple-dose vials of erythropoietin-stimulating agents containing benzyl alcohol are not medically necessary for use in neonates, infants, pregnant women, and lactating women (U.S. Food and Drug Administration, 2017a, 2017b, 2018).

**Alternative covered services:**

Guideline-directed patient evaluation and management by a network health care provider.

**Background**

Kidney damage can cause a reduction in erythropoietin production with resultant anemia. Inflammatory states and deficiencies in iron, vitamin B12, and folate are treatable causes of anemia, and their correction can reduce the severity of anemia and enhance the effectiveness of other treatments for anemia.

Erythropoiesis-stimulating agents are synthetic recombinant human erythropoietin used to replace insufficient endogenous erythropoietin production related to chronic kidney disease progression and other disease states. The goal of therapy is to use the lowest dose needed to stabilize hemoglobin levels to minimize the need for red blood cell transfusion. In the United States, available synthetic erythropoiesis-stimulating agents are epoetin alfa, epoetin beta, and darbepoetin alfa (U.S. Food and Drug Administration, 2017a, 2017b, 2018).

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- The Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.

We conducted searches on October 25, 2018. Search terms were: “erythropoietin,” “kidney failure, chronic” (MeSH), “hematinetics” (MeSH), and “erythropoietin” (MeSH).

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 inconclusive. Two Cochrane reviews found a paucity of evidence to support either early versus delayed erythropoietin administration for end-stage renal disease (Coronado, 2015) or to endorse longer intervals of administration except in the setting of conventional adult renal hemodialysis (Hahn, 2014).

Erythropoiesis-stimulating agents are indicated after all correctable causes of anemia (including iron deficiency and inflammatory states) have been addressed (U.S. Food and Drug Administration, 2017a, 2017b, 2018). Supplemental iron therapy may be indicated during a course of erythropoiesis-stimulating agent therapy (i.e., when serum ferritin < 100 µg/L or serum transferrin saturation < 20 percent). The majority of patients with chronic kidney disease will require supplemental iron during the course of erythropoiesis-stimulating agent therapy.

The thresholds for diagnosing anemia differ from target thresholds for treating anemia, and target hemoglobin levels on erythropoiesis-stimulating agent therapy continue to evolve. According to the U.S. Food and Drug Administration (2011), several randomized controlled trials found that target hemoglobin levels > 11 g/dL increased the risk of stroke, heart attack, heart failure, and thromboembolism without any additional benefit to patients. For persons with chronic kidney disease regardless of dialysis status, erythropoiesis-stimulating agent therapy can start when the hemoglobin level < 10 g/dL. Therapy should be lowered or stopped if the hemoglobin level approaches or exceeds 11 g/dL for persons on dialysis, and 10 g/dL for persons not on dialysis. Target hemoglobin thresholds for maintenance therapy in pediatric populations are less defined and should follow product labeling or guideline-directed care.

**Policy updates:**

In 2019, we added five systematic reviews and meta-analyses (Hahn, 2017; Roger, 2017; Saglimbene, 2017; Cody, 2016; Collister, 2016; Ferguson, 2015) and one guideline update (National Institute for Health and Care Excellence, 2015) to the policy. The new information demonstrates that erythropoietin-stimulating agents positively impact clinical outcomes, disease progression, and mortality. Hypertension and arthralgia were the most common adverse effects in adults and children. Health-related quality of life was not significantly different using higher target hemoglobin thresholds, and attempts to define the optimal agent, timing for initiation, and dosing of erythropoietin in patients with any stage of chronic kidney disease remain inconclusive.

The Kidney Disease: Improving Global Outcomes (2012a) and National Institute for Health and Care Excellence (2015) guidelines emphasize the importance of treating correctable causes of anemia, including iron deficiency, before initiating erythropoietin-stimulating agents in persons with chronic
kidney disease. Optimizing iron therapy before and during erythropoietin-stimulating agent therapy can significantly reduce the dosage needed to treat anemia and its associated adverse effects (Roger, 2017).

This policy on erythropoiesis-stimulating agent therapy was modified: 1) to emphasize the importance of treating correctable causes of anemia prior to therapy; 2) to incorporate U.S. Food and Drug Administration-recommended thresholds for initiating and maintaining adequate hemoglobin during therapy; and 3) to add contraindications from product labelling to the Limitations section.

The policy ID was changed from CP# 00.02.07 to CCP.1088.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, methods, recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn (2017)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Short-acting erythropoiesis-stimulating agents for anemia in pre-dialysis patients Cochrane review</td>
<td>Systematic review of 14 randomized controlled trials (n = 2,616 patients) and meta-analysis of seven randomized controlled trials assessing the benefits and harms of different routes, frequencies, and doses of epoetin alpha, epoetin beta, and other short-acting epoetins for anemia in adults and children with chronic kidney disease not receiving dialysis; nine studies were multi-centered and two studies involved children. Overall quality: low with high risk of bias in most studies. Poor reporting of adverse events, mortality, and quality-of-life data. Low-quality evidence suggests epoetin alpha given at higher doses for extended intervals (two or four weekly) is non-inferior to more frequent dosing intervals in maintaining final hemoglobin levels with no significant differences in adverse effects in non-dialyzed patients. For other epoetins, inconclusive evidence or product withdrawn.</td>
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<tr>
<td>Roger (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Intravenous iron and erythropoiesis-stimulating agents in hemodialysis</td>
<td>Systematic review and meta-analysis of seven randomized controlled trials evaluating intravenous iron and erythropoiesis-stimulating agents in patients on hemodialysis for end-stage kidney disease. Optimal iron therapy was defined as dosing of intravenous iron in concordance with the Kidney Disease Improving Global Outcomes (2012) guideline. Optimal intravenous iron usage resulted in an average reduction in erythropoiesis-stimulating agents dosage of 31% (range -8% to -55%), which may reduce the adverse effects associated with higher dosages. Suboptimal iron use may require higher erythropoiesis-stimulating agent dosing to manage anemia.</td>
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<tr>
<td>Saglimbene (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Continuous erythropoiesis receptor activator for the anemia of chronic kidney disease</td>
<td>Systematic review and meta-analysis of 27 randomized controlled trials of at least three months' duration (n = 5,410 total adults with any stage of chronic kidney disease): seven studies of 1,273 participants not on dialysis; 19 studies of 4,209 participants on dialysis; and one study of 71 kidney transplant recipients. No studies of children were found. Compared continuous erythropoiesis receptor activator to other erythropoiesis receptor</td>
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<tr>
<td>Citation</td>
<td>Content, methods, recommendations</td>
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| Cochrane review       | activators (darbepoitin alfa [nine studies], epoetin alfa versus beta [nine studies], or both [two studies]); placebo (one study); standard care; or to different dosing strategies [five studies] of continuous erythropoiesis receptor activator. Treatment duration = 24 weeks on average.  
- Overall quality: low with high or unclear risk of bias from allocation concealment and blinding of outcomes.  
- Compared to epoetin alfa/beta or darbepoetin alfa, continuous erythropoiesis receptor activator achieved comparable health outcomes in mortality, major adverse cardiovascular events, hypertension, need for blood transfusion, and additional iron therapy. Insufficient evidence compared to placebo.  
- Different doses or frequencies (twice versus once monthly) of continuous erythropoiesis receptor activator administration resulted in no significant differences in health outcomes (all-cause mortality, hypertension, or blood cell transfusions).  
- Health-related mortality, hypertension, or blood cell transfusions not reported. |
| Cody (2016)            | **Key points:**  
- Systematic review and meta-analysis of 19 randomized or quasi-randomized controlled trials (n = 993 participants) of the pre-dialysis treatment effects of recombinant human erythropoietin.  
- Overall quality: low with unclear risk of bias. Most studies published prior to 2000.  
- Recombinant human erythropoietin improved hemoglobin (mean difference 1.90 gm/L, 95% confidence interval -2.34 to -1.47) and hematocrit (mean difference 9.85%, 95% confidence interval 8.35 to 11.34), and decreased the number of patients requiring blood transfusions (relative risk 0.32, 95% confidence interval 0.12 to 0.83).  
- Limited data reporting improvement in quality of life or exercise capacity.  
- No statistically significant difference in measures of disease progression.  
- No significant increase in adverse events. |
| Collister (2016)       | **Key points:**  
- Systematic review of 17 randomized controlled trials (13 trials reported SF-36 outcomes and four reported Kidney Dialysis Questionnaire outcomes); in patients not on dialysis (n = 12 trials), those on dialysis (n = 4 trials), or a mixed sample (n = 1 trial).  
- Overall quality: low risk of bias in only four of 13 studies, statistically significant heterogeneity and possible publication bias.  
- Pooled analyses suggest higher hemoglobin targets resulted in no statistically or clinically significant differences in health-related quality-of-life domains. Differences were further attenuated in studies at low risk of bias and in subgroups of dialysis recipients. |
| Ferguson (2015)        | **Key points:**  
- Systematic review of seven studies evaluating the cost-effectiveness of erythropoietin-stimulating agents compared to red blood cell transfusions, lower hemoglobin targets, or no erythropoietin-stimulating agent in patients with kidney failure on dialysis.  
- There is substantial variability in reported cost/quality-adjusted life-year ratios (range USD 931 to 677,749) comparing erythropoietin-stimulating agents to red blood cell transfusions (five studies).  
- Heterogeneous results suggest higher hemoglobin targets to be both dominant and... |
<table>
<thead>
<tr>
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</thead>
</table>
| **UK National Institute for Health and Care Excellence (2015)** | Anemia in chronic kidney disease | **Key points:**  
- 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.  
- Insufficient evidence to determine superiority of erythropoiesis-stimulating agents. Choice should consider the patient's preferences and dialysis status, the route of administration, and local availability.  
- Individual aspirational hemoglobin ranges should take into account patient preferences, symptoms and comorbidities, and the required treatment. |
| Hahn (2014) | Frequency of administration of erythropoiesis-stimulating agents for anemia of end-stage kidney disease in dialysis patients. | **Key points:**  
- Longer-acting erythropoiesis-stimulating agents administered at one- to four-week intervals are non-inferior to recombinant human erythropoiesis-stimulating agents given one to three times per week in terms of achieving hemoglobin targets.  
- There are no significant differences in adverse events in hemodialysis patients attributable to either agent. |
| Kidney Disease: Improving Global Outcomes (2012a) | Anemia in chronic kidney disease | **Key points:**  
- Address all correctable causes of anemia (iron deficiency, inflammation) first.  
- Balance potential benefits (reducing blood transfusions and anemia-related symptoms) against risks (stroke, vascular access loss, and hypertension).  
- The hemoglobin level and its rate of decline and response to iron therapy should dictate frequency of hemoglobin monitoring regardless of chronic kidney disease stage.  
- Recommended hemoglobin thresholds for initiating epoetin therapy:  
  - Adults not on dialysis < 10.0 g/dL.  
  - Adults on dialysis: 9.0 – 10.0 g/dL.  
  - For pediatric patients, insufficient data to recommend specific target threshold for initiating therapy, other than consider the balance of potential benefits and harms.  
- Recommended hemoglobin thresholds for epoetin maintenance therapy:  
  - Adults: < 11.5 g/dL.  
  - Pediatric patients: 11.0 to 12.0 g/dL.  
- Higher thresholds can be individualized to improve quality of life balancing higher risk. |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Roger SD, Tio M, Park HC, et al. Intravenous iron and erythropoiesis-stimulating agents in haemodialysis:


**U.S. Food and Drug Administration:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

- L36276 Erythropoiesis Stimulating Agents.

- A56100 Erythropoiesis Stimulating Agents L36276 Coding Guidelines.

- L34356 Erythropoiesis Stimulating Agents (ESA).

- L34633 Erythropoiesis Stimulating Agents (ESAs).
A52377 Erythropoiesis Stimulating Agents (ESA) – Supplemental Instructions Article.

**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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<thead>
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<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>96372,96374-96376</td>
<td>Therapeutic, prophylactic, or diagnostic injection</td>
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<td>D63.1</td>
<td>Anemia in chronic kidney disease</td>
<td></td>
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<tr>
<td>N18.1-N18.9</td>
<td>Chronic kidney disease (CKD)</td>
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<td>J0881</td>
<td>Injection, darbepoetin alfa, 1 mcg (non-ESRD use)</td>
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<td>J0882</td>
<td>Injection, darbepoetin alfa (ESRD on dialysis)</td>
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<td>J0885</td>
<td>Injection, epoetin alfa, (for non-ESRD use), 1,000 units</td>
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<td>J0887</td>
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<tr>
<td>Q5105</td>
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<tr>
<td>Q5106</td>
<td>Injection, epoetin alfa, biosimilar, (Retacrit) (for non-esrd use), 1000 units</td>
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