INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Erythropoiesis Stimulating Agents (ESA) includes the following products:

- Aranesp® (darbepoetin alfa)
- Epogen®, Procrit® (epoetin alfa)
- Mircera® (methoxy polyethylene glycol-epoetin beta)
- Retacrit™ (epoetin alfa-epbx)

I. Epoetin alfa (Epogen, Procrit), epoetin alfa-epbx (Retacrit) are considered medically necessary when BOTH of the following criteria are met:

- Presence of adequate iron stores defined as EITHER of the following:
  - For anemia secondary to a malignancy, EITHER of the following:
    - Serum ferritin is greater than or equal to 30 mcg/L
    - Serum transferrin saturation is greater than or equal to 20%
  - For anemia secondary to a non-malignancy OR Chronic Kidney Disease, EITHER of the following:
    - Serum ferritin is greater than or equal to 100 mcg/L
    - Serum transferrin saturation is greater than or equal to 20%
• Treatment of anemia defined by ANY of the following indications:
  o Chemotherapy-Induced Anemia and EITHER of the following:
    ▪ Initial treatment, ALL of the following:
      • Pre-treatment hemoglobin (Hgb) < 10.0 g/dL
      • Myelosuppressive chemotherapy is anticipated for at least 2 months for the treatment of non-myeloid malignancies
      • Anticipated outcome of chemotherapy is not cure
        (Initial authorization: 12 weeks)
    ▪ Established treatment, ALL of the following:
      • Additional myelosuppressive chemotherapy is anticipated for at least 2 months for the treatment of non-myeloid malignancies
      • Anticipated outcome of chemotherapy is not cure
      • Hgb not exceeding 12.0 g/dL
        (Reauthorization: 6 months)
  o Chronic Kidney Disease Anemia and EITHER of the following:
    ▪ Individual is on dialysis.
    ▪ Individual is not on dialysis and EITHER of the following:
      • Initial treatment and ONE of the following:
        o The patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL
          OR
        o The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL
          (Initial authorization: 1 year)
      • Established treatment and ONE of the following:
        o The patient is ≥ 18 years of age with a hemoglobin < 11.5 g/dL
          OR
        o The patient is < 18 years of age with a hemoglobin ≤ 12.0 g/dL
          (Reauthorization: 1 year)
  o Hepatitis C Treatment Anemia and EITHER of the following:
    ▪ Initial treatment, ALL the following:
      • Pretreatment Hgb < 10.0 g/dL
      • Individual is currently receiving ribavirin in combination with either interferon alfa or peginterferon alfa
        (Initial authorization: 6 months)
    ▪ Established treatment, ALL of the following:
      • Hgb not exceeding 12.0 g/dL
      • Individual is currently receiving ribavirin in combination with either interferon alfa or peginterferon alfa
        (Reauthorization: 6 months)
  o Myelodysplastic Syndrome (MDS) Anemia and EITHER of the following:
    ▪ Initial treatment: Endogenous serum erythropoietin level less than or equal to 500 mU/ml (Initial authorization: 12 weeks)
    ▪ Established treatment, ALL of the following:
      • Hgb increased by 1 g/dL compared to pre-treatment baseline within initial 12 weeks of therapy
      • Hgb not exceeding 12.0 g/dL
        (Reauthorization: 6 months)
  o Myelofibrosis Anemia and EITHER of the following:
    ▪ Initial treatment: Endogenous serum erythropoietin level less than or equal to 500 mU/ml (Initial authorization: 12 weeks)
    ▪ Established treatment, ALL of the following:
      • Hgb increased by 1 g/dL compared to pre-treatment baseline within initial 12 weeks of therapy
      • Hgb not exceeding 12.0 g/dL
        (Reauthorization: 6 months)
  o Preoperative Anemia and ALL of the following:
• Hgb ≤ 13.0 g/dL
• Individual scheduled for elective non-cardiac, non-vascular surgery
• Individual is not willing or able to donate autologous blood prior to surgery
• Anemia is not secondary to autologous blood donation

(One-time authorization, up to 4 weeks)

o Zidovudine Treatment Anemia and EITHER of the following:
  • Initial treatment, ALL of the following:
    • Pre-treatment hemoglobin (Hgb) < 10 g/dL
    • HIV-infected individual currently receiving zidovudine treatment
    (Initial authorization: 6 months)
  • Established treatment, ALL of the following:
    • Hgb not exceeding 12.0 g/dL
    • Individual is currently receiving zidovudine treatment
    (Reauthorization: 6 months)

Coverage for epoetin alfa varies across plans. Refer to the customer’s benefit plan document for coverage details. Where coverage requires the use of preferred products, the following criteria apply.

For Individual and Family Plans:

<table>
<thead>
<tr>
<th><strong>Epogen</strong> (epoetin alfa)</th>
<th>Covered when the medical necessity criteria (as noted above) AND the individual has a documented intolerance to or is not a candidate for Procrit.</th>
</tr>
</thead>
</table>

II. Darbepoetin alfa (Aranesp) is considered medically necessary when BOTH of the following criteria are met:

- **Presence of adequate iron stores** defined as EITHER of the following:
  - For anemia secondary a malignancy, EITHER of the following:
    • Serum ferritin is greater than or equal to 30 mcg/L
    • Serum transferrin saturation is greater than or equal to 20%
  - For anemia secondary a non-malignancy OR Chronic Kidney Disease, EITHER of the following:
    • Serum ferritin is greater than or equal to 100 mcg/L
    • Serum transferrin saturation is greater than or equal to 20%

- **Treatment of anemia** defined by ANY of the following indications:
  - Chemotherapy-Induced Anemia and EITHER of the following:
    • Initial treatment, ALL of the following:
      • Pre-treatment hemoglobin (Hgb) < 10.0 g/dL
      • Myelosuppressive chemotherapy is anticipated for at least 2 months for the treatment of non-myeloid malignancies
      • Anticipated outcome of chemotherapy is not cure
      (Initial authorization: 12 weeks)
    • Established treatment, ALL of the following:
      • Additional myelosuppressive chemotherapy is anticipated for at least 2 months for the treatment of non-myeloid malignancies
      • Anticipated outcome of chemotherapy is not cure
      • Hgb not exceeding 12.0 g/dL
      (Reauthorization: 6 months)
  - Chronic Kidney Disease Anemia and EITHER of the following:
    • Individual is on dialysis.
    • Individual is not on dialysis and EITHER of the following:
      • Initial treatment and ONE of the following:
        • The patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL OR
        • The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL
III. Methoxy polyethylene glycol-epoetin beta (Mircera) is considered medically necessary when BOTH of the following criteria are met:

- Presence of adequate iron stores defined as EITHER of the following:
  - Serum ferritin is greater than or equal to 100 mcg/L
  - Serum transferrin saturation is greater than or equal to 20%

- Treatment of anemia defined by the following indication:
  - Chronic Kidney Disease Anemia and EITHER of the following:
    - Individual is on dialysis.
    - Individual is not on dialysis and EITHER of the following:
      - Initial treatment and ONE of the following:
        - The patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL OR
        - The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL
        (Initial authorization: 1 year)
      - Established treatment and ONE of the following:
        - The patient is ≥ 18 years of age with a hemoglobin < 11.5 g/dL;
        OR
        - The patient is < 18 years of age with a hemoglobin ≤ 12.0 g/dL
        (Reauthorization: 1 year)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Erythropoiesis Stimulating Agents (ESA) are considered experimental, investigational or unproven for any other indication including the following:

- Anemia of prematurity
- Anemia associated with rheumatoid arthritis
- Acute ST-segment elevation myocardial infarction
- Autologous stem-cell transplantation
- Major blunt trauma
- Carbon monoxide poisoning
- Graft function following kidney transplantation
- Heart failure and a preserved ejection fraction
- Post cardiac surgery
- Postpartum iron deficiency anemia
- Systolic heart failure
- Traumatic brain injury

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
</table>
| **Aranesp** (darbepoetin alfa) | **Anemia Due to Chronic Kidney Disease**
Aranesp is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.  

**Anemia Due to Chemotherapy in Patients with Cancer**
Aranesp is indicated for the treatment of anemia in patients with 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.

**Limitations of Use**
Aranesp 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.

| **Epogen, Procrit** (epoetin alfa) | **Anemia Due to Chronic Kidney Disease**
Epogen is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.  

**Anemia Due to Zidovudine in Patients with HIV-infection**
Epogen is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.  

**Anemia Due to Chemotherapy in Patients With Cancer**
Epogen is indicated for the treatment of anemia in patients with 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.

**Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery**
Epogen is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epogen is not indicated for patients who are willing to donate autologous blood preoperatively.

**Limitations of Use**
Epogen has not been shown to improve quality of life, fatigue, or patient well-being. Epogen 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.
- 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.

<table>
<thead>
<tr>
<th>Mircera (methoxy polyethylene glycol-epoetin beta)</th>
<th>Anemia Due to Chronic Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mircera is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in:</td>
<td></td>
</tr>
<tr>
<td>adult patients on dialysis and adult patients not on dialysis.</td>
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</tr>
<tr>
<td>pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.</td>
<td></td>
</tr>
</tbody>
</table>

**Limitations of Use**
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.
Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life.

<table>
<thead>
<tr>
<th>Retacrit (epoetin alfa-epbx)</th>
<th>Anemia Due to Chronic Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retacrit is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.</td>
<td></td>
</tr>
</tbody>
</table>

**Anemia Due to Zidovudine in Patients with HIV-infection**
Retacrit is indicated for the treatment of anemia due to zidovudine administered at ≤ 4,200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.

**Anemia Due to Chemotherapy in Patients with Cancer**
Retacrit is indicated for the treatment of anemia in patients with 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.

**Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery**
Retacrit is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to < 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Retacrit is not indicated for patients who are willing to donate autologous blood pre-operatively.
## Limitations of Use
Retacrit has not been shown to improve quality of life, fatigue, or patient well-being. Retacrit 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.
- 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.

## Recommended Dosing

**Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Recommended Dosing</th>
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</thead>
</table>
| Aranesp       | - Recommended starting dose for patients with CKD on dialysis:  
- 0.45 mcg/kg intravenously or subcutaneously weekly, or  
- 0.75 mcg/kg intravenously or subcutaneously every 2 weeks  
- Intravenous route is recommended for patients on hemodialysis  
- Recommended starting dose for patients with CKD not on dialysis:  
- 0.45 mcg/kg intravenously or subcutaneously at 4 week intervals  
- Recommended starting dose for pediatric patients with CKD:  
- 0.45 mcg/kg intravenously or subcutaneously weekly  
- patients with CKD not on dialysis may also be initiated at 0.75 mcg/kg every 2 weeks  
- Recommended starting dose for patients with cancer on chemotherapy:  
- 2.25 mcg/kg subcutaneously weekly, or  
- 500 mcg subcutaneously every 3 weeks |
| Epogen, Procrit | - Evaluate iron status before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia before initiating treatment.  
- In pregnant women, lactating women, neonates, infants: Use only single-dose vials.  
- Patients with CKD: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (pediatric patients). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis.  
- Patients on Zidovudine due to HIV-infection: 100 Units/kg 3 times weekly.  
- Patients with Cancer on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (pediatric patients ≥ 5 years).  
- Surgery Patients: 300 Units/kg per day daily for 15 days or 600 Units/kg weekly. |
| Mircera       | In adult patients, Mircera is administered by subcutaneous or intravenous injection.  
- Initial Treatment: 0.6 mcg/kg body weight administered once every two weeks.  
- Conversion from Another ESA: dosed once monthly or once every two weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion. In pediatric patients, Mircera is administered by intravenous injection only.  
- Conversion from Another ESA: dosed once every 4 weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion. |
| Retacrit      | - Evaluate iron status before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia before initiating treatment. |
• Patients with CKD: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (pediatric patients). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis.
• Patients on Zidovudine due to HIV-infection: 100 Units/kg 3 times weekly.
• Patients with Cancer on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (pediatric patients > 5 years).
• Surgery Patients: 300 Units/kg per day daily for 15 days or 600 Units/kg weekly.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aranesp (darbepoetin alfa)</td>
<td>Supplied in single-dose vials and single-dose prefilled syringes as follows:</td>
</tr>
<tr>
<td></td>
<td>• Single-dose vials: 25 mcg, 40 mcg, 60 mcg, 100 mcg 200 mcg and 300 mcg</td>
</tr>
<tr>
<td></td>
<td>• Single-dose prefilled syringes: 10 mcg/0.4 mL, 25 mcg/0.42 mL, 40 mcg/0.4 mL,</td>
</tr>
<tr>
<td></td>
<td>60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL,</td>
</tr>
<tr>
<td></td>
<td>500 mcg/1 mL</td>
</tr>
<tr>
<td>Epogen, Procrit (epoetin alfa)</td>
<td>Supplied in multi-dose vials and single-dose vials as follows:</td>
</tr>
<tr>
<td>Mircera (methoxy polyethylene glycol-epoetin beta)</td>
<td>Supplied in single-dose prefilled syringes as follows:</td>
</tr>
<tr>
<td></td>
<td>• Multi-dose vials: 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, 10,000 Units/mL</td>
</tr>
<tr>
<td></td>
<td>• Single-dose vials: 20,000 Units/2 mL (10,000 Units/mL)</td>
</tr>
<tr>
<td>Retacrit (epoetin alfa-epbx)</td>
<td>Supplied in single-dose vials as follows:</td>
</tr>
<tr>
<td></td>
<td>• 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL</td>
</tr>
</tbody>
</table>

**General Background**

**Pharmacology**
Aranesp is an erythropoiesis-stimulating protein manufactured by recombinant DNA technology that is administered by intravenous (IV) injection or subcutaneous (SC) injection. (Aranesp, 2019) The agent is also known as an erythropoiesis-stimulating agent (ESA). Aranesp has indications for: 1) the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis; and 2) the treatment of anemia in patients with 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. The prescribing information notes that it is not indicated for use in: 1) patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy; 2) in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; 3) in patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion; and 4) as a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia. The prescribing information for Aranesp recommends that therapy should be initiated for adult patients with CKD on dialysis when the hemoglobin (Hb) level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the Aranesp dose. For adult patients with CKD not on dialysis, Aranesp should be initiated when Hb is < 10.0 g/dL and other considerations apply (for example, patient is likely to need transfusions). If the Hb level exceeds 10.0 g/dL, reduce or interrupt the Aranesp dose and use the lowest dose sufficient to reduce the need for RBC transfusions. Initiate Aranesp for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL. Use the lowest dose of Aranesp to avoid RBC transfusions. For pediatric patients with CKD, initiate Aranesp when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of Aranesp.

**Professional Societies/Organizations**
The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall
below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL. (Kidney, 2012) The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (for example, prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (for example, iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for failure to adequately respond to ESAs. Iron deficiency can occur following continued ESA use and, therefore, iron supplementation is required in most patients to maintain an optimal response.

ESAs have a role in the management of patients with anemia due to cancer chemotherapy. (Rizzo, 2010; NCCN, 2019) Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) for myelodysplastic syndrome (MDS) [version 2.2019 – October 18, 2018] list Aranesp as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL. (NCCN, 2019) Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb ≤ 12.0 g/dL. Data suggest Aranesp may provide some benefits in MDS. (Stasi, 2005; Mannone, 2006; Kelaidi, 2013; Oliva, 2010; Park, 2016; Platzbecker, 2017) The NCCN guidelines for myeloproliferative neoplasms (version 2.2019 – October 29, 2018) address Aranesp and epoetin alfa products as options for treatment with of patients with anemia related to myelofibrosis having a serum erythropoietin level ≤ 500 mU/mL. (NCCN, 2019) Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

Clinical Efficacy
Chronic Kidney Disease
In regards to the use of ESAs in CKD, the FDA label states the following:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents 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 ESA dose sufficient to reduce the need for red blood cell transfusions.

A recent Cochrane review of 33 studies involving more than 5500 dialysis patients revealed comparable results in mean final Hgb levels were achieved without regard to which particular ESA was used. (Hahn et al, 2014)

In 2014, a Cochrane review of 56 studies in more than 15,000 CKD patients comparing the safety and efficacy of epoetin alfa and beta, darbepoetin alfa, Mircera, and biosimilar ESAs was published. Analyses indicated moderate to low evidence that ESAs, when compared to placebo, were able to avert blood transfusions. The authors determined there is inadequate evidence supporting superiority in regards to safety and efficacy of any particular ESA. (Palmer et al, 2014)

In a systematic review of the tolerability and efficacy of Mircera compared to darbepoetin alfa in addressing anemia in non-dialysis CKD patients (N=1155), fluctuations in hemoglobin levels from baseline showed that Mircera was clinically non-inferior to darbepoetin alfa. (Alsalimi et al 2014)

Hepatitis C
Small studies have indicated that hematopoietic growth factors may be useful in treating anemia associated with interferon and ribavirin therapy in patients with hepatitis C. There are two randomized controlled trials and two open-label trials evaluating epoetin alfa in patients being treated with interferon and ribavirin. There is one
abstract of a study using darbepoetin alfa in this patient population. Additional information regarding standardized dosing administration and frequency are indicated.

**Off Label Uses**
AHFS Drug Information 2019 Edition does not support any off-label uses of darbepoetin, or methoxy polyethylene glycol-epoetin.

AHFS Drug Information 2019 Edition does not have a monograph for epoetin alfa-epbx.

AHFS Drug Information 2019 Edition lists the following off-label uses for epoetin alfa: Gaucher’s disease, Castleman’s disease, anemia of prolonged acute renal failure, high dosages for the correction of ineffective hematopoiesis associated with paroxysmal nocturnal hemoglobinuria, sickle cell anemia, anemia of prematurity, anemia associated with rheumatoid arthritis and rheumatic disease. However, there is limited data to support these uses; further study is needed.

**Experimental, Investigational, Unproven Uses**

**Anemia Associated with Prematurity**
Aher and Ohlsson conducted a Cochrane Review to assess the safety and effectiveness of early versus late initiation of EPO in reducing red blood cell (RBC) transfusions in preterm and/or low birth weight (LBW) infants. Two randomized controlled trials (n=262) met inclusion criteria. There was no significant reduction in RBC transfusions or in the total volume of blood transfused. The early administration of EPO led to a significant increase in the risk of retinopathy. There is a lack of evidence that either early or late administration of EPO improved outcomes. (Aher, 2012)

**Anemia Associated with Rheumatoid Arthritis**
In a Cochrane Review, Marti-Carvajal et al. assessed the clinical benefits and harms of ESA for the treatment of rheumatoid arthritis. Three randomized controlled trials (n=133) with patients, age 16 years and over, were included in the analysis. ESAs were compared to placebo. Due to the inconsistencies in the reporting results, meta-analysis of the trials was not performed. There was conflicting evidence that ESAs increased the hemoglobin level and quality of life in this population. The authors also concluded that the safety profile of EPO was unclear. (Marti-Carvajal, 2013)

**Postpartum Iron Deficiency Anemia**
A Cochrane Review conducted by Markova and colleagues reviewed treatment for women with postpartum iron deficiency anemia. Treatment options reviewed included intravenous iron, erythropoietin and red blood cell transfusion. The review found 7 studies that evaluated the use of erythropoietin for postpartum iron deficiency anemia. Citing insufficient, high-quality evidence, the reviewers were unable make any conclusions as to the effectiveness of erythropoietin in this condition and suggested additional studies to evaluate treatment effect and clinical outcomes. (Markova, 2015)

**Other Indications**
Case series, randomized controlled trials, systematic reviews, and/or meta-analysis have investigated ESAs for numerous conditions/indications. Studies have reported that there were no significant improvements with ESAs and/or the studies were limited by small and/or heterogeneous patient populations; short-term follow-ups; lack of a control group; potential reporting and publication bias; and heterogeneity of inclusion criteria, outcome measures and ESA dosing. (Mauerer, et al., 2013; Pang, et al., 2013; Swedberg, et al., 2013; Li, et al., 2012; Luchette, et al., 2012; de Seigneux et al., 2012; Surehskumar, et al., 2012; Talving, et al., 2012; Ballen, et al., 2004; Dodd, et al., 2004)

**Coding/ Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0881</td>
<td>Injection, darbepoetin alfa, 1 microgram (non-ESRD use)</td>
</tr>
<tr>
<td>J0882</td>
<td>Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)</td>
</tr>
<tr>
<td>J0885</td>
<td>Injection, epoetin alfa, (for non-ESRD use), 1000 units</td>
</tr>
<tr>
<td>J0887</td>
<td>Injection, epoetin beta, 1 microgram (for ESRD on dialysis)</td>
</tr>
<tr>
<td>J0888</td>
<td>Injection, epoetin beta, 1 microgram (for non-ESRD use)</td>
</tr>
<tr>
<td>Q4081</td>
<td>Injection, epoetin alfa, 100 units (for ESRD on dialysis)</td>
</tr>
<tr>
<td>Q5105</td>
<td>Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for ESRD on dialysis), 100 units</td>
</tr>
<tr>
<td>Q5106</td>
<td>Injection, epoetin alfa-epbx, biosimilar, (Retacrit) (for non-ESRD use), 1000 units</td>
</tr>
</tbody>
</table>

References


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