INSTRUCTIONS FOR USE

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Coverage Policy

Erythropoiesis Stimulating Agents (ESA) includes the following products:

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

Cigna covers Erythropoiesis Stimulating Agents (ESA) as medically necessary for the treatment of anemia in the presence of adequate iron stores (serum ferritin is greater than or equal to 100 mcg/L or serum transferrin saturation is greater than or equal to 20% or individual is receiving supplemental iron) for specific product and related criteria as listed in the following table:

<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>epoetin alfa (Epogen®, Procrit®)</td>
<td>• chronic kidney disease with a hemoglobin (Hgb) &lt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>• myelosuppressive cancer chemotherapy-induced anemia with a Hgb &lt; 10 g/dL when additional chemotherapy is anticipated for at least another 2 months for the treatment of non-myeloid malignancies, and the anticipated outcome of chemotherapy is not cure</td>
</tr>
<tr>
<td></td>
<td>• elective non-cardiac, non-vascular surgery with preoperative anemia (Hgb &gt; 10 g/dL and ≤13 g/dL) except when the anemia is secondary to autologous blood donation</td>
</tr>
<tr>
<td></td>
<td>• HIV infected individual receiving zidovudine treatment with a Hgb &lt; 11 g/dL</td>
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<tr>
<td></td>
<td>• anemia secondary to hepatitis C treatment with a Hgb &lt; 10 g/dL</td>
</tr>
<tr>
<td>Product</td>
<td>Criteria for Use</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• anemia associated with myelodysplastic syndrome (MDS) and both of the following:</td>
</tr>
<tr>
<td></td>
<td>▪ the individual has symptomatic anemia with lower risk disease</td>
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<tr>
<td></td>
<td>▪ the endogenous serum erythropoietin level is less than or equal to 500 mU/ml</td>
</tr>
<tr>
<td></td>
<td>• anemia associated with myelofibrosis with an endogenous serum erythropoietin level less than or equal to 500 mU/ml</td>
</tr>
<tr>
<td>darbepoetin alfa (Aranesp®)</td>
<td>• chronic kidney disease in an individual with a hemoglobin (Hgb) &lt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>• myelosuppressive cancer chemotherapy-induced anemia with a Hgb &lt; 10 g/dL when additional chemotherapy is anticipated for at least another 2 months for the treatment of non-myeloid malignancies and the anticipated outcome of chemotherapy is not cure</td>
</tr>
<tr>
<td></td>
<td>• anemia associated with myelodysplastic syndrome (MDS) and both of the following:</td>
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</tr>
<tr>
<td></td>
<td>• anemia associated with myelofibrosis with an endogenous serum erythropoietin level less than or equal to 500 mU/ml</td>
</tr>
<tr>
<td>Methoxy polyethylene glycol-epoetin beta (Mircera®)</td>
<td>• chronic kidney disease in an individual with a hemoglobin (Hgb) &lt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>Cigna covers continued use of Erythropoiesis Stimulating Agents (ESA) as medically necessary when ANY of the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 11.0 g/dL for an individual with chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 12.0 g/dL for an individual with cancer receiving at least 2 more months of myelosuppressive chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 12.0 g/dL for a HIV infected individual receiving zidovudine treatment</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 13.0 g/dL for an individual with scheduled elective surgery and persistent preoperative anemia</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 12.0 g/dl for an individual with myelodysplastic syndrome</td>
</tr>
<tr>
<td></td>
<td>• Hgb does not exceed 12.0 g/dL for an individual with myelofibrosis</td>
</tr>
<tr>
<td></td>
<td>Cigna does not cover the use of Erythropoiesis Stimulating Agents (ESA) for any other indications, including but not limited to the following, because they are considered experimental, investigational or unproven.</td>
</tr>
<tr>
<td></td>
<td>• Anemia of prematurity</td>
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<td></td>
<td>• Anemia associated with rheumatoid arthritis</td>
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<td></td>
<td>• Acute ST-segment elevation myocardial infarction</td>
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<td></td>
<td>• Autologous stem-cell transplantation</td>
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<td></td>
<td>• Major blunt trauma</td>
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<td></td>
<td>• Carbon monoxide poisoning</td>
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<td>• Graft function following kidney transplantation</td>
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<td></td>
<td>• Heart failure and a preserved ejection fraction</td>
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<td></td>
<td>• Post cardiac surgery</td>
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<td></td>
<td>• Postpartum iron deficiency anemia</td>
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<tr>
<td></td>
<td>• Systolic heart failure</td>
</tr>
<tr>
<td></td>
<td>• Traumatic brain injury</td>
</tr>
</tbody>
</table>
Cigna does not cover the continued use of Erythropoiesis Stimulating Agents (ESA), other than chronic kidney disease, when the Hgb has failed to rise by 1 g/dL compared to pre-treatment baseline within 8 weeks of therapy despite appropriate dose escalation.

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

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

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**FDA Approved Indications, FDA Recommended Dosing and Drug Availability**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Indications</th>
<th>FDA Recommended Dosing/Drug Availability</th>
</tr>
</thead>
</table>
| Darbepoetin Alfa (Aranesp) | *Anemia Due to Chronic Kidney Disease (CKD)*  
Aranesp is indicated for the treatment of anemia due to 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:**  
- Has not been shown to improve quality of life or patient well-being, or to reduce fatigue.  
- Not indicated for use in cancer patients who are not being treated with concomitant myelosuppressive chemotherapy but who are receiving therapy only with hormonal agents, biologics, or radiotherapy. May be used in cancer patients being treated with concomitant myelosuppressive chemotherapy in conjunction with hormonal agents, biologics, or radiotherapy  
- Not indicated for use in cancer patients receiving potentially curative chemotherapy  
- Not indicated as a substitute for transfusions when anemia must be corrected immediately  
| For all patients with CKD  
- When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. A single hemoglobin excursion may not require a dosing change.  
- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.  
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose by 25% or more as needed to reduce rapid responses.  
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.  
- For patients who do not respond adequately over a 12-week escalation period, increasing the dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia.  
- Discontinue if responsiveness does not improve.  
For patients with CKD on dialysis  
- Initiate treatment when the hemoglobin level is less than 10 g/dL. |
• If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose
• The recommended starting dose is 0.45 mcg/kg intravenously or subcutaneously as a weekly injection or 0.75 mcg/kg once every 2 weeks as appropriate. 
The IV route is recommended for patients on hemodialysis.

For patients with CKD not on dialysis
• Consider initiating treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  o The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and
  o Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.
• If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of and use the lowest dose of sufficient to reduce the need for RBC transfusions
• The recommended starting dose is 0.45 mcg/kg body weight intravenously or subcutaneously given once at four week intervals as appropriate.

For pediatric patients with CKD
• Initiate Aranesp treatment when the hemoglobin level is less than 10 g/dL
• If the hemoglobin level approaches or exceeds 12 g/dL, reduce or interrupt the dose of Aranesp
• The recommended starting dose for pediatric patients (less than 18 years) is 0.45 mcg/kg body weight administered as a single subcutaneous or intravenous injection once weekly; patients not receiving dialysis may also be initiated at a dose of 0.75 mcg/kg once every 2 weeks

Drug Availability:
• Single dose vials: 25, 40, 60,
<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Indications</th>
<th>FDA Recommended Dosing/ Drug Availability</th>
</tr>
</thead>
</table>
| Epoetin Alfa (Epogen and Procrit)        | Anemia Due to CKD  
Epogen is indicated for the treatment of anemia due to CKD, including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.  
Anemia Due to Zidovudine in HIV-infected Patients  
Epogen is indicated for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients 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. | For all patients with CKD  
When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. A single hemoglobin excursion may not require a dosing change.  
Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.  
If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose by 25% or more as needed to reduce rapid responses.  
For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.  
For patients who do not respond adequately over a 12-week escalation period, increasing the dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a Hgb level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia.  
Discontinue if responsiveness does not improve. |

| Drug                                      | Anemia Due to CKD  
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When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. A single hemoglobin excursion may not require a dosing change.  
Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.  
If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose by 25% or more as needed to reduce rapid responses.  
For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.  
For patients who do not respond adequately over a 12-week escalation period, increasing the dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a Hgb level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia.  
Discontinue if responsiveness does not improve. |

For patients with CKD on dialysis  
Initiate treatment when the hemoglobin level is less than 10 g/dL  
If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose  
The recommended starting dose for adult patients is 50 to 100 mcg.
- Has not been shown to improve quality of life or patient wellbeing, or to reduce fatigue
- Not indicated for use in cancer patients who are not being treated with concomitant myelosuppressive chemotherapy but who are receiving therapy only with hormonal agents, biologics, or radiotherapy. May be used in cancer patients being treated with concomitant myelosuppressive chemotherapy in conjunction with hormonal agents, biologics, or radiotherapy.
- Not indicated for use in cancer patients receiving potentially curative chemotherapy.
- Not indicated for use in patients scheduled for elective surgery who are willing to donate autologous blood.
- Not indicated for use in patients who are undergoing cardiac or vascular surgery
Not indicated as a substitute for transfusions when anemia must be corrected immediately.

<table>
<thead>
<tr>
<th>units/kg</th>
<th>3 times weekly IV or subcutaneously</th>
</tr>
</thead>
<tbody>
<tr>
<td>For pediatric patients, a starting dose of 50 Units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis.</td>
<td></td>
</tr>
</tbody>
</table>

**For patients with CKD not on dialysis**
- Consider initiating treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose and use the lowest dose sufficient to reduce the need for RBC transfusions.
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

**For pediatric patients with CKD**
- Initiate treatment only when the hemoglobin level is less than 10 g/dL
- If the hemoglobin level approaches or exceeds 12 g/dL, reduce or interrupt the dose of Epogen.
- The recommended starting dose for pediatric patients (ages 1 month or older) is 50 Units/kg 3 times weekly IV or subcutaneously.

**Zidovudine-treated HIV-infected Patients**
- The recommended starting dose in adults is 100 Units/kg as an intravenous or subcutaneous injection 3 times per week.
- If hemoglobin does not increase after 8 weeks of therapy,
increase dose by approximately 50 to 100 units/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 units/kg. 
- Withhold if hemoglobin exceeds 12 g/dL.
- Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.
- Discontinue if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

Patients on Cancer Chemotherapy
- Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense.
- Initiate in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.
- Use the lowest dose necessary to avoid RBC transfusions.
- Recommended starting dose for adults: 150 Units/kg subcutaneously 3 times per week until completion of a chemotherapy course or 40,000 Units subcutaneously weekly until completion of a chemotherapy course.
- Recommended starting dose for pediatric patients (5 to 18 years) - 600 Units/kg intravenously weekly until completion of a chemotherapy course.
- Reduce dose by 25% if hemoglobin increases greater than 1 g/dL in any 2-week period or hemoglobin reaches a level needed to avoid RBC transfusion.
- Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.
After the initial 4 weeks of therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to 300 Units/kg three times per week in adults or 60,000 Units weekly in adults 900 Units/kg (maximum 60,000 Units) weekly in children.

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue.

**Surgery Patients**

The recommended 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, and 7 days before surgery and on the day of surgery.

Deep venous thrombosis prophylaxis is recommended during therapy.

**Drug Availability:**

- Single dose vials, preservative-free: 2,000, 3,000, 4,000, 10,000, or 40,000 units/mL
- Multidose vials, preserved (contains 0.9% benzyl alcohol): 20,000 units/2 mL or 20,000 units/1 mL.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Indications</th>
<th>FDA Recommended Dosing/Drug Availability</th>
</tr>
</thead>
</table>
| Methoxy polyethylene glycol-epoetin beta (Mircera)  | Anemia Due to CKD Mircera is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and patients not on dialysis. Limitations of Use:  
  - Not indicated and not recommended in the treatment of anemia due to cancer chemotherapy  
  - Not indicated and not recommended as a substitute for RBC transfusions in patients who require immediate correction of anemia | For all patients with CKD:  
  When initiating or adjusting therapy, monitoring hemoglobin levels at least weekly until stable, then monitor at least monthly,  
  When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may nor require a dosing change.  
  - Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments. |
If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Mircera by 25% or more as needed to reduce rapid responses.

For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.

For patients who do not respond adequately over a 12-week escalation period, increasing the Mircera dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Mircera if responsiveness does not improve.

**For Patients with CKD on dialysis:**
- Initiate Mircera treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Mircera.
- The recommended starting dose of Mircera for the treatment of anemia in adult CKD patients who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single IV or SC injection once every two weeks. The IV route is recommended for patients receiving hemodialysis because the IV route may be less immunogenic.
- Once the hemoglobin has been stabilized, Mircera may be administered once monthly using a dose that is twice that of the every-two-week dose and subsequently titrated as necessary.

**For Patients with CKD not on dialysis:**
- Consider initiating Mircera treatment only when the
hemoglobin level is less than 10 g/dL and the following considerations apply:
  o The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and
  o Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
• If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Mircera, and use the lowest dose of Mircera sufficient to reduce the need for RBC transfusions
• The recommended starting dose of Mircera for the treatment of anemia in adult CKD patients who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single IV or SC injection once every two weeks.
• Once the hemoglobin has been stabilized, Mircera may be administered once monthly using a dose that is twice that of the every-two-week dose and subsequently titrated as necessary.

**Drug Availability:**
- Prefilled syringes: 50mcg, 75mcg, 100mcg, 150mcg, 200mcg, or 250mcg per 0.3ml

**General Background**

**Pharmacology**
Epoetin alfa is a recombinant form of erythropoietin that may be given intravenously (IV) or subcutaneously. Darbepoetin alfa is a long-acting ESA which contains 2 more amino-linked oligosaccharide chains than epoetin alfa. This structural difference prolongs the half-life of darbepoetin alfa and reduces administration frequency, compared to epoetin alfa. Methoxy ployethyleneglycol-epoetin beta is an erythropoietin receptor activator with greater activity in vivo as well as increased half-life, in contrast to erythropoietin.

**Guidelines**

**National Comprehensive Cancer Network (NCCN)**
In certain conditions, the NCCN suggests there is a place for ESAs in the treatment of anemia caused by myelosuppressive chemotherapy. The guidelines discuss ESAs as a group and do not mention preference of one agent over another. NCCN recognizes it is not always clear if chemotherapy will be curative. In this circumstance, if no other cause of the anemia found, management should start with red blood cell transfusions and a clinical trial if available. If ESAs are used in this circumstance, the dose prescribed should be the lowest possible to manage symptoms and avoid transfusion.
ESAs also have a role in the treatment of symptomatic anemia in lower risk MDS and anemia associated with myelofibrosis, with a target Hgb goal of up to 12.0 g/dL. The guidelines do not preference one ESA over another. (NCCN, 2017)

NCCN defines lower risk in MDS as IPSS-R (Revised International Prognostic Scoring System; Very Low, Low, Intermediate), IPSS (International Prognostic Scoring System; Low/Intermediate-1), or WPSS (WHO Prognostic Scoring System; Very Low, Low, Intermediate). NCCN expresses treatment recommendations based on prognostic categories of MDS. Although there are various methods to determine risk stratification, NCCN prefers the IPSS-R (Revised International Prognostic Scoring System) method because of its accuracy. (NCCN, 2017). Published in 2012, this system takes into consideration prognostic variables including cytogenetics, percentage of bone marrow blasts, hemoglobin, platelets and absolute neutrophil count. Based on the calculated score, individuals are then stratified into five risk groups correlating to an estimated overall survival time in years and median time for progression to AML (acute myeloid leukemia) in years. The risk groups include very low, low, intermediate, high and very high. (Greenberg, 2012)

**European Society for Clinical Oncology (ESMO)**

ESMO clinical practice guidelines for MDS comment that recombinant epoetin or darbepoetin are first line therapies for anemia associated with lower risk MDS without del(5q). The organization notes there is no data suggesting superiority of any ESA. (Fenaux, 2014)

**American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)**

The 2010 updated ASCO/ASH joint guidelines, based on systematic reviews and meta-analyses, consider darbepoetin alfa and epoetin alfa equivalent in efficacy and safety. The guidelines consider ESA therapy an appropriate treatment option for patients with a baseline Hgb less than 10 g/dL. Therapy with an ESA may also be appropriate in patients with Hgb between 10 g/dL and 12 g/dL, depending on the clinical situation, evaluation of the benefits and risks of therapy, and patient preference. RBC transfusion is also an appropriate treatment option for a Hgb in this range. The current guidelines decline to set a target Hgb concentration, but recommend maintaining Hgb at the lowest level sufficient to avoid transfusion. The guidelines are summarized in the table below. (Rizzo, 2010)
<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
<th>Rationale</th>
<th>Special Circumstances</th>
</tr>
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<tbody>
<tr>
<td>Anemic Patients Receiving Concurrent Myelosuppressive Chemotherapy</td>
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<tr>
<td>Patients with chemotherapy-associated anemia</td>
<td>Initiate therapy with an ESA if Hgb is $&lt; 10$ g/dL.</td>
<td>Supported by randomized, placebo-controlled trials.</td>
<td>RBC transfusion is an option depending on clinical situation and anemia severity.</td>
</tr>
<tr>
<td></td>
<td>If Hgb is $10 – 12$ g/dL, ESA therapy may be considered based on clinical situation, evaluation of therapy benefits and risks, and patient preference.</td>
<td>There is not sufficient evidence to determine when to initiate an ESA for Hgb $10–12$ g/dL.</td>
<td>RBC transfusion is an option depending on clinical situation.</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>If Hgb has not risen by $1–2$ g/dL after 6–8 weeks of therapy or transfusion requirements have not diminished, discontinue therapy.</td>
<td>Recommendation based on expert opinion.</td>
<td>Evaluate patient for underlying tumor progression, iron deficiency, or other causes of anemia.</td>
</tr>
<tr>
<td>Maximal Hgb concentration</td>
<td>There is not sufficient evidence to determine an optimal target Hgb concentration. Adjust ESA dose to maintain Hgb at the lowest acceptable level to avoid RBC transfusion. Reduce dose if Hgb increases by $&gt; 1$ g/dL in any 2 week period or if Hgb is sufficient to avoid transfusion.</td>
<td>Recommendation based on 3 meta-analyses.</td>
<td>No RCTs or meta-analyses have been conducted to support benefit of increasing Hgb above the minimum level needed to avoid RBC transfusion.</td>
</tr>
<tr>
<td>Anemic Patients Not Receiving Concurrent Myelosuppressive Chemotherapy</td>
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<tr>
<td>Anemic patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia</td>
<td>May consider ESA if Hgb does not increase after chemotherapy. Follow dosing and monitoring guidelines given above.</td>
<td>Recommendation based on expert opinion and a systematic review.</td>
<td>Begin treatment with chemotherapy or corticosteroids and observe outcomes before starting an ESA. RBC transfusion may be an alternative to ESAs depending on clinical situation.</td>
</tr>
<tr>
<td>Anemic patients with myelodysplasia</td>
<td>Evidence supports use of ESAs in patients with low-risk myelodysplastic syndrome. In one randomized controlled trial (n=87), response was more common with epoetin alfa (37%) than with placebo (11%, $p=0.007$).</td>
<td>Recommendation based on one trial.</td>
<td>Data limited to patients with low-risk myelodysplastic syndrome.</td>
</tr>
<tr>
<td>Anemic patients with other malignancies</td>
<td>Avoid use of ESAs in cancer patients who are not receiving concurrent myelosuppressive chemotherapy.</td>
<td>Increased risk of death in randomized controlled trial (Study 20010103) submitted to FDA. No significant benefit observed in 5 clinical trials.</td>
<td>None</td>
</tr>
</tbody>
</table>

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Coverage Policy Number: 5016

2010 ASCO/ASH Joint Guidelines for the Use of ESA
National Kidney Foundation:
According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group, prior to initiating ESAs in chronic kidney disease (CKD), correctable causes of anemia should be treated, and potential benefits and risks should be assessed for the patient. In adult non-dialysis dependent CKD patients, KDIGO does not recommend initiating ESAs with a Hgb level of ≥ 10.0 g/dl. For adult dialysis dependent CKD patients, the work group suggests starting ESAs when the Hgb level is between 9.0-10.0 g/dl, so as to avoid dropping below 9.0 g/dl. It is also suggested that ESAs not be used in order to maintain a Hgb level greater than 11.5 g/dl. Dosing should be individualized, and the dose should be reduced, rather than withheld in circumstances where the Hgb level needs to be decreased. KDIGO makes no recommendation for use of any particular ESA. (KDIGO, 2012)

Clinical Efficacy- Covered uses
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. (Alsalmiy 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.

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

Covered when medically necessary:

<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>
</tbody>
</table>

References


