Erythropoiesis Stimulating Agents (ESAs) (Non-ESRD use: J0881, J0885, J0888), and (ESRD on dialysis use: Q5106, J0882, J0887, Q4081 and Q5105) – LCD L34633 and NCD 110.21

Indications and Coding Requirements:

Medicare covers erythropoietin stimulating agents (ESAs) to treat patients who:

- have one of the United States Food and Drug Administration (FDA) approved conditions; and
- have either symptomatic anemia or are transfusion dependent.

Medicare divides the FDA approved conditions into the following three groups, A, B and C. Each group has separate indications and required diagnosis codes.

HCPCS Procedure Codes:

1. Non-End Stage Renal Disease (ESRD) Codes: J0881, J0885, J0888
2. End Stage Renal Disease (ESRD) on Dialysis Codes: Q5106, J0882, J0887, Q4081, and Q5105

Group A: End Stage Renal Disease (ESRD) ON dialysis

1. The hemoglobin level prior to initiation of ESA treatment is less than 10 g/dL (or the hematocrit is less than 30%)
2. **Two** diagnoses are required:
   D63.1 Anemia in chronic kidney disease; ***AND***
   N18.6 End stage renal disease

Group B: Chronic Kidney Disease (CKD) NOT on dialysis

1. The hemoglobin level prior to initiation of ESA treatment is less than 10 g/dL (or the hematocrit is less than 30%)
2. Serum creatinine equal to or greater than 3, creatinine clearance less than 60 ml/min, or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2
3. **Two** diagnoses are required:
   D63.1 Anemia in chronic kidney disease
   AND one of the following:
   I12.0 Hypertensive CKD with stage 5 CKD or end stage renal disease
   I12.9 Hypertensive CKD with stage 1 through 4 CKD, or unspecified CKD
   I13.0 Hypertensive heart and CKD with heart failure and stage I through 4 CKD
   I13.10 Hypertensive heart and CKD without heart failure, with stage 1 – 4 CKD
   I13.11 Hypertensive heart and CKD without heart failure, with stage 5 CKD or ESRD
   I13.2 Hypertensive heart and CKD with heart failure and with stage 5 CKD, or ESRD
   N18.30 CKD, stage 3 unspecified
   N18.31 CKD, stage 3a
   N18.32 CKD, stage 3b
   N18.4 CKD, stage 4 (severe)
   N18.5 CKD, stage 5 (not requiring dialysis)

Group C: Indications other than renal disease

1. Anemia associated with cancer and related neoplastic conditions (for patients receiving chemotherapy)

   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:

   a. The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is less than 10 g/dL (or the hematocrit is < 30%)
   b. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/3 times weekly for epoetin and 2.25 mcg/kg/1 time weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.
   c. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is <30%) 4 weeks after the initiation of therapy and the rise in hemoglobin is >= 1g/dL (hematocrit >= 3%)
   d. For patients whose hemoglobin rises <1 f/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 < 1 g/dL (hematocrit rise <3%) compared to pretreatment baseline by 8 weeks of treatment.
   e. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/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.
   f. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

   Two diagnoses are required for medical necessity:
   D64.81 Anemia due to antineoplastic chemotherapy, **AND**
   _____ Diagnosis for site and type of non-myeloid malignancy

2. Anemia related to therapy with Zidovudine (AZT) and/or other nucleoside Reverse Transcriptase Inhibitors (NRTI) therapy for acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC)

   a. The hemoglobin level prior to administration of ESA treatment is < 10 g/dL (or the hematocrit is < 30%)
   b. **Two** diagnoses are required:
      D61.1 Drug-induced aplastic anemia
      AND one of the following:
      B20 Human immunodeficiency virus [HIV] disease
      B97.35 Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere

3. Anemia associated with chemotherapeutic medications when medically necessary for a **non-cancer diagnosis** or following stem cell transplantation and associated immunosuppression
    a. The hemoglobin level prior to administration of ESA treatment is <10 g/dL (or the hematocrit is < 30%)
    b. **Requires multiple diagnoses**:
    D64.81 Anemia due to antineoplastic chemotherapy, **AND**
    _____ Diagnosis for any additional drug therapy, i.e., long-term (current) use of injectable non-insulin antidiabetic drugs or other long-term (current) drug therapy, **AND**
    _____ Diagnosis for the non-cancer condition being treated

4. Myelodysplastic Syndrome (MDS)
    a. Clinical indications for ESA therapy for patients with MDS include:
    Have a confirmed diagnosis of MDS with a bone marrow biopsy
    The anemia is symptomatic
    There is a reasonable expectancy of longer survival
    Therapy will end or reduce the need for transfusions
    b. One week before the initial injection, the hemoglobin is <= 10 g/dL, or the hematocrit is <= 30%
    c. Stop erythropoietin analogs if after two months of treatment either or both occurs:
        - There is no significant increase in Hgb/HCT
        - There is a significant decrease in transfusion requirements
    d. Diagnosis for the specific type of MDS:
    D46.0 through D46.9 Myelodysplastic syndrome

5. Myelofibrosis
    Primary myelofibrosis (PMF) may be treated with ESA drug therapy with the following indications:
    a. Confirmed diagnosis by bone marrow pathology
    b. Diagnosis for the specific type of myelofibrosis:
    D75.81 Myelofibrosis (or *see link at the end of document to LCD Article A56795 for the complete list of myelofibrosis diagnoses*)

6. Anemia of chronic disease (anemia of inflammatory disease)
    Medicare will cover the use of epoetin alfa or darbepoetin alfa for the refractory anemia of chronic disease for patients with Rheumatoid Arthritis, Systemic Lupus Erythematosis, Chronic Hepatitis C, Crohn's Disease and Ulcerative Colitis when one of the conditions listed below in A is met along with both B and C criteria:
    a. At least **one** of the conditions below:
        - Low or normal serum iron
        - Low or normal iron binding capacity
        - Normal or elevated serum ferritin
        - Adequate iron stores in bone marrow
    b. The pretreatment HCT level is 30 percent or less and/or if the patient has been transfusion dependent
    c. The pretreatment erythropoietin level is 100 mU/mL or less
    d. **Two** diagnoses are required:
    D63.8 Anemia in other chronic diseases classified elsewhere, **AND**
    _____ Diagnosis for the chronic inflammatory disease (Rheumatoid Arthritis, Systemic Lupus Erythematosis, Chronic Hepatitis C, Crohn's disease, or Ulcerative Colitis)

7. Prophylactic pre-operative use for allogenic blood transfusions prior to elective hip or knee replacement surgery
    a. Epoetin alfa or Darbepoetin alfa are covered for use in specific patients prior to surgery to reduce risk of transfusion:
        - who are undergoing hip or knee surgery
        - have an anemia with a hemoglobin between 10 and 13 gm/dL
        - must have a lead time of at least 3 weeks prior to surgery
        - are not candidates for autologous blood transfusion
        - are expected to lose more than 2 units of blood
        - have had a work-up so that their anemia appears to be that of chronic disease
    b. A weekly dose regimen for 3 weeks prior to surgery (e.g., days 21, 14, 7) an on day of surgery will be covered
    c. The components listed above must be documented in the medical record
    d. Deep venous thrombosis prophylaxis is recommended
    e. **Two** diagnoses are required:
    D63.8 Anemia in other chronic diseases classified elsewhere, **AND**
    Z01.818 Encounter for other preprocedural examination

8. Prophylactic pre-operative use for reduction of allogenic blood transfusions prior to elective noncardiac or nonvascular surgery
    a. Epoetin alfa-epbx (biosimilar) is covered for use in specific patients who are at high risk for perioperative blood loos prior to surgery to reduce risk of transfusion:
        - Who are undergoing elective, noncardiac or nonvascular surgery
        - Have an anemia with a hemoglobin > 10 to < 13 gm/dL
        - Are not candidates for autologous blood transfusion
    b. The recommended Epoetin alfa-epbx (biosimilar) regimens are:
        - 300 Units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery
        - 600 Units/kg subcutaneously in 4 doses administered 21, 14, 7 days before surgery and on the day of surgery
    c. The components listed above must be documented in the medical record
    d. Deep venous thrombosis prophylaxis is recommended during Epoetin alfa-epbx (biosimilar) therapy
    e. **Two** diagnoses are required:
    D63.8 Anemia in other chronic diseases classified elsewhere, **AND**
    Z01.818 Encounter for other preprocedural examination

General Information
Documentation Requirements
Myelodysplastic Syndrome When ESAs are used for the treatment of Myelodysplastic Syndrome (MDS), the following information must be included in the patient's record: 1. An Erythropoietin level (less than equal to 500 IU/L) is required 2. Report of bone marrow biopsy supporting diagnosis of myelodysplastic syndrome or chronic myelomonocytic leukemia as listed above 3. The start date at the beginning of the trial period

4. If treatment is responsive or non-responsive at the end of the trial. A trial need not take the entire 12 weeks, if it is determined earlier that the patient is not responding this must be documented in the patient's record.
5. Pretreatment Hgb or HCT level obtained within one week of the initial injection
6. Laboratory results pertinent to treatment such as serum ferritin, serum transferrin, Hgb or HCT with date obtained
7. A narrative evaluation regarding response to the therapy.

ESRD/CKD

When ESAs are given for ESRD/CKD the following information must be in the patient's record:

1. Creatinine and weight
2. Date of patient's most recent HCT or Hgb
3. Date of most recent HCT or Hgb level – (prior to initiation of EPO therapy)
4. Patient's most recent serum creatinine – (within the last month, prior to initiation of EPO therapy)
5. Date of most recent serum creatinine – (prior to initiation of EPO therapy)
6. Patient's weight in kilograms
7. Patient's starting dose per kilogram – (The usual starting dose is 50-100 units per kilogram)

Nationally non-covered indications for ESA treatment:

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 effect related to ESA use. These conditions include:

1. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12-deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers
3. The anemia of cancer not related to cancer treatment
4. Any anemia associated only with radiotherapy
5. Prophylactic use to prevent chemotherapy-induced anemia
6. Prophylactic use to reduce tumor hypoxia
7. Patients with erythropoietin-type resistance due to neutralizing antibodies
8. Anemia due to cancer treatment if patients have uncontrolled hypertension

*See the ESA coverage rules in the Local Coverage Determination (L34633): https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=34633

*See the ESA article for billing and Coding Guidelines (A56795): https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56795&ver=31

*See the National Coverage Determination (NCD) Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions 110.21: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=322&ncdver=1&bc=0

The above CMS and WPS-GHA guidelines are current as of: 04/01/2025.