Evolent Clinical Guideline 3076 for Erythropoiesis Stimulating Agents (ESAs)

Guideline Number: Evolent_CG_3076	**Applicable Codes**	
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STATEMENT

Purpose

To define and describe the accepted indications for Erythropoiesis Stimulating Agents (ESAs): Epogen and Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (epoetin beta), and Retacrit (epoetin alfa-epbx) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Anemia of Chronic Kidney Disease (CKD)

- Erythropoiesis Stimulating Agents (ESAs) may be used in Anemia of Chronic Kidney Disease as follows:
    - The member has chronic kidney disease defined as GFR less than 60 mL/min over a period of at least three months AND
    - Concomitant iron deficiency has been ruled out with a serum ferritin greater than or equal to 30 ng/mL AND/OR transferrin saturation greater than or equal to 20% with levels obtained within the last 12 months) AND
    - For initiation of therapy, a Hgb of less than 10 g/dL is required (levels are obtained within the last 4 weeks) OR
    - For continuation of therapy, a Hgb of 11 g/dL or less is required (levels are obtained within the last 4 weeks).

Chemotherapy induced anemia (CIA)

- Erythropoiesis Stimulating Agents (ESAs) may be used in members at risk of requiring red blood cell transfusions within 30 days of anemia with solid tumors or non-myeloid malignancies receiving myelosuppressive chemotherapy without curative intent and such chemotherapy is ongoing or has been completed less than or equal to 8 weeks prior to initiation or continuation of ESA and the member meets the following criteria:
    - For initial/continuation requests the baseline Hgb less than 10 g/dL or HCT less than 30 prior to the initiation of ESA therapy (levels are obtained within the last 4 weeks) AND
    - Prior to initiating ESA therapy concomitant iron deficiency has been ruled out and serum ferritin is greater than or equal to 30 ng/mL AND/OR transferrin saturation is greater than or equal to 20%. For continuation requests, the above levels should be available at least 12 months prior to the continuation request.

Myelodysplastic Syndrome (MDS)

- The member has lower risk MDS (IPSS Low and INT-1) AND Erythropoiesis Stimulating Agents (ESAs) may be used for the following:
    - For member with symptomatic anemia with serum erythropoietin level less than or equal to 500 mU/mL AND
    - For initiation of Erythropoiesis Stimulating Agents (ESAs): Hgb less than 10 g/dL or HCT less than 30 (levels are obtained within the last 4 weeks) OR
    - For Continuation of Therapy: Hgb is 11g/dL or less (levels are obtained within the last 4 weeks) AND
    - Serum ferritin greater than or equal to 30 ng/mL AND/OR transferrin saturation greater than or equal to 20% (levels are obtained within the last 12 months) OR if iron stains in the bone marrow show adequate iron AND
    - Member’s bone marrow biopsy shows less than 10% blasts in the bone marrow OR
    - Erythropoiesis Stimulating Agents (ESAs) may be used in combination with filgrastim in members with less than 10% blasts in the bone marrow and the Hgb is unresponsive to a trial of ESA therapy.

CONTRAINDICATIONS/WARNINGS

- Contraindications
    - Epoetin alfa and epoetin alfa-epbx
        - Serious allergic reactions to epoetin alfa products or any component of the formulations
        - Uncontrolled hypertension
        - Pure red cell aplasia (PRCA) that begins after treatment with epoetin alfa or other

epoetin protein drugs

- Multidose vials contain benzyl alcohol and are contraindicated in neonates, infants, pregnant women, and breastfeeding women

- Darbepoetin alfa
  - Serious allergic reaction to darbepoetin alfa or any component of the formulation
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with darbepoetin alfa or other erythropoietin protein drugs.
- Epoetin beta
  - Serious or severe hypersensitivity to methoxy polyethylene glycol-epoetin beta (eg, anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria)
  - Pure red cell aplasia (PRCA) that begins after treatment with methoxy polyethylene glycol-epoetin beta or other erythropoietin protein drugs
  - Uncontrolled hypertension

- US Boxed Warning
  - Epoetin alfa and epoetin alfa-epbx
    - Cardiovascular events
      - Erythropoiesis-stimulating agents (ESAs) increase the risk of death, MI, stroke, venous thromboembolism, thrombosis of vascular access.
    - Chronic Kidney Disease
      - In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.
      - No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
      - Use the lowest epoetin alfa dose sufficient to reduce the need for RBC transfusions.
    - Cancer
      - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
      - To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
      - Use ESAs only for anemia from myelosuppressive chemotherapy.
      - ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

        - Discontinue following the completion of a chemotherapy course.
    - Perisurgery
        - Due to increased risk of DVT, DVT prophylaxis is recommended.
- Darbepoetin alfa
    - Cardiovascular events
        - Erythropoiesis-stimulating agents (ESAs) increase the risk of death, MI, stroke, venous thromboembolism, thrombosis of vascular access.
    - Chronic Kidney Disease
        - In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.
        - No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
        - Use the lowest darbepoetin alfa dose sufficient to reduce the need for RBC transfusions.
    - Cancer
        - ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
        - To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
        - Use ESAs only for anemia from myelosuppressive chemotherapy.
        - ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
        - Discontinue following the completion of a chemotherapy course.
- Epoetin beta
    - Cardiovascular events
        - Erythropoiesis-stimulating agents (ESAs) increase the risk of death, MI, stroke, venous thromboembolism, thrombosis of vascular access.
    - Chronic Kidney Disease
        - In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.
        - No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
        - Use the lowest epoetin beta dose sufficient to reduce the need for RBC transfusions.

- Cancer
  - Epoetin beta is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy.
  - A dose-ranging study was terminated early because of more deaths among patients receiving epoetin beta than another ESA.
  - ESAs have shown shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.

EXCLUSION CRITERIA

- For MDS: Lack of response after 12 weeks trial (response defined as 1 g/dL hemoglobin increase or decrease of transfusion requirements).
- The member is on chemotherapy with curative intent.
- The member completed myelosuppressive chemotherapy more than 8 weeks prior to initiation of Erythropoiesis Stimulating Agents (ESAs) for CIA.
- Erythropoiesis Stimulating Agent (ESA) is used for myeloid malignancies (e.g., acute, and chronic myeloid leukemia, myelofibrosis, polycythemia vera, or essential thrombocytopenia) or intermediate risk and high risk MDS OR MDS with a bone marrow blast count of greater than or equal to 10%.
- The member has any of the following causes of anemia:
  - Deficiencies in B12, folate, or iron
  - Hemolysis, occult blood loss, hypothyroidism, or nutritional deficiency.
- Erythropoiesis Stimulating Agent (ESA) is being used for the acute correction of anemia or as a substitute for RBC transfusions.
- Investigational use of Erythropoiesis Stimulating Agents (ESAs) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, considering the drugs and conditions under

investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).

- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J0881 - Injection, darbepoetin alfa, 1 microgram (non-esrd use)
- J0882 - Injection, darbepoetin alfa, 1 microgram (for esrd on dialysis)
- J0885 - Injection, epoetin alfa, (for non-esrd use), 1000 units
- J0887 - Injection, epoetin beta, 1 microgram, (for esrd on dialysis)
- J0888 - Injection, epoetin beta, 1 microgram, (for non esrd use)
- Q4081 - Injection, epoetin alfa, 100 units (for esrd on dialysis)
- Q5105 - Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units
- Q5106 - Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

Applicable Lines of Business

☒	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
June 2026	• Updated references
June 2025	• Updated exclusion criteria
April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1138 Erythropoiesis Stimulating Agents (ESAs) • Updated references
April 2024	• Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

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12. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: **http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm**.