Reference number(s)
5563-A

JURISDICTION SPECIFIC MEDICARE PART B

EPOGEN-PROCRIT-RETACRIT (epoetin alfa)

POLICY

I. COVERED USES

The indications below are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. Anemia in patients with non-myeloid malignancies where anemia is specifically due to concomitantly administered chemotherapy
B. Anemia related to end-stage renal disease (ESRD) and Stages IIIb, IV and V chronic kidney disease (CKD)
C. Anemia induced by AZT (Zidovudine) used in HIV/AIDS therapy
D. Anemia related to low prognostic risk myelodysplastic syndrome and some myeloproliferative neoplasms in select patients
E. Peri-surgical adjuvant therapy for purposes of allogenic RBC transfusion reduction

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions. For a complete list of requirements, please consult Billing and Coding: Erythropoiesis Stimulating Agents (A58982) and LCD – Erythropoiesis Stimulating Agents (L39237).

A. For patients receiving any erythropoiesis stimulating agent (ESA):
    1. All documentation must be maintained in the patient's medical record and made available to the contractor upon request.
    2. Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, dates of service[s]). The documentation must include the legible signature of the physician or non-physician practitioner responsible for and providing the care to the patient.
    3. The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must describe the service performed.
    4. For any ESA, the medical record must reflect that ESA therapy for the individualized patient is reasonable and necessary. The medical record must document the most recent blood pressure and demonstrate reasonable control not in significant excess of a baseline range for a given patient, weight in kilograms, date and results of hematocrit (HCT) or hemoglobin (Hb) level prior to the administration of ESA therapy, evidence of assessment ruling out other causative factors of anemia or, if causative factors are present, that they have been managed and that it is still necessary to initiate ESA (evaluation and treatment must occur at anytime after initiation of ESA as needed for lack of

responsiveness, where applicable). The dosage and route of administration (as well as frequency, where applicable) must be documented.
5. The medical record should reflect the clinical reason for dose changes and HCT levels outside the range of 30-36% (Hb levels 10-12 g/dL)
6. Relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures. The indication for ESA administration must be evident within the medical record.
7. Medical justification for any ESA doses that differ from FDA label instructions. Documentation of dose reductions, dose continuation at lowest dose to avoid recurrent RBC transfusions, and dose increases where applicable.
8. Pretreatment Hb/HCT results and iron storage laboratory results. In the case of low iron stores, documentation regarding treatment that was given in terms of repletion. Iron stores, as evidenced by a transferrin saturation of at least 20% and a ferritin level at least 100 ng/mL must be resulted in order to continue with ESA treatment. Where applicable, hematological parameters should be monitored at least weekly during therapy until Hb is stable and sufficient to minimize the need for transfusion, and then Hb should be monitored at least monthly; iron storage must be checked prior to dosage increases and at least every 3 months during ongoing ESA therapy.
9. There are very rare patients whose cardiac, pulmonary or other medical conditions warrant the use of ESAs to maintain a Hb/HCT higher than the FDA target levels discussed. Documentation to support this practice must be available upon request. (This instruction does not apply to ESA therapy for anemia related to cancer chemotherapy, which follow the rules mandated by the National Coverage Determination [NCD] 110.21.)

B. For dialysis patients:
   1. Use of the ESA for specific diagnoses indicating symptomatic anemia of chronic kidney disease (CKD) on dialysis
   2. Documentation must include dialysis schedule
   3. Most recent creatinine level within the past month prior to initiation or next dosing of ESA
   4. For ESRD patients on home dialysis, the following must be maintained in the medical record and available upon request: a care plan, evidence of home monitoring (including a record of the ESA supplied to the patient and a record of dose administered), patient instructions and patient selection protocol.
   5. If the initial dose of an ESA was administered in another setting (i.e. hospital, in a state outside our jurisdiction, or in another facility); subsequent office-administered ESA claims may prompt a Medicare Administrative Contractor request for documentation regarding clinical criteria supporting initial administration as well as the need to continue the ESA. This may require review of outside medical records and confirmation that needed pre-treatment lab results and evaluation were completed appropriately.

C. For non-dialysis patients:
   1. For CKD patients:
      i. Use of the ESA for specific diagnoses indicating symptomatic anemia of CKD not on dialysis
      ii. Most recent creatinine level within the past month prior to initiation or next dosing of ESA
      iii. Documentation must include stable baseline eGFR with the accompanying accurate, most specific stage of disease per ICD-10-CM
      iv. If the initial dose of an ESA was administered in another setting (i.e. hospital, in a state outside our jurisdiction, or in another facility); subsequent office-administered ESAs must still meet all requirements. This may require review of outside medical records and confirmation that needed pre-treatment lab results and evaluation were completed appropriately.
   2. For patients with anemia related to their myelodysplastic syndrome (MDS):

i. ESA will be used for symptomatic anemia or transfusion dependence and a Hb < 10 g/dL within one week of the initial ESA treatment
ii. The medical record must include the diagnostic bone marrow biopsy report with cytogenetic analysis, the date of initiation of ESA therapy, and documentation of the response to ESA administration via changes in Hb/HCT measurements and/or transfusion requirements
iii. Documented evaluation for other anemia contributing factors such as blood loss, hemolysis, renal failure, medications, nutritional deficiencies, thyroid dysfunction, autoimmune disorders and anemia of chronic disease
iv. Documentation of anemia related symptoms
v. Documentation of reasonable expectancy of longer survival with reduced need for transfusion support
vi. Serum EPO ≤ 500 mU/mL
vii. Documented Revised International Prognostic Scoring System (IPSS-R) result of 3 or less for very low, low risk MDS or IPSS-R result of 3.5 or less for an intermediate risk MDS or International Prognostic Scoring System (IPSS) score of 0-1 or WHO Prognostic Scoring System (WPSS) score of 0-2
viii. Narrative regarding ongoing response to therapy
ix. If the initial dose of an ESA was administered in another setting (i.e. hospital, in a state outside our jurisdiction, or in another facility); subsequent office-administered ESAs must still meet all requirements. This may require review of outside medical records and confirmation that need pre-treatment lab results and evaluation were completed appropriately.

3. For anemia in non-myeloid malignancies:
   i. Use of the ESA for symptomatic anemia due to antineoplastic chemotherapy
   ii. A diagnosis of non-myeloid malignancy (solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia)
   iii. An ESA should only be started if there is a minimum of two additional months of planned chemotherapy
   iv. ESAs should not be used in a patient with cancer receiving myelosuppressive chemotherapy when the anticipated outcome for the cancer is cure
   v. If the initial dose of an ESA was administered in another setting (i.e., hospital, in a state outside our jurisdiction, or in another facility); subsequent office-administered ESAs must still meet all requirements. This may require review of outside medical records and confirmation that need pre-treatment lab results and evaluation were completed appropriately.
4. For anemia related to treatment with zidovudine (AZT) for HIV/AIDS:
   i. Use of the ESA for symptomatic anemia due to AZT therapy
   ii. Zidovudine therapy at a dose ≤ 4200 mg/week
   iii. Endogenous baseline pre-transfusion serum EPO level ≤ 500 mUnits/mL
5. For peri-surgical adjuvant therapy to reduce allogenic transfusion:
   i. A presurgical Hb > 10 but < 13 g/dL
   ii. A high-risk for perioperative blood loss related to planned elective orthopedic hip or knee surgery with an expectation for 2 units or more of blood loss
   iii. Inability or unwillingness by the patient to donate autologous blood
   iv. A workup for anemia that suggests anemia of chronic disease
   v. Iron supplementation ongoing during the entire course of ESA
   vi. Deep vein thrombosis (DVT) prophylaxis ongoing during the entire course of ESA

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:

A. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
B. The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers
C. The anemia of cancer not related to cancer treatment
D. Any anemia associated only with radiotherapy
E. Prophylactic use to prevent chemotherapy-induced anemia
F. Prophylactic use to reduce tumor hypoxia
G. Patients with erythropoietin-type resistance due to neutralizing antibodies
H. Non-ESRD ESA services within the context of other medical conditions for which resolution would be reasonably expected prior to starting or continuing ESA administration (including, but not limited to: iron/vitamin B12/folate deficiencies, G6PD deficiency, pyridoxine deficiency, various forms of hemolysis, hereditary spherocytosis, and pure red cell aplasias).
I. Epoetin alfa is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.
J. ESA use within the context of uncontrolled hypertension.
K. ESA use to replace RBC transfusions in members who need immediate urgent correction of anemia.

IV. CRITERIA FOR APPROVAL

Note: The following causes of anemia should be considered, documented, and corrected before starting or continuing ESA therapy for any of the covered indications: iron deficiency; underlying infection, inflammatory or malignant processes; underlying hematological disease; hemolysis; vitamin deficiencies (e.g. folic acid or B12); blood loss- overt or occult; aluminum intoxication; osteitis fibrosis cystica; or pure red blood cell aplasia.

A. Anemia of end stage renal disease (ESRD) in a member on dialysis
Authorization of 12 weeks may be granted for treatment of anemia of ESRD in a member on dialysis when all of the following criteria is met:
1. Member has a diagnosis of end stage renal disease.
2. Hb < 10 g/dL or HCT < 30% at initiation of therapy.
3. The provider will document the most recent creatinine within the past month prior to initiation or next dosing of ESA.

B. Anemia of chronic kidney disease (CKD) in a member not on dialysis
Authorization of 12 weeks may be granted for treatment of anemia of CKD in a member not on dialysis when all of the following criteria is met:
1. Hb < 10 g/dL or HCT < 30% at initiation of therapy.
2. Glomerular filtration rate (GFR) < 45 mL/min/1.73m^2.
3. The provider will document the most recent creatinine within the past month prior to initiation or next dosing of ESA.

C. Anemia due to chemotherapy in members with non-myeloid malignancies
Authorization of 8 weeks may be granted for treatment of anemia due to chemotherapy in members with non-myeloid malignancies when all of the following criteria is met:
1. Diagnosis of a non-myeloid malignancy (solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia).

2. Hb level immediately prior to initiation of ESA treatment is < 10 g/dL (or HCT < 30%).
3. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

D. **Anemia related to treatment with zidovudine (AZT) for HIV/AIDS**
Authorization of 12 weeks may be granted for treatment of anemia related to AZT treatment for HIV/AIDS when all of the following criteria is met:
1. Hb < 10 g/dL or HCT < 30% at initiation of therapy.
2. The member's AZT dose ≤ 4200 mg/week.
3. The member has an endogenous baseline pre-transfusion serum EPO (sEPO) ≤ 500mU/mL.

E. Peri-surgical adjuvant therapy to reduce allogenic transfusion
Authorization of 30 days may be granted as peri-surgical adjuvant therapy to reduce allogenic transfusion when all of the following criteria are met:
1. Member is undergoing planned elective major hip or knee surgery.
2. Member has presurgical anemia with Hb between 10 and 13 g/dL at least 3 weeks prior to surgery.
3. Member is not a candidate for autologous blood transfusion or is unwilling to donate autologous blood.
4. Member's expectation for peri-operative blood loss is two units or more.
5. Member has undergone previous evaluation to ensure that the existing anemia is likely due to chronic disease rather than another reversible condition.

F. Anemia related to myelodysplastic syndrome (MDS)
Authorization of 12 weeks may be granted for treatment of anemia in members with MDS when all of the following criteria are met:
1. Member has a diagnosis of MDS confirmed by bone marrow aspiration and/or biopsy report.
2. Hb < 10 g/dL (or HCT < 30%) at initiation of therapy.
3. Member meets one of the following:
   i. IPSS-R score correlating to very low, low risk
   ii. IPSS-R correlating to a low score intermediate risk
   iii. IPSS score of low or intermediate-1 risk
   iv. WPSS score of very low, low or intermediate risk
4. Member has a pretreatment EPO ≤ 500 mU/mL.
5. Member meets one of the following:
   i. MDS without del(5q)
   ii. MDS with del(5q) and no chromosome 7 associated abnormalities, on or before starting lenalidomide
6. Member has documented anemia related symptoms such as fatigue, pallor, infection, bleeding or bruising or transfusion dependence.
7. Member has documentation of a reasonable expectancy of longer survival with a reduced need for transfusion support.

V. CONTINUATION OF THERAPY

Note: The following causes of anemia should be considered, documented, and corrected before starting or continuing ESA therapy for any of the covered indications: iron deficiency; underlying infection, inflammatory or malignant processes; underlying hematological disease; hemolysis; vitamin deficiencies (e.g. folic acid or B12); blood loss- overt or occult; aluminum intoxication; osteitis fibrosis cystica; or pure red blood cell aplasia.

A. Anemia of ESRD in a member on dialysis, Anemia of CKD in a member not on dialysis

Authorization of 12 weeks may be granted when all of the following criteria is met:
1. The goal of therapy is to maintain a stable Hb and HCT, with target ranges of 10-12 g/dL and 30-36% respectively.
2. The provider will document the most recent creatinine within the past month prior to next dosing of ESA.

B. Anemia due to chemotherapy in members with non-myeloid malignancies
Authorization of 12 weeks may be granted when all of the following criteria is met:
1. Hb < 10 g/dL or HCT < 30%
2. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

C. Anemia related to treatment with zidovudine (AZT) for HIV/AIDS
Authorization of 12 weeks may be granted when the goal of therapy is to maintain a stable Hb and HCT, with target ranges of 10-12 g/dL and 30-36% respectively.

D. Peri-surgical adjuvant therapy to reduce allogenic transfusion
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

E. Anemia related to myelodysplastic syndrome (MDS)
Authorization of 12 weeks may be granted when all of the following criteria is met:
1. The goal of therapy is to maintain a stable Hb and HCT, with target ranges of 10-12 g/dL and 30-36% respectively
2. ESAs should not be continued for more than twelve weeks if no response is observed.

VI. DOSAGE AND ADMINISTRATION

A. For anemia due to chemotherapy in members with non-myeloid malignancies, must meet all of the following, where applicable:
   1. The starting dose for ESA treatment is the recommended FDA label starting dose.
   2. Maintenance of ESA therapy is the starting dose if the Hb level remains below 10 g/dL (or HCT is < 30%) 4 weeks after initiation of therapy and the rise in Hb ≥ 1 g/dL (HCT ≥ 3%).
   3. For patients whose Hb rises < 1 g/dL (HCT rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose Hb remains < 10 g/dL after the 4 weeks of treatment (or HCT < 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 Hb rises < 1 g/dL (HCT rise < 3%) compared to pretreatment baseline by 8 weeks of treatment.
   4. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in Hb > 1 g/dL (HCT > 3%) over 2 weeks of treatment unless the Hb remains below or subsequently falls to < 10 g/dL (or the HCT is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.

B. For all other indications, the starting dose and subsequent dose adjustments must be in accordance with FDA-approved labeling or dosing provided in Billing and Coding: Erythropoiesis Stimulating Agents (A58982) or LCD – Erythropoiesis Stimulating Agents (L39237). Doses must be titrated according to the patient's response.

VII. REFERENCES

1. Erythropoiesis Stimulating Agents LCD (L39237) Original Version. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed August 15, 2022.
2. Billing and Coding: Erythropoiesis Stimulating Agents (ESA) (A58982) Version R2. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed September 29, 2022.
3. National Coverage Determination (NCD) 110.21 Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions Version 1. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed August 17, 2022.
4. Epogen [package insert]. Thousand Oaks, CA: Amgen Inc.; July 2018.
5. Procrit [package insert]. Horsham, PA: Janssen Products; July 2018.
6. Retacrit [package insert]. Lake Forest, IL: Hospira, Inc.; June 2020.