Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM001.1225	**HEMATOLOGY** **ERYTHROPOIESIS STIMULATING AGENTS** See Appendix A for medications covered by policy
Effective Date: 2/1/2026	**Review/Revised Date**: 06/02, 02/05, 02/06, 12/06, 04/07, 04/08, 08/08, 12/08, 02/09, 02/10, 12/10, 10/11, 02/12, 10/12, 04/13, 12/13, 10/14, 10/15, 08/16, 09/17, 07/18, 09/18, 05/19, 11/19, 03/20, 10/20, 10/21, 10/22, 11/23, 10/24, 11/24, 11/25 (JEF)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit and medically accepted indications outlined below.

REQUIRED MEDICAL INFORMATION:
For patients initiating therapy:

1. All diagnoses, with the exception of 2e,2f (preoperative use in patients scheduled for elective non-cardiac, nonvascular, and cardiac surgery), must have **documented Hemoglobin (HGB) levels of less than or equal to 10g/dl within the 45 days prior** to initiation of therapy

AND

2. Must meet all of the listed criteria below for each specific diagnosis:
    a. **Treatment of Anemia in Chronic Kidney Disease (CKD)**
        i. Adequate iron stores as indicated by current (within the last three months) serum ferritin level greater than or equal to 100 mcg/L or serum transferrin saturation greater than or equal to 20%
    b. **Treatment of anemia in patients with cancer:**
        i. Adequate iron stores as indicated by current (within the last three months) serum ferritin level more than or equal to 100 mcg/L or serum transferrin saturation more than or equal to 20%

        AND

        ii. One of the following clinical scenarios:
            1) Patient has comorbid chronic kidney disease

2) Patient undergoing palliative treatment
3) Patient is currently on myelosuppressive chemotherapy and anemia is not able to be managed by transfusion therapy (for example: refusal due to religious beliefs or shortage of PRBCs)

c. **Treatment of Anemia in Myelodysplastic Syndromes (MDS) or with myelofibrosis**
   i. Adequate iron stores as indicated by current (within the last three months) serum ferritin level more than or equal to 100 mcg/L or serum transferrin saturation more than or equal to 20%
   ii. Must have documented current (within last three months) endogenous serum erythropoietin levels less than or equal to 500 mU/mL
d. **Anemia associated with zidovudine-treated HIV-infection patients**
   i. Current (within last three months) endogenous serum erythropoietin level is less than or equal to 500 mU/ml
   ii. Zidovudine dose is less than or equal to 4200 mg/week
e. **Preoperative use in patients scheduled for elective noncardiac and nonvascular surgery, all of the following criteria must be met:**
   i. Member has preoperative HGB between 10 and 13 g/dL
   ii. The surgery has a high-risk for perioperative blood loss (for example, expected to lose more than two units of blood)
   iii. Patient is unwilling to donate autologous blood pre-operatively
f. **Preoperative use in patients scheduled for cardiac surgery (including elective cardiac surgery), one of the following criteria must be met:**
   i. Patient has preoperative anemia, defined as HGB less than 13 g/dL for adult males or less than 12 g/dL for non-pregnant adult females
   ii. Patient refuses blood transfusions
   iii. Patient is deemed high-risk for postoperative anemia
g. **Mircera only: For the treatment of anemia associated with CKD in pediatric patients three months to 17 years of age (with or without dialysis) who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA:**
   i. Stable maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa for at least eight weeks prior to initiation of therapy
   ii. Stable hemoglobin (HGB) levels for at least eight weeks prior to initiation of therapy.

For patients established on therapy (Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy)**:**

1. Attestation of continued medical necessity (such as ongoing CKD)

2. HGB levels of less than or equal to 12 g/dl within previous 45 days

EXCLUSION CRITERIA:
- Patients with uncontrolled hypertension

PRESCRIBER RESTRICTIONS: N/A

AGE RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization and reauthorization will be for one year

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Erythropoietin is a glycoprotein that stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of erythroid progenitors in the bone marrow. The level of tissue oxygenation regulates endogenous production of erythropoietin. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. Production of endogenous erythropoietin is impaired in patients with CKD and erythropoietin deficiency is the primary cause of their anemia. There are three commercially available Erythropoietin Stimulating Agents (ESAs) that are structurally identical to endogenous erythropoietin; Epogen®, Procrit®, and Retacrit®.

Darbepoetin alfa (Aranesp®) is an ESA that is an epoetin analog that stimulates erythropoiesis by the same mechanism as epoetin. Darbepoetin was created to increase the serum half-life of epoetin by increasing the amount of sialic acid-

containing carbohydrate content. This modification also results in a product with a three-fold longer half-life which allows for less frequent dosing.

Mircera® (methoxy polyethylene glycol – epoetin beta) is an erythropoietin receptor activator with greater in vivo activity and a longer half-life than endogenous erythropoietin. In adult patients, Mircera® is administered either intravenously or subcutaneously and patients may be taught to self-administer. In pediatric patients, Mircera® is administered intravenously.

FDA APPROVED INDICATIONS:

Darbepoetin alfa (Aranesp®)

1. Anemia due to chronic kidney disease in patients on dialysis and patients not on dialysis
2. Anemia in patients with non-myeloid malignancies where anemia is due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

    Limitations of Use: has not been shown to improve quality of life, fatigue, or patient well-being. Aranesp® is not indicated for use:
    - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy
    - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
    - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
    - As a substitute for RBC transfusions in patients who require immediate correction of anemia

Epoetin alfa (Epogen®/Procrit®/Retacrit®)

1. Anemia due to chronic kidney disease, including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion
2. Anemia due to chemotherapy for non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
3. Anemia associated with zidovudine administered at less than or equal to 4200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL
4. Reduction of allogeneic red blood cell transfusions among patients with perioperative hemoglobin more than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, non-cardiac, nonvascular

surgery. Epogen®/Procrit®/Retacrit® is not indicated for patients who are willing to donate autologous blood pre-operatively.

Limitations of Use: has not been shown to improve quality of life, fatigue, or patient well-being. Epogen®/Procrit®/Retacrit® are not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia

Mircera® (methoxy polyethylene glycol – epoetin beta)

1. Treatment of anemia associated with chronic kidney disease (CKD) in:
    - Adult patients with or without dialysis
    - Pediatric patients three months to 17 years of age with or without dialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

Limitations of use:

- has not been shown to improve symptoms, physical functioning, or health-related quality of life.
- Mircera® is not indicated and is not recommended:
    - In the treatment of anemia due to cancer chemotherapy
    - As a substitute for RBC transfusions in patients who require immediate correction of anemia

POSITION STATEMENT:

For all ESAs (Aranesp®, Epogen®, Procrit®, Retacrit®, Mircera®), all diagnoses, the product labeling dosing and administration section recommends that the following criteria for iron stores must be met prior to initiation of therapy:

- Iron stores should be repleted to TSAT more than 20% or serum ferritin more than 100mcg/L
    - If iron levels are not adequate, oral iron therapy is preferred, but if patient is intolerant, IV iron therapy is an alternative

- Iron stores should be monitored periodically throughout therapy

Additionally, the product labeling for all ESAs also recommends that the following also be met prior to initiation of therapy:

- For patients with hypertension, blood pressure should be adequately controlled before initiation and closely monitored and controlled during therapy
- All other causes of anemia need to be ruled out and corrected prior to starting ESA treatment including folate deficiency, B-12 deficiency, iron deficiency (see above), hemolysis, bleeding, or bone marrow fibrosis

Anemia in chronic kidney disease (CKD)

These products carry a **FDA boxed warning** in this indication that states "in controlled trials with CKD patients, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target hemoglobin (Hgb) level of greater than 11 g/dL."[1-3]

Additionally, the FDA issued recommendations in 2011 for initiation of ESA therapy in this indication (see Appendix for specific dosing regimens/adjustments):

- Consider starting ESA treatment when the Hgb level is less than 10 g/dL. This advice does not define how far below 10 g/dL is appropriate for an individual to initiate. This advice also does not recommend that the goal is to achieve a Hgb of 10 g/dL or a Hgb more than 10 g/dL.
- Individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. Target Hgb levels have been removed from product labeling.[1-5]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for anemia in CKD follow these FDA recommendations. They recommend a full workup, including performing iron studies, to determine any treatable causes of anemia before initiating ESA therapy (for example, iron deficiency). They state that ESA therapy should only be used when Hgb less than 10 g/dL, to avoid falling below 9 g/dL, and the benefits are determined to outweigh risks.[6]

The KDIGO guidelines do not recommend maintaining Hgb levels more than 11.5 g/dL and strongly recommend against intentionally increasing the Hgb more than 13 g/dL.[6]

In addition, the KDIGO guidelines state that untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment. They recommend that for all adult patients both on ESA therapy and not on ESA therapy who are not receiving iron supplementation to receive a trial of IV iron (or in CKD nondialysis patients alternatively a 1-3 month trial of oral iron therapy) if their TSAT is less than or equal to 30% and ferritin is less than or equal to 500 ng/ml. They also recommend that for

all pediatric CKD patients with anemia both on ESA therapy and those not on ESA therapy who are not receiving iron supplementation to receive oral iron (or IV iron in CKD hemodialysis patients) when TSAT is less than or equal to 20% and ferritin is less than or equal to 100 ng/mL.[6]

Anemia in patients with cancer

These products carry **FDA boxed warnings** for this indication:

- 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.[1-3]

"In 2017, the FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS), which was limited to the use of Epogen/Procrit and Aranesp to treat patients with anemia due to associated myelosuppressive chemotherapy is no longer necessary to ensure that the benefits of Epogen/Procrit and Aranesp outweigh its risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer

The REMS Assessment showed that:

- The results from surveyed prescribers demonstrate acceptable knowledge of the product risks of decreased survival and/or the increased risk of tumor progression or recurrence and the need to counsel patients about these risks.
- The drug utilization data indicates appropriate prescribing of ESAs consistent with the intended use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy"[4]

The National Comprehensive Cancer Network (NCCN) guidelines for use of Hematopoietic Growth Factors in patients with cancer recommend a full workup of anemia to identify possible causes. This includes evaluation for possible iron deficiency and underlying comorbidities (such as bleeding, hemolysis, nutritional deficiencies, renal insufficiency). If patients have symptomatic anemia, the decision to use ESA is based on a risk/benefit evaluation, as both ESAs and red blood cell transfusions carry inherent risks. The guideline recommends to "consider the use of ESAs for select patients by FDA dosing/dosing adjustments, given there is no option for transfusion[7]". If ESAs are initiated, NCCN recommends adjusting doses to maintain an Hgb level that avoids red blood cell transfusions.[7]

Treatment of anemia in patients with myelodysplastic syndrome (MDS)
NCCN guidelines outline that the treatment of symptomatic anemia with ESAs for patients with MDS should be reserved to patients with low basal serum erythropoietin as this is a predictor of positive response. Other predictors of positive response include low percentage of marrow blasts and few prior red blood cell transfusions.[8]

Reduction of allogeneic blood transfusion in surgery patients
Due to increased risk of deep venous thrombosis (DVT) seen in clinical trials of patients on ESAs undergoing surgical orthopedic procedures, DVT prophylaxis is strongly recommended.

Anemia secondary to Hepatitis C therapy
The American Association for the Study of Liver Disease practice guidelines do not recommend use of growth factors for the treatment of anemia, but instead taking into account the risks of anemia associated with treatment regimens containing ribavirin. Recommendations are made to reduce the dose of ribavirin for those patients that do develop significant anemia (hemoglobin < 10 g/dL). The newer treatments currently available without ribavirin do not have a large risk of anemia.[9]

Anemia in Cardiac Operations
The 2021 STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management, recommend (class IIA recommendation, level B-R), that in patients who have preoperative anemia, refuse blood transfusions or are deemed high-risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin stimulating agents (ESAs) and iron supplementation several days prior to cardiac operations to increase red cell mass.[13] Anemia in preoperative patients is defined as a hemoglobin level of less than 13g/dL in adult males and less than 12g/dL in adult non-pregnant females.[14] The 2021 STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management states that treatment of anemia is warranted in the elective surgical patient.[13] Additionally, a meta analysis by Ali et al. reviewed eight clinical studies regarding the role of preoperative erythropoietin in the optimizations of preoperative anemia among surgical patients and concluded that preoperative erythropoietin provides better outcomes considering the optimization of preoperative anemia for elective surgical procedures.[14] Of note, epoetin alfa (Epogen®/Procrit®/Retacrit®) carries a boxed warning for perisurgery stating “due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended.”[1] Darbepoetin alfa (Aranesp®) and Mircera® (methoxy polyethylene glycol – epoetin beta) do not contain the same boxed warning.[1]

REFERENCE/RESOURCES:

1. Aranesp® (darbepoetin alfa) prescribing information. Thousand Oaks, CA: Amgen, Inc.; 2024 Dec.
2. Epogen® (epoetin alfa) prescribing information. Thousand Oaks, CA: Amgen, Inc. 2025 April.
3. Procrit® (epoetin alfa) prescribing information. Horsham, PA: Janssen products, LP. 2025 April.
4. U.S. Food and Drug Administration. Postmarket Drug Safety Information for Patients and Providers. Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp) Available at https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin (Accessed November 5, 2019)
5. CMS. Decision Memo for Erythropoiesis Stimulating Agents (ESA) for non-renal disease Indications (CAG-00383N). July 30, 2007. Available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=203&ver=12&NcaName=Erythropoiesis+Stimulating+Agents+&bc=BEAAAAAAIAAA& (accessed September 13, 2018)
6. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Supp*. 2012;2(4):288–98.
7. National Comprehensive Cancer Network (NCCN). Hematopoietic Growth Factors version 1.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf (Accessed October 12,)
8. National Comprehensive Cancer Network (NCCN). Myelodysplastic Syndromes version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf (Accessed October 12,).
9. AASLD/IDSA/IAS–USA. HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. Revised Date: October 24, 2022. Available at: https://www.aasld.org/sites/default/files/2022-07/PracticeGuidelines-HCV-November2018.pdf (Accessed October 26, 2022)
10. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): Erythropoiesis Stimulating Agents (L24301). Jurisdiction includes both Washington and Oregon. Available at: https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. (accessed November 2, 2021)
11. Retacrit® (epoetin alfa) prescribing information. Lake Forest, IL: Pfizer; 2025 June.

12. Mircera® (methoxy polyethylene glycol-epoetin beta injection, solution) prescribing information. Gallen, Switzerland: Vifor (International) Inc., 2024 June.
13. Tibi P, Mclure S, Huang J, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Annals of Thoracic Surgery. 2021: 112(3): 981-1004. Available at: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0003497521005567?scrollTo=%23hl0000841 (Accessed November 9, 2023).
14. Ali S, Hafeez M, Nisar O, et al. Role of preoperative erythropoietin in the optimization of preoperative anemia among surgical patients – a systematic review and meta-analysis. *Hematology, Transfusion and Cell Therapy*. January-March 2022. 44(1):76-84. Available at: https://www.sciencedirect.com/science/article/pii/S2531137921000067.

APPENDIX A. BILLING GUIDELINES AND CODING:

HCPCS	Coding Description	Brand Name
Prior Authorization Required		
J0881	Injection, darbepoetin alfa, 1 microgram (non-esrd use)	Aranesp (Albumin Free)
J0885	Injection, epoetin alfa, (for non-esrd use), 1000 units	Epogen; Procrit
Q5106	Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units	Retacrit
J0888	Injection, epoetin beta, 1 microgram, (for non esrd use)	Mircera
No Prior Authorization Required		
J0882	Injection, darbepoetin alfa, 1 microgram (for esrd on dialysis)	Aranesp (Albumin Free)
Q4081	Injection, epoetin alfa, 100 units (for esrd on dialysis)	Epogen; Procrit
Q5105	Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units	Retacrit
J0887	Injection, epoetin beta, 1 microgram, (for esrd on dialysis)	Mircera
ADMINISTRATION CODES◊		
96372	Ther/proph/diag inj sc/im	
96374	Ther/proph/diag inj iv push	

*Coding Notes:

• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

Appendix
Dosing Considerations for ESAs

Position Statement for ESA dosing in anemia in CRF(Subject to Audit)

- Response to dose changes can take up to 2-6 weeks, dose increases should not occur more frequently than once per month
- If hemoglobin does not increase by > 1g/dl per week or 1.5-2g/dl over 4-6 weeks and iron stores are adequate, dose should be increased by 25%. If hemoglobin is increasing by > 1g/dl in a two-week period or if it is approaching 11g/dl, dose should be decreased by 25%. If hemoglobin continues to rise, dose should be withheld until hemoglobin begins to decrease, at which time dose should be reinstated at a reduction of 25% below previous dose.
- Discontinue therapy after three months of therapy if no response

Position Statement for ESA dosing in cancer and related neoplastic Conditions (Subject to Audit)

- Starting dose is the recommended FDA labeled starting dose (equivalent doses may be given over other approved time periods)
    - Epoetin – no more than 150 U/kg/three times weekly
    - Darbepoetin – no more than 2.25 mcg/kg/week
- Maintain starting dose if HGB level remains less than 10g/dL (or HCT less than 30%) 4 weeks after initiation and the rise in HGB is more than or equal to 1g/dL (HCT more than or equal to 3%)
- If HGB rises less than 1g/dL (HCT rise of less than 3%) compared to pretreatment baseline over 4 weeks of treatment and whose HGB level remains less than 10 g/dL (or HCT less than 30%) FDA labeled starting dose may be increased by 25%
    - **If, after 8 weeks of therapy, HGB rises less than 1g/dL (HCT less than 3%), compared to pretreated baseline, continued use of the drug is not considered reasonable and necessary**
- If there is a rapid rise in HGB more than 1g/dL (HCT more than 3%) over 2 weeks of treatment, continued use of drug is not reasonable and necessary

unless the HGB remains below or subsequently falls to less than 10g/dL (or HCT less than 30%)

- Continuation and reinstitution of therapy must include a 25% dose reduction from previous dose