Erythropoiesis-Stimulating Agents (ESA's)

Medicare Advantage Medical Policy No.: MNG-013

The Health Plan reserves the right to amend this policy and procedure at any time. Exceptions to this policy and procedure will be made on a case-by-case basis at the total discretion of the Health Plan.

Effective Date: April 16, 2024

Instructions for use

This policy serves to provide guidance in determining coverage based on medical necessity. It also gives a list of resources used to create these guidelines. Medical necessity determinations will be made in accordance with generally accepted standards of medical practice, taking into account credible scientific evidence published in peer reviewed medical literature generally recognized by the relevant medical community, physician specialty society recommendations, and the views of the physicians practicing in relevant clinical areas, and other relevant factors, as they relate to the member's clinical circumstances.

Medicare Advantage Members

Coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria will be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of the coverage criteria and is to be used by all plans and lines of business unless Federal or State law, contract language, including member or provider contracts, take precedence over the policy.

Basic Requirements for Clinical Appropriateness:

1. Before diagnostic or therapeutic intervention, a clinician must confirm the diagnosis or establish the likelihood based on a history and physical exam and, when appropriate, a review of laboratory studies, previous diagnostic testing and response to any prior interventions, specifically relevant to the clinical situation.
2. An alternative treatment or other appropriate intervention should not offer any greater benefit based on standards of medical practice and/or current literature.
3. The potential benefit to the patient should outweigh the risk of the diagnostic or therapeutic intervention.
4. A reasonable likelihood of the intervention changing management and/or leading to an improved outcome for the patient must exist, based on the clinical evaluation, current literature and standards of medical practice.

If these requirements are not apparent in the request for authorization, including the clinical documentation provided, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous ordering of multiple diagnostic or therapeutic interventions and/or repeated diagnostic or therapeutic interventions in the same anatomic area may be denied, unless individual circumstances support the medical necessity of performing interventions simultaneously or repeatedly. This should be apparent in the clinical documentation or in peer-to-peer conversations.

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Erythropoiesis-Stimulating Agents (ESA's): epoetin alfa (Procrit® or Epogen®), epoetin alfa-epbx (Retacrit™), darbopoetin alfa (Aranesp®), and pegylated epoetin beta (Mircera®) are covered for all FDA approved indications. All ESA's referenced above are covered at parity status.

When Services are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of epoetin alfa (Epogen or Procrit)‡, epoetin alfa-epbx (Retacrit)‡, darbopoetin alfa (Aranesp)‡ or pegylated epoetin beta (Mircera)‡ for non-FDA approved indications to be investigational.* Off label use may be considered with appropriate clinical documentation.

Based on review of available data, the Health Plan considers injection of allograft (e.g., VIA Disc Matrix) into the intervertebral disc for the treatment of degenerative disc disease as not covered, as it is considered investigational.*

Background/Overview

EPO (erythropoietin) is a glycoprotein hematopoietic growth factor synthesized by cells near the renal tubules in response to changes in the blood oxygen concentration. When a patient is anemic, the ability of the blood to carry oxygen is decreased. An oxygen-sensing protein in the kidney detects the decrease in blood oxygen concentration and induces the production of erythropoietin, which then acts on the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood hemoglobin (Hgb) concentrations. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin results in anemia in several disease processes, including chronic kidney disease, many types of cancer treatment, other chronic diseases, and use of certain drugs.

Erythropoiesis-stimulating agents (ESAs) are produced using recombinant DNA technologies. They were initially developed as replacement therapy to treat anemia due to endogenous erythropoietin deficiency that commonly occurs in patients with chronic renal failure secondary to chronic kidney disease. Patients with chronic renal failure will become severely anemic and experience severe fatigue and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia by ESA treatment of patients with chronic renal failure reduces the need for red blood cell (RBC) transfusions and enhances physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms: Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B12) essential for RBC production. Antibodies and/or immunoregulatory abnormalities associated with certain tumor types (most commonly, B cell malignancies) may cause increased erythrocyte destruction (hemolysis). Tumors may cause blood loss via tissue invasion, for example gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. However, marrow dysfunction can occur even in the absence of frank invasion. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization, as well as a direct suppression of RBC production. Cancer treatments also may cause anemia: radical cancer surgery can result in acute blood loss; and radiotherapy and many cytotoxic chemotherapeutic agents suppress marrow to varying degrees. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage; antimetabolites damage DNA indirectly; and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

Red blood cell transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, this approach carries risk for several potential adverse events. The highest adverse event risk (1 per 432 whole blood units transfused) is for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (e.g., type mismatch) are estimated to occur at a rate of 1 per 5,000 to 10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), HIV (<1 in 1,000,000), and bacterial contaminants (1 per 10,000 to 100,000) have fallen dramatically since the early 1990s. Therefore, although the initial impetus to commercialize erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those risks. Nonetheless, blood shortages, transfusion errors, and risks of alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Four ESA products (and one biosimilar) have been licensed in the United States: Epoetin alfa is manufactured, distributed, and marketed by Amgen, Inc. under the proprietary name, Epogen. The same epoetin alfa product manufactured by Amgen Inc. is also marketed and distributed by Janssen Products, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit. Under a contractual agreement with Amgen, Janssen Products LP has rights to develop and market Procrit for any indication other than for treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all FDA-approved indications. A second ESA, darbepoetin alfa, is marketed solely by Amgen, under the

proprietary name, Aranesp. The third ESA product, peginesatide, was co-developed and commercialized by Affymax Inc. and Takeda Pharmaceuticals, who market it under the proprietary name, Omontys. In February 2013, Affymax, Takeda, and the FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. FDA currently lists peginesatide (Omontys) as discontinued. Pegylated-epoetin beta was FDA-approved in 2007 and is marketed outside the U.S. by Hoffmann-LaRoche under the proprietary name Mircera. In 2018, A biosimilar to Epogen and Procrit was released (Retacrit). Retacrit carries the same indications as Procrit and Epogen and is manufactured by Pfizer.

Epoetin alfa and epoetin beta have the same amino acid sequence as endogenous erythropoietin but differ from each other in glycosylation; clinical effects are considered interchangeable. Darbepoetin alfa is similar to endogenous erythropoietin but has 2 additional oligosaccharide chains. In contrast, peginesatide lacks any amino acid sequence homology to erythropoietin. It is a synthetic dimer of identical 21-amino acid peptides bound to a linker and to polyethylene glycol, with a total molecular weight of approximately 45,000 Da. (The molecular weight of endogenous erythropoietin is approximately 34,000 Da.) However, the epoetins, darbepoetin, and peginesatide all have pharmacologic actions similar to those of the endogenous hormone. Each binds to and activates the human erythropoietin receptor and thus increases the number of RBCs and the blood concentration of hemoglobin, when given to individuals with functioning erythropoiesis. Both epoetin alfas, pegylated-epoetin beta, and darbepoetin are FDA-approved to treat anemia in patients with CKD who are on dialysis or not on dialysis. Epoetin alfa and darbepoetin also are approved for other indications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The major regulatory timelines for approval actions pertaining to new indications are summarized next:

epoetin alfa (Epogen/Procrit):

- 1989: Approved for use in patients with anemia due to chronic renal failure.
- 1991: Approved for use in zidovudine-treated, HIV-infected patients.
- 1993: Approved for chemotherapy-induced anemia in patients with nonmyeloid malignancies.
- 1996: Approved for presurgical use in certain patients undergoing surgery darbepoetin alfa (Aranesp).
- 2001: Approved for use in patients with anemia due to chronic renal failure.
- 2002: Approved for chemotherapy-induced anemia in patients with nonmyeloid malignancies peginesatide (Omontys).
- 2012: Approved for use in adults with anemia due to chronic kidney disease who are on dialysis.
- 2013: Voluntary recall of all lots due to post marketing reports of serious hypersensitivity pegylated epoetin-beta (Mircera).
- 2007: Approved for use in patients with anemia due to chronic renal failure who are on dialysis or not on dialysis.

- 2009: Injunction prohibiting U.S. sales until mid- 2014 due to copyright infringement.
- 2014: Resumption of U.S. sales anticipated Epoetin alfa-epbx (Retacrit).
- 2018: Approved for same indications as Procrit and Epogen.

Centers for Medicare and Medicaid Services (CMS)

In July 2007, CMS released a Decision Memorandum on the use of ESAs for non-renal disease indications (CAG-00383N). Safety concerns such as thrombosis, cardiovascular events, tumor progression, and reduced survival, derived from clinical trials in several cancer and non-cancer populations, prompted CMS to review its coverage of ESAs. The CMS reviewed a large volume of scientific literature, including basic science research, to see if safety findings observed in RCTs could be reasonably explained in whole or in part by the actions of ESAs on normal or cancerous cells. Based on this review, CMS proposed conditions of coverage based on expression of EPO receptors. However, the scientific understanding of this mechanism is controversial and requires additional study. The CMS also reviewed comments on ESAs treatment of myelodysplastic syndrome (MDS), a precursor of acute myeloid leukemia (AML) in many patients. The CMS retains interest in these specific issues but does not differentiate ESA coverage by the EPO receptor status of the underlying disease and has decided to make no national coverage determination (NCD) at this time on ESAs in MDS. The CMS has determined that evidence is sufficient to conclude that ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA 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.
- Any anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers.
- 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 EPO-type resistance due to neutralizing antibodies.
- Anemia due to cancer treatment if patients have uncontrolled hypertension.

The CMS also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

- The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).
- The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150U/kg/3 times weekly for epoetin and 2.25mcg/kg/weekly for darbepoetin alpha.

Equivalent doses may be given over other approved time periods.

- Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is > 1g/dL (hematocrit > 3%).
- For patients whose hemoglobin rises < 1g/dL (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10g/dL after the 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1g/dl (hematocrit rise < 3% compared to pretreatment baseline by 8 weeks of treatment.
- Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1g/dL (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dl (or the hematocrit is < 30%.) Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
- ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Pegylated epoetin beta is not addressed in the Decision Memorandum or NCD.

This decision by CMS also allows local Medicare contractors to continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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Policy History

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Coding

The five-character codes included in this medical policy are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No Codes
HCPCS	J0881, J0882, J0885, J0887, J0888, J0890, Q4081, Q5105, Q5106
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

    1. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

    2. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.