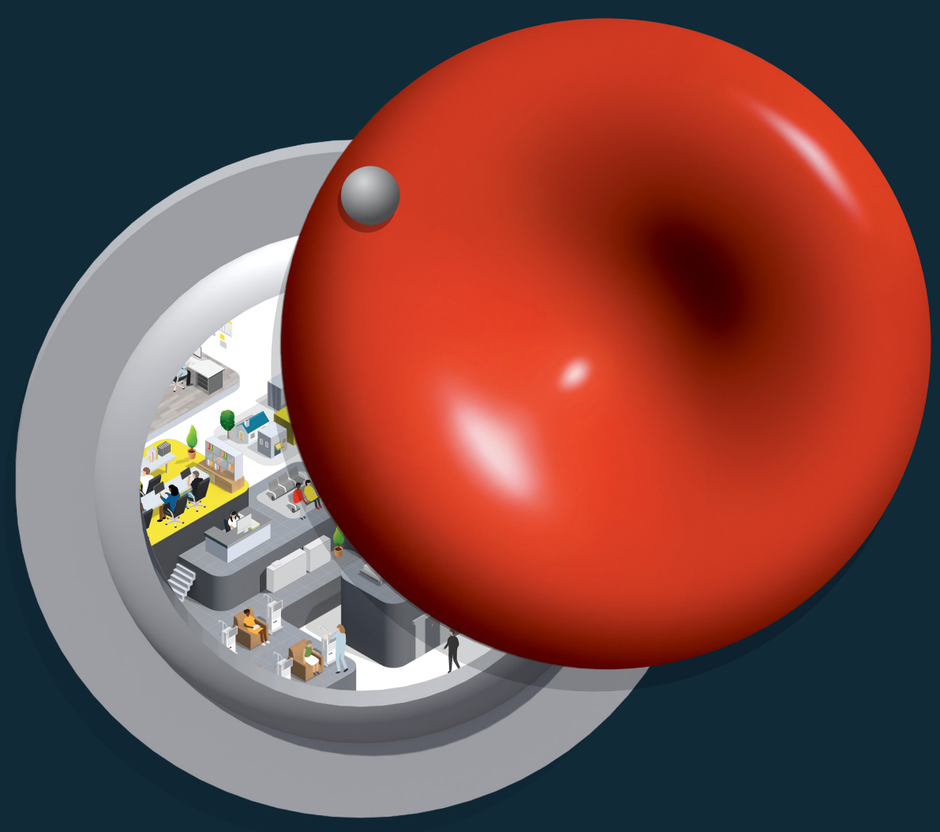
There's More to Aranesp®: *Assessing and Managing Anemia*



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

Hb = hemoglobin; CKD = chronic kidney disease.

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.

Please see Important Safety Information, including ***Boxed WARNINGS about INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE,*** *on page 8.*

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Assessing ***clinical factors***

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

CLINICAL FACTORS THAT MAY BE ASSOCIATED WITH DECREASE IN Hb*		
Iron deficiency[1]	• Ferritin < 100 ng/mL (or facility-established target)	• TSAT < 20% (or facility-established target)
Hospitalization[2]	• Blood loss during hospitalization (eg, surgery, blood draws)[3,4]	• Not identified for Hb monitoring after discharge[5]
Infection or inflammation[4]	• ↑ Ferritin with ↓ TSAT[6] • ↑ WBC count[7]	• ↑ CRP[8]
Blood loss[4]	• Known occult blood loss[4] • ↑ Reticulocyte count[7] • Low TSAT (or facility-established target)[7]	• Clotted dialyzer[9] • Gastrointestinal tract bleeding[4]
Secondary HPT[4]	• ↑ iPTH[10]	• Osteitis fibrosa[10]
Comorbid conditions	• Aluminum toxicity[11] • Chronic infections[4]	• Chronic inflammation[12]
Medications[7]	• Certain analgesics[2]	• Certain antibiotics
Hemodialysis treatment-related factors	• Dialysis missed/shortened[13] • URR < 65%[14] • Kt/V < 1.2[15]	• Nonadherence to dosing[3] • Interdialytic weight gain[16]
Nutrition or vitamin deficiency	• Protein energy malnutrition[17] – Protein intake below recommended level[17] – ↓ Serum albumin or prealbumin[18,19] – Low BMI[19]	• Vitamin deficiency[20] – ↑ MCV[7] – B_{12} < 140 pg/mL[21] – Folic acid < 3 ng/mL[22] – B_6 < 5 ng/mL[22]
Hemolysis[4]	• ↑ Bilirubin[23] • Abnormal Coombs' test[23] • ↓ Serum haptoglobin[4] • ↑ Reticulocyte count[7] • ↑ TSAT[7]	• ↑ Ferritin[7] • Cherry-red to port-wine-colored blood[23] • Problems with water supply, dialysate, or dialysis equipment (especially if more than one patient is suspected of hemodialysis)[23]
Aranesp® dose-related factors	• 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)[1] • Frequent dose changes[24]	• Hb not monitored appropriately following initiation or dose change[1] • Prolonged discontinuation of ESA dose[25]

*Please note the information provided in this material is not intended to be an exhaustive list of all potential clinical events and conditions associated with decreases in Hb. This material is not a substitute for clinical assessment provided by a qualified healthcare professional.

TSAT = transferrin saturation; WBC = white blood cell; CRP = C-reactive protein; HPT = hyperparathyroidism; iPTH = intact parathyroid hormone; URR = urea reduction ratio; Kt/V = volume of blood cleared (Kt) and modeled area volume (V); BMI = body mass index; MCV = mean corpuscular volume; PI = prescribing information; ESA = erythropoiesis-stimulating agent.

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.**

Evaluating ***lab trends***

Identify lab trends associated with certain clinical conditions

	LABORATORY MEASUREMENTS								
	Hb[1] (g/dL)	**TSAT**[1,6] (%)	**Ferritin**[1] (ng/mL)	**TIBC**[7] (µg/dL)	**Reticulocyte count**[26] (% of total RBC count)	**WBC**[7] (cells/mm³)	**Albumin**[27] (g/dL)	**Kt/V**[15]	**URR**[15]
	REFERENCE VALUES								
Condition†	Individualize[2]	> 20%	≥ 100	250–460	0.5%–1.5%	5,000–10,000	≥ 4.0	> 1.2	65%
Chronic blood loss[4,7]	↓	↓	↓		↑				
Hemolysis[4,7]	↓	↑	↑		↑ or ↓				
Infection[1,4,7,22,26]	↓	↓	↑	↓		↑	↓		
Inflammation[1,4,7,8,27]	↓	↓	↑	↓		↑	↓		
Iron deficiency-absolute[1,4,7,26]	↓	↓	↓	↑					
Iron deficiency-functional[1,4,7,26,28,§]	↓	↓	↑	↓		↑	↓		
Secondary HPT[3,4,7,29]	↓				↓				
Inadequate dialysis[4,13,15]	↓							< 1.2	< 65%
Malnutrition[7,18]	↓						↓		

Initiate Aranesp® when the Hb level is < 10 g/dL.

†Please note the information provided in this material is not intended to be an exhaustive list, and other conditions not named may impact anemia. This material is not a substitute for clinical assessment provided by a qualified healthcare professional.

‡In patients with anemia due to CKD, individualize dosing and use the lowest dose of Aranesp® sufficient to reduce the need for RBC transfusions. Reduce or interrupt dose if the Hb level approaches or exceeds 11 g/dL.[1]

§Functional iron deficiency may be caused by infection, inflammation, or increased erythropoiesis. Iron stores may be present but are not available to the body.[28]

Absolute iron deficiency is a depletion of iron stores, generally accompanied by low or absent stainable iron in the bone marrow.[30]

Albumin value is a simple protein that represents the synthesis and degradation of albumin and is a potential indicator of nutritional status.[31,32]

Chronic blood loss refers to ongoing loss of blood due to factors such as the dialysis procedure, menses, and/or comorbid conditions.[4,33]

Ferritin is the major iron storage protein; 1 ng/mL of serum ferritin corresponds to approximately 8 mg of stored iron.[34]

Functional iron deficiency is the simultaneous presence of adequate iron stores (ie, normal or high ferritin levels) and insufficient delivery of iron to the bone marrow to support erythropoiesis (ie, low TSAT levels).[30]

Hemoglobin is the red respiratory protein of RBCs that transports oxygen from the lungs to the tissues.[31]

Hemolysis is the destruction or dissolution of RBCs, with subsequent release of hemoglobin.[31]

Inadequate dialysis is the failure to achieve a URR of 65% or a Kt/V ≥ 1.2/dialysis session in patients on hemodialysis, or a Kt/V ≥ 1.7/week in patients on peritoneal dialysis.[15]

Infection is the invasion of the body by microorganisms that have the potential to cause disease.[31]

Inflammation is a protective tissue response to cellular injury, marked by pain, heat, redness, swelling, and loss of function.[31]

Kt/V is a formula for measuring dialysis adequacy, where K = dialyzer clearance, t = time, and V = volume of urea distribution in a patient's body.[15]

Malnutrition is a condition of nutritional imbalance, marked by the consumption of insufficient or improper food.[35]

Reticulocyte count is the percent of immature RBCs in the bloodstream.[26]

Secondary HPT is the excessive secretion of PTH caused by a disruption in the interactions among PTH, calcium, phosphorus, and vitamin D in patients with CKD.[29]

TIBC, or total iron binding capacity, is a measure of all proteins available for binding mobile iron.[34]

TSAT is the percent of transferrin and other mobile iron-binding proteins saturated with iron.[34]

URR is the percent reduction in blood urea nitrogen during a single hemodialysis session.[15]

WBC count with differential is the number of white blood cells, and the percentage of each type of white blood cell, in the blood and is a marker of small-solute diffusion across the dialyzer.[27]

TIBC = total iron binding capacity; RBC = red blood cell.

IMPORTANT SAFETY INFORMATION

- For lack or loss of hemoglobin response to Aranesp®, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA.

*Please see Important Safety Information, including **Boxed WARNINGS**, on page 8.*

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Managing
anemia due to CKD

Monitor and evaluate Hb levels over time to identify opportunities for anemia management[1]

MONITOR
and track Hb over time[1]

- Monitor weekly at initiation and at every dose adjustment until Hb is stable[1]
- Monitor at least monthly when Hb is stable[1]

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[1]

QW = once weekly; Q2W = once every 2 weeks.

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

- Convenience of less frequent dosing with QW and Q2W intervals vs TIW dosing[1]
- Multiple dosing options can be combined for precise titration and individualized treatment of patients[1]

10 mcg | 25 mcg | 40 mcg | 60 mcg | 100 mcg

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.

TIW = three times weekly; IV = intravenous.

Please see dosing information for Aranesp® on pages 6 and 7.
*Please see Important Safety Information, including **Boxed WARNINGS**, on page 8.*

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Dosing information

Aranesp® (darbepoetin alfa) for anemia due to CKD

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a Hb level of greater than 11 g/dL.**
- **No trial has identified a Hb target level, Aranesp® dose, or dosing strategy that does not increase these risks.**
- **Individualize dosing and use 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%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy.
- Appropriately control hypertension prior to initiation of and during treatment with Aranesp®.
  - Reduce or withhold Aranesp® if blood pressure becomes difficult to control.

INITIATING ARANESP® FOR ADULT PATIENTS WITH CKD ON DIALYSIS

- **Initiate Aranesp® treatment when the Hb level is < 10 g/dL.**
- **QW recommended starting dose:** 0.45 mcg/kg as an IV or SC injection once weekly, as appropriate.
- **Q2W recommended starting dose:** 0.75 mcg/kg as an IV or SC injection once every 2 weeks, as appropriate.
  - The IV route of administration is recommended for patients on hemodialysis.

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 Hb 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
- **Q4W recommended starting dose:** 0.45 mcg/kg body weight as an IV or SC injection once at 4 week intervals as appropriate.

INITIATING ARANESP® FOR PEDIATRIC PATIENTS (LESS THAN 18 YEARS) WITH CKD

- **Initiate Aranesp® treatment when the Hb level is < 10 g/dL.**

On dialysis and not on dialysis:

- **QW recommended starting dose:** 0.45 mcg/kg as an IV or SC injection once weekly, as appropriate.

Not on dialysis:

- **Q2W recommended starting dose:** 0.75 mcg/kg as an IV or SC injection once every 2 weeks, as appropriate.

SC = subcutaneous; Q4W = once every 4 weeks.

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 transfusion.

- Thereafter, Hb should be monitored at least monthly, provided that Hb levels remain stable.

DOSE ADJUSTMENTS

When adjusting therapy, consider Hb rate of rise, rate of decline, ESA responsiveness, and Hb variability.

- A single Hb 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.

REDUCE OR INTERRUPT DOSE

- If Hb rises rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 25% or more, as needed, to reduce rapid responses.

FOR ADULT PATIENTS WITH CKD

- **On dialysis: reduce** or **interrupt** dose if the Hb level approaches or exceeds 11 g/dL.
- **Not on dialysis:** if the Hb level exceeds 10 g/dL, **reduce** or **interrupt** the dose of Aranesp®, and use the lowest dose of Aranesp® sufficient to reduce the need for RBC transfusions.

FOR PEDIATRIC PATIENTS (LESS THAN 18 YEARS) WITH CKD

- If the hemoglobin level approaches or exceeds 12 g/dL, **reduce** or **interrupt** the dose of Aranesp®.

INCREASE DOSE

- If the Hb has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25% when appropriate.

Patients 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.
- If typical causes of lack or loss of Hb response are excluded, evaluate for pure red cell aplasia (PRCA).
- Discontinue Aranesp® if responsiveness does not improve.

Patients with CKD and an insufficient Hb response to ESA therapy or a rate of Hb rise of > 1 g/dL over 2 weeks may be at even greater risk for cardiovascular reactions and mortality than other patients.

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Important Safety Information including **Boxed WARNINGS**

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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.**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.**
- **To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.**
- **Use ESAs only for anemia from myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.**
- **Discontinue following the completion of a chemotherapy course.**

- Aranesp® is contraindicated in patients with:
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with Aranesp® or other erythropoietin protein drugs
  - Serious allergic reactions to Aranesp®
- Use caution in patients with coexistent cardiovascular disease and stroke.
- 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.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic 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 or loss of hemoglobin response to Aranesp®, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA.
- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp®.
  - This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration.
  - PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Aranesp® is not approved).
  - If severe anemia and low reticulocyte count develop during treatment with Aranesp®, withhold Aranesp® and evaluate patients for neutralizing antibodies to erythropoietin.
  - Permanently discontinue Aranesp® in patients who develop PRCA following treatment with Aranesp® or other erythropoietin protein drugs. Do not switch patients to other ESAs.
- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with Aranesp®. Immediately and permanently discontinue Aranesp® if a serious allergic reaction occurs.
- Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including Aranesp®) in the postmarketing setting. Discontinue Aranesp® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.
- Adverse reactions (≥ 10%) in Aranesp® clinical studies in patients with CKD were hypertension, dyspnea, peripheral edema, cough, and procedural hypotension.

Please click on the link for the Aranesp® full Prescribing Information, including Boxed WARNINGS and Medication Guide.

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Aranesp® provides ***more than treatment***

- More than 1.2 million patient-years of experience[38,*]
- Committed to training, education, and nephrology community support
- Consistently supplied since 2001[39,†]
- Multiple dosing options in prefilled syringes with QW and Q2W intervals[1]
- The ability to intervene when patients experience frequent changes to their Hb levels[1,40]

*US exposure estimate methodology based on total monthly dollar revenue, assumed monthly revenue per patient, assumed patient loss rate, and assumed route of administration share 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.

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IMPORTANT SAFETY INFORMATION

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