Determining the clinical cause of Hb changes for patients with anemia due to CKD on dialysis

INDICATION
Aranesp® (darbepoetin alfa) is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.

LIMITATIONS OF USE
• Aranesp® has not been shown to improve quality of life, fatigue, or patient well-being.
• Aranesp® is not indicated for use as a substitute for red blood cell transfusions in patients who require immediate correction of anemia.

Hb = hemoglobin; CKD = chronic kidney disease.

There’s More to Aranesp®:
Assessing and Managing Anemia

Determining the clinical cause of Hb changes for patients with anemia due to CKD on dialysis
Assessing **clinical factors**

For a lack of or loss of Hb response to Aranesp®, initiate a search for causative factors.

### CLINICAL FACTORS THAT MAY BE ASSOCIATED WITH DECREASE IN Hb

- **Inadequate dialysis**: 
  - (Kt/V) < 1.2
  - URR < 65%

- **Infection or inflammation**: 
  - SIRS
  - WBC count
  - CRP

- **Hemolysis**: 
  - Prolonged discontinuation of ESA dose
  - Problems with water supply, dialysate, or dialysis equipment (especially if more than one patient is suspected of hemodialysis)

- **Abnormal Coombs' test**: 
  - Kt/V < 1.2
  - URR < 65%

- **Frequent dose changes**: 
  - Starting dose for patients on dialysis lower than recommended in PI (< 0.45 mcg/kg once weekly or < 0.75 mcg/kg once every 2 weeks)

- **Iron deficiency–functional**: 
  - Low TSAT (or facility-established target)
  - Chronic infections

- **Iron deficiency–absolute**: 
  - Low TSAT (or facility-established target)
  - Functional iron deficiency may be caused by infection, inflammation, or increased erythropoiesis. Iron stores may be present but are not available to the body.

- **Secondary HPT**: 
  - Prolonged discontinuation of ESA dose

- **Hemodialysis treatment-related factors**: 
  - Frequent dose changes
  - Problems with water supply, dialysate, or dialysis equipment (especially if more than one patient is suspected of hemodialysis)

- **Medication therapy**: 
  - Certain antibiotics
  - Certain antineoplastics
  - Certain anticonvulsants

### Laboratory Measurements

#### Laboratory values

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic blood loss</td>
<td>↓</td>
</tr>
<tr>
<td>Infections**</td>
<td>↓</td>
</tr>
<tr>
<td>Inflammation*</td>
<td>↓</td>
</tr>
<tr>
<td>Iron deficiency–absolute***</td>
<td>↓</td>
</tr>
<tr>
<td>Iron deficiency–functional****</td>
<td>↓</td>
</tr>
<tr>
<td>Malnutrition†</td>
<td>↓</td>
</tr>
</tbody>
</table>

#### Reference values

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>&lt; 12 g/dL</td>
</tr>
</tbody>
</table>

*Infections** and inflammation* are associated with decreases in Hb levels.** Significant declines in Hb levels are not associated with hypoxic foci.** For the purposes of this instruction, hypoxic foci are not available to the Hb.

**Significant declines in Hb levels are not associated with hypoxic foci.**

Please see Important Safety Information, including Dosage RANGES in page 6.

### Boxed WARNINGS

**CHRONIC KIDNEY DISEASE:**

**WARNING: ESAS INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, SEPSIS, MORTALITY, AND MORTALITY RELATED TO CARDIOVASCULAR EVENTS.**

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered an erythropoiesis-stimulating agent (ESA) to target a hemoglobin level of greater than 10 g/dL.

- No trial has identified a hemoglobin target level, Aranesp® dose, or dosing strategy that does not increase these risks.

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- No trial has identified a hemoglobin target level, Aranesp® dose, or dosing strategy that does not increase these risks.

### IMPORTANT SAFETY INFORMATION

- **Please see Important Safety Information, including Dosage RANGES in page 6.**
Managing anemia due to CKD

Monitor and evaluate Hb levels over time to identify opportunities for anemia management

**MONITOR** and track Hb over time
- Monitor weekly at initiation and at every dose adjustment until Hb is stable
- Monitor at least monthly when Hb is stable

**EVALUATE** changes in Hb response
- Assess iron status
- Assess for causes of low Hb levels
- Assess for Hb overshoot

**ADDRESS** Hb changes as appropriate
- Identify and manage factors affecting Hb level
- For factors associated with anemia due to CKD, determine appropriate physician-prescribed Aranesp® dose adjustments
- Individualize dosing and use the lowest dose sufficient to reduce the need for RBC transfusions

Aranesp® multiple dosing options allow for the ability to address individual patient needs through QW and Q2W dosing intervals

**IMPORTANT SAFETY INFORMATION**
- Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

Aranesp® dosing options

Designed for individualized treatment
- Comparison of less frequent dosing with QW and Q2W intervals to TIW dosing
- Multiple dosing options can be combined for precise titration and individualized treatment of patients

Aranesp® is also available in 150, 200, 300, and 500 mcg dose strengths. Aranesp® is available in single-dose vials and prefilled syringes, except the 10, 150, and 500 mcg dose strengths, which are available only as prefilled syringes.

The IV route of administration is recommended for adult patients on hemodialysis.
Dosing information

Aranesp® (darbepoetin alfa) for anemia due to CKD

- Initiated trials, patients experienced greater risk for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a Hb level of greater than 10 g/dL.
- No trial has identified a Hb target level, Aranesp® dose, or dosing strategy that does not increase these risks.
- Individual dosing due to the lowest dose of Aranesp® sufficient to reduce the need for RBC transfusions.
- Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

**Considerations**
- Correct or exclude other causes of anemia before initiating Aranesp®.
- Evaluate the iron status in all patients before and during treatment.
- Administer supplemental iron therapy if serum ferritin is < 100 mcg/L or serum transferrin saturation is < 20%.
- Correct or exclude other causes of anemia before initiating Aranesp®.

**Risks of death and other serious cardiovascular adverse events.**
- Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.
- Individual dosing due to the lowest dose of Aranesp® sufficient to reduce the need for RBC transfusions.
- Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

**Initiating Aranesp® for Adult Patients with CKD on Dialysis**

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**Initiating Aranesp® for Adult Patients with CKD not on Dialysis**

- Consider initiating Aranesp® treatment only when the Hb level is < 10 g/dL and the following considerations apply:
  - The rate of change of ESA indicates the likelihood of requiring a RBC transfusion.
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  - The rate of change of ESA indicates the likelihood of requiring a RBC transfusion.
- Administer supplemental iron therapy if serum ferritin is < 100 mcg/L or serum transferrin saturation is < 20%.
- Appropriate control hypertension prior to initiation of and during treatment with Aranesp®.
- Reduce or withhold Aranesp® if blood pressure becomes difficult to control.

**Patient who do not respond adequately to Aranesp®**

- For patients who do not respond adequately over a 12-week escalation period, increasing the Aranesp® dose further is unlikely to improve response and may increase risks.
- Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions.
- Evaluate other causes of anemia.
- Appropriate control hypertension prior to initiation of and during treatment with Aranesp®.

**Boxed WARNINGS**

- Following initiation of therapy, consider the risk of death, serious adverse cardiovascular reactions, and stroke. Patients who are older than 65 years or have a history of cardiovascular disease may be at even greater risk for cardiovascular reactions and mortality than other patients.

**MONITORING**

- Following initiation of therapy and after each dose adjustment, monitor Hb at least weekly until the Hb is stable and sufficient to minimize the need for RBC transfusions.
- Thereafter, Hb should be monitored at least every 4 weeks, provided that Hb levels remain stable.

**DOSE ADJUSTMENTS**

- When adjusting therapy, consider the risk of death, serious adverse cardiovascular reactions, and stroke.
- Decrease the dose more frequently than once every 4 weeks.
- Decrease in dose can occur more frequently.
- Avoid frequent dose adjustments.

**Reducing the Risk of Alloimmunization and/or Other RBC Transfusion-Related Risks is a Goal**

- The IV route of administration is recommended for patients on hemodialysis.
- Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.
- The rate of Hb decline indicates the likelihood of requiring a RBC transfusion.

**For Pediatric Patients (less than 18 years) with CKD**

- Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions.
- Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions.
- For pediatric patients less than 18 years with CKD:
  - Any hematocrit levels or hematocrit levels of 32% or lower should be considered for RBC transfusion.
  - Reduce or interrupt the dose of Aranesp®.

**Monitoring**

- Following initiation of therapy and after each dose adjustment, monitor Hb at least weekly until the Hb is stable and sufficient to minimize the need for RBC transfusions.
- Thereafter, Hb should be monitored at least every 4 weeks, provided that Hb levels remain stable.

**Dose Adjustments**

- When adjusting therapy, consider the risk of death, serious adverse cardiovascular reactions, and stroke.
- Do not increase the dose more frequently than once every 4 weeks.
- Decrease in dose can occur more frequently.
- Avoid frequent dose adjustments.

**Reducing the Risk of Alloimmunization and/or Other RBC Transfusion-Related Risks is a Goal**

- The IV route of administration is recommended for patients on hemodialysis.
- Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.
- The rate of Hb decline indicates the likelihood of requiring a RBC transfusion.

**For Pediatric Patients less than 18 years with CKD**

- Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions.
- For pediatric patients less than 18 years with CKD:
  - Any hematocrit levels or hematocrit levels of 32% or lower should be considered for RBC transfusion.
  - Reduce or interrupt the dose of Aranesp®.

**Monitoring**

- Following initiation of therapy and after each dose adjustment, monitor Hb at least weekly until the Hb is stable and sufficient to minimize the need for RBC transfusions.
- Thereafter, Hb should be monitored at least every 4 weeks, provided that Hb levels remain stable.

**Dose Adjustments**

- When adjusting therapy, consider the risk of death, serious adverse cardiovascular reactions, and stroke.
- Decrease the dose more frequently than once every 4 weeks.
- Decrease in dose can occur more frequently.
- Avoid frequent dose adjustments.

**Reducing the Risk of Alloimmunization and/or Other RBC Transfusion-Related Risks is a Goal**

- The IV route of administration is recommended for patients on hemodialysis.
- Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.
- The rate of Hb decline indicates the likelihood of requiring a RBC transfusion.

**For Pediatric Patients (less than 18 years) with CKD**

- Use the lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions.
- For pediatric patients less than 18 years with CKD:
  - Any hematocrit levels or hematocrit levels of 32% or lower should be considered for RBC transfusion.
  - Reduce or interrupt the dose of Aranesp®.
Important Safety Information including Boxed WARNINGS

**WARNINGS—DO INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE.**

**Chronic Kidney Disease:**
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 9 g/dL.
- No trials identified a hemoglobin target, Aranesp® dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp® dose sufficient to reduce the need for red blood cell (RBC) transfusions.

**Cancer:**
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, thyroid, and cervical cancers.
- To minimize 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.

- Aranesp® is contraindicated in patients with:
  - Intrauterine hypertension
  - Fever and neutropenia
  - Hemoglobin greater than 15.0 g/dL
  - Serious allergic reactions to Aranesp®

- Precautions to administer Aranesp®:
- Patients with CKD may have an increased risk for cardiovascular reactions and mortality. These effects may be higher at doses of 120 mcg/kg weekly (28 mcg/kg daily), which were more common in clinical trials.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of atheroembolic events in CKD patients undergoing angiography procedures.
- Control hypertension prior to initiating and during treatment with Aranesp®.
- Aranesp® increases the risk of seizures in patients with CKD. Monitor patients closely for new-onset seizures, premonitory symptoms, or change in seizure frequency.
- For lack of evidence of hemoglobin response to Aranesp®, initiate a search for causative factors. (Hypothetical causes of lack of response are presented in the Medication Guide).
- Cases of ST elevation and/or severe anemia, with or without other symptoms, as well as following the development of neuromuscular antibodies to erythropoietin have been reported in patients treated with Aranesp®.

**References:**
Aranesp® provides more than treatment

- More than 1.2 million patient-years of experience
- Committed to training, education, and nephrology community support
- Consistently supplied since 2001
- Multiple dosing options in prefilled syringes with QW and Q2W intervals
- The ability to intervene when patients experience frequent changes to their Hb levels

* US exposure estimate methodology based on total monthly dollar revenue, assumed monthly revenue per patient, assumed patient to box ratio, and assumed sales of administration from 2002 through November 30, 2017. It assumes an increase on the patient level, not accounting for dose increases, and does not reflect price increases since 2008.

† Based upon 99.9% of product shipped to Amgen Authorized Distributors of Record only.

Visit Aranesp.com for more information

IMPORTANT SAFETY INFORMATION

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, Aranesp® dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp® dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Please see Important Safety Information, including Boxed WARNINGS, on page 8.
Please click on the link for the Aranesp® Full Prescribing Information, including Boxed WARNINGS and Medication Guide.

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