EPOGEN® (EPOETIN ALFA) RECOMBINANT

Every vial tells a story.

The EPOGEN® story begins with patients.

Vials shown are not actual size.

Assessing and Managing Anemia

Determining the clinical cause of Hb changes for patients with anemia due to CKD on dialysis to reduce the need for red blood cell transfusions

Hb = hemoglobin; CKD = chronic kidney disease.

Indication

EPOGEN® (epoetin alfa) is indicated for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis to decrease the need for red blood cell (RBC) transfusion.

Limitations of Use:

- EPOGEN® has not been shown to improve quality of life, fatigue, or patient well-being.
- EPOGEN® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Please see Important Safety Information for EPOGEN® including ***Boxed WARNINGS*** *about* ***INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE,*** *on pages 8 and 9.*

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

Assessing clinical factors

For a lack or loss of Hb response to EPOGEN®, 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[4]	• Osteitis fibrosa[10]
Comorbid conditions	• Aluminum toxicity[11] • Chronic infections[4]	• Chronic inflammation[12]
Medications[7]	• Certain analgesics	• 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]
EPOGEN® dose-related factors	• Starting dose lower than recommended in PI (< 50–100 Units/kg three times weekly [TIW])[1] • Frequent dose changes[24]	• Hb not monitored at least weekly to establish appropriate maintenance dose or after a dose change[1] • Prolonged discontinuation of EPOGEN® dose[25] • Diagnosed with PRCA[1,3]

*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.

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

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

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, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest EPOGEN® dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

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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/mm^3)	Albumin[27] (g/dL)	Kt/V[15]	URR[15]
		REFERENCE VALUES							
Condition[†]	Individualize[‡]	≥ 20%	≥ 100	250–460	0.5%–1.5%	5,000–10,000	≥ 4.0	> 1.2	> 65%
Chronic blood loss[1,4,7]	↓	↓	↓		↑				
Hemolysis[4,7]	↓	↑	↑		↑ or ↓				
Infection[1,4,7,22,26]	↓	↓	↑	↓		↑	↓		
Inflammation[1,4,6,7,8,27]	↓	↓	↑	↓		↑	↓		
Iron deficiency–absolute[1,4,7,26]	↓	↓	↓	↑					
Iron deficiency–functional[1,4,7,28,§]	↓	↓	↑						
Secondary HPT[3,4,7,29]	↓								
Inadequate dialysis[4,13,15]	↓							< 1.2	< 65%
Malnutrition[7,18]	↓						↓		

Initiate EPOGEN® when the Hb level is < 10 g/dL.[1]

[†]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 EPOGEN® 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.[4,28]

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.[6,33]

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 urea 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.[34]

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.[36]

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.[37]

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

IMPORTANT SAFETY INFORMATION

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

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EPOGEN® (EPOETIN ALFA) RECOMBINANT

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 EPOGEN® dose adjustments
- Individualize dosing and use the lowest dose sufficient to reduce the need for RBC transfusions

The flexibility of EPOGEN® TIW dosing allows for timely intervention to help address Hb changes[1]

CKD = chronic kidney disease; TIW = three times weekly.

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.

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EPOGEN® Dosing Options

EPOGEN® is designed with flexible TIW dosing options and IV administration that you control

Dose and corresponding rise in Hb in 2 weeks with EPOGEN® TIW dosing[1]

STARTING DOSE (3 times weekly intravenously)	HEMOGLOBIN INCREASE IN 2 WEEKS
50 Units/kg	0.5 g/dL
100 Units/kg	0.8 g/dL

Data from 13 clinical studies involving IV administration of EPOGEN® to 1010 anemic adult patients on dialysis. Starting doses were 50 to 150 Units/kg TIW. In the 3 largest studies, the median maintenance dose necessary to maintain the Hb between 10 and 12 g/dL was approximately 75 Units/kg TIW.[1]

EPOGEN® is available in single-dose and multidose vials[1]

EPOGEN® vials not shown at actual size. Not all vial sizes shown.

EPOGEN is also available in 20,000 Units/mL and 20,000 Units/2mL vials.

TIW = three times weekly.

IMPORTANT SAFETY INFORMATION

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.

Please see dosing information for EPOGEN® on pages 6 and 7.
*Please see Important Safety Information, including **Boxed WARNINGS**, on pages 8 and 9.*

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EPOGEN® (EPOETIN ALFA) RECOMBINANT

Dosing information

EPOGEN® (epoetin 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.[1]**
- **No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks.[1]**
- **Individualize dosing and use the lowest dose of EPOGEN® sufficient to reduce the need for RBC transfusions.[1]**
- **Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse reactions.[1]**

Considerations[1]

- Correct or exclude other causes of anemia before initiating EPOGEN®
- Evaluate the iron status of 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
- In pregnant women, lactating women, neonates, and infants use only single-dose vials (the benzyl alcohol-free formulation). Do not mix EPOGEN® with bacteriostatic saline (which contains benzyl alcohol) when administering to these patients
- Appropriately control hypertension prior to initiation of and during treatment with EPOGEN®
  - Reduce or withhold EPOGEN® if blood pressure becomes difficult to control

INITIATING EPOGEN® FOR ADULT PATIENTS WITH CKD ON DIALYSIS[1]

- **Initiate EPOGEN® treatment when the Hb level is < 10 g/dL**
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. The intravenous route of administration is recommended for patients on hemodialysis

INITIATING EPOGEN® FOR PEDIATRIC PATIENTS (AGES 1 MONTH OR OLDER)[1]

- **Initiate EPOGEN® treatment only when the Hb level is < 10 g/dL**
- The recommended starting dose for pediatric patients is 50 Units/kg 3 times weekly intravenously or subcutaneously.

MONITOR AND ASSESS HB REGULARLY[1]

Following initiation of therapy and after each dose adjustment, monitor Hb at least weekly until the Hb level 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.

CKD = chronic kidney disease; ESA = erythropoiesis stimulating agents; HB = hemoglobin; RBC = red blood cell

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DOSAGE ADJUSTMENTS[1]

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[1]

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:

• Reduce or interrupt dose if the Hb level approaches or exceeds 11 g/dL

For pediatric patients (ages 1 month or older):

• Reduce or interrupt dose if the Hb level approaches or exceeds 12 g/dL

INCREASE DOSE[1]

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 EPOGEN®[1]

- For patients who do not respond adequately over a 12-week escalation period, increasing the EPOGEN® 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 EPOGEN® 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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EPOGEN® (EPOETIN ALFA) RECOMBINANT

Indication

EPOGEN® (epoetin alfa) is indicated for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis to decrease the need for red blood cell (RBC) transfusion.

Limitations of Use:

- EPOGEN® has not been shown to improve quality of life, fatigue, or patient well-being.
- EPOGEN® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Important Safety Information, including **Boxed WARNINGS**

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, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest EPOGEN® 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.**

Perisurgery:

- **Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended.**

- EPOGEN® is contraindicated in patients with:
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with EPOGEN® or other erythropoietin protein drugs
  - Serious allergic reactions to EPOGEN®
- EPOGEN® from multidose vials contains benzyl alcohol and is contraindicated in neonates, infants, pregnant women, and lactating women.
- 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 EPOGEN®.
- EPOGEN® 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 EPOGEN®, 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 EPOGEN®.
  - 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 EPOGEN® is not approved).
  - If severe anemia and low reticulocyte count develop during treatment with EPOGEN®, withhold EPOGEN® and evaluate patients for neutralizing antibodies to erythropoietin.
  - Permanently discontinue EPOGEN® in patients who develop PRCA following treatment with EPOGEN® 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 EPOGEN®. Immediately and permanently discontinue EPOGEN® if a serious allergic reaction occurs.

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

Important Safety Information (cont'd)

- 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 EPOGEN®) in the postmarketing setting. Discontinue EPOGEN® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.
- Serious and fatal reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including EPOGEN® multiple-dose vials. There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
- Adverse reactions (≥ 5%) in EPOGEN® clinical studies in patients with CKD were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection.

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1. EPOGEN® (epoetin alfa) prescribing information, Amgen. **2.** Solid CA, Foley RN, Gilbertson DT, Collins AJ. Perihospitalization hemoglobin-epoetin associations in U.S. hemodialysis patients, 1998 to 2003. *Hemodial Int*. 2007;11(4):442-447. **3.** Kidney Disease: Improving Global Outcomes (KDIGO®) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279-335. **4.** Fishbane S. Hematologic abnormalities. In: Daugirdas JT, Blake PG, Ing TS, eds. *Handbook of Dialysis*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:522-541. **5.** Chan KE, Lazarus JM, Wingard RL, Hakim RM. Association between repeat hospitalization and early intervention in dialysis patients following hospital discharge. *Kidney Int*. 2009;76(3);331-341. **6.** National Kidney Foundation. 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EPOGEN®
(EPOETIN ALFA)
RECOMBINANT

Every vial tells a story.

The EPOGEN® story begins with patients.

- More than 2.8M patients have received EPOGEN® since FDA approval[38,*]
- Committed to training, education, and nephrology community support
- Consistently supplied since 2001[39,†]
- Multiple dosing options available (single-dose and multidose vials)[1]
- The ability to intervene when patients experience frequent changes to their Hb levels[1,40]

EPOGEN® vials not shown at actual size. Not all vial sizes shown.

*In the postmarketing setting from launch through December 31, 2020. Data on incident and prevalent number of patients on dialysis and market share are used to estimate number of patients exposed.
†Based upon 99.9% of product shipped to Amgen Authorized Distributors of Record only.

Visit AmgenESAs.com/Epogen 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, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest EPOGEN® dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

*Please see Important Safety Information, including **Boxed WARNINGS**, on pages 8 and 9.*

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

AMGEN
Nephrology

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EPOGEN® (EPOETIN ALFA) RECOMBINANT

Every vial tells a story.

The EPOGEN® story begins with patients.

Vials shown are not actual size.

Assessing and Managing Anemia

Determining the clinical cause of Hb changes for patients with anemia due to CKD on dialysis to reduce the need for red blood cell transfusions

Hb = hemoglobin; CKD = chronic kidney disease.

Indication

EPOGEN® (epoetin alfa) is indicated for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis to decrease the need for red blood cell (RBC) transfusion.

Limitations of Use:

- EPOGEN® has not been shown to improve quality of life, fatigue, or patient well-being.
- EPOGEN® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

*Please see Important Safety Information for EPOGEN® including **Boxed WARNINGS** about **INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE,** on pages 8 and 9.*

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Assessing clinical factors

For a lack or loss of Hb response to EPOGEN®, 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[4]	• Osteitis fibrosa[10]
Comorbid conditions	• Aluminum toxicity[11] • Chronic infections[4]	• Chronic inflammation[12]
Medications[7]	• Certain analgesics	• 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]
EPOGEN® dose-related factors	• Starting dose lower than recommended in PI (< 50–100 Units/kg three times weekly [TIW])[1] • Frequent dose changes[24]	• Hb not monitored at least weekly to establish appropriate maintenance dose or after a dose change[1] • Prolonged discontinuation of EPOGEN® dose[25] • Diagnosed with PRCA[1,3]

*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.

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

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

IMPORTANT SAFETY INFORMATION

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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, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest EPOGEN® dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

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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/mm^3)	Albumin[27] (g/dL)	Kt/V[15]	URR[15]
		REFERENCE VALUES							
Condition[†]	Individualize[‡]	≥ 20%	≥ 100	250–460	0.5%–1.5%	5,000–10,000	≥ 4.0	> 1.2	> 65%
Chronic blood loss[1,4,7]	↓	↓	↓		↑				
Hemolysis[4,7]	↓	↑	↑		↑ or ↓				
Infection[1,4,7,22,26]	↓	↓	↑	↓		↑	↓		
Inflammation[1,4,6,7,8,27]	↓	↓	↑	↓		↑	↓		
Iron deficiency–absolute[1,4,7,26]	↓	↓	↓	↑					
Iron deficiency–functional[1,4,7,28,§]	↓	↓	↑						
Secondary HPT[3,4,7,29]	↓								
Inadequate dialysis[4,13,15]	↓							< 1.2	< 65%
Malnutrition[7,18]	↓						↓		

Initiate EPOGEN® when the Hb level is < 10 g/dL.[1]

[†]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 EPOGEN® 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.[4,28]

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.[6,33]

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 urea 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.[34]

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.[36]

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.[37]

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

IMPORTANT SAFETY INFORMATION

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

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EPOGEN® (EPOETIN ALFA) RECOMBINANT

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 EPOGEN® dose adjustments
- Individualize dosing and use the lowest dose sufficient to reduce the need for RBC transfusions

The flexibility of EPOGEN® TIW dosing allows for timely intervention to help address Hb changes[1]

CKD = chronic kidney disease; TIW = three times weekly.

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.

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EPOGEN® Dosing Options

EPOGEN® is designed with flexible TIW dosing options and IV administration that you control

Dose and corresponding rise in Hb in 2 weeks with EPOGEN® TIW dosing[1]

STARTING DOSE (3 times weekly intravenously)	HEMOGLOBIN INCREASE IN 2 WEEKS
50 Units/kg	0.5 g/dL
100 Units/kg	0.8 g/dL

Data from 13 clinical studies involving IV administration of EPOGEN® to 1010 anemic adult patients on dialysis. Starting doses were 50 to 150 Units/kg TIW. In the 3 largest studies, the median maintenance dose necessary to maintain the Hb between 10 and 12 g/dL was approximately 75 Units/kg TIW.[1]

EPOGEN® is available in single-dose and multidose vials[1]

EPOGEN® vials not shown at actual size. Not all vial sizes shown.

EPOGEN is also available in 20,000 Units/mL and 20,000 Units/2mL vials.

TIW = three times weekly.

IMPORTANT SAFETY INFORMATION

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.

Please see dosing information for EPOGEN® on pages 6 and 7.
*Please see Important Safety Information, including **Boxed WARNINGS**, on pages 8 and 9.*

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EPOGEN® (EPOETIN ALFA) RECOMBINANT

Dosing information

EPOGEN® (epoetin 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.[1]**
- **No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks.[1]**
- **Individualize dosing and use the lowest dose of EPOGEN® sufficient to reduce the need for RBC transfusions.[1]**
- **Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse reactions.[1]**

Considerations[1]

- Correct or exclude other causes of anemia before initiating EPOGEN®
- Evaluate the iron status of 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
- In pregnant women, lactating women, neonates, and infants use only single-dose vials (the benzyl alcohol-free formulation). Do not mix EPOGEN® with bacteriostatic saline (which contains benzyl alcohol) when administering to these patients
- Appropriately control hypertension prior to initiation of and during treatment with EPOGEN®
  - Reduce or withhold EPOGEN® if blood pressure becomes difficult to control

INITIATING EPOGEN® FOR ADULT PATIENTS WITH CKD ON DIALYSIS[1]

- **Initiate EPOGEN® treatment when the Hb level is < 10 g/dL**
- The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. The intravenous route of administration is recommended for patients on hemodialysis

INITIATING EPOGEN® FOR PEDIATRIC PATIENTS (AGES 1 MONTH OR OLDER)[1]

- **Initiate EPOGEN® treatment only when the Hb level is < 10 g/dL**
- The recommended starting dose for pediatric patients is 50 Units/kg 3 times weekly intravenously or subcutaneously.

MONITOR AND ASSESS HB REGULARLY[1]

Following initiation of therapy and after each dose adjustment, monitor Hb at least weekly until the Hb level 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.

CKD = chronic kidney disease; ESA = erythropoiesis stimulating agents; HB = hemoglobin; RBC = red blood cell

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DOSAGE ADJUSTMENTS[1]

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[1]

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:

• Reduce or interrupt dose if the Hb level approaches or exceeds 11 g/dL

For pediatric patients (ages 1 month or older):

• Reduce or interrupt dose if the Hb level approaches or exceeds 12 g/dL

INCREASE DOSE[1]

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 EPOGEN®[1]

• For patients who do not respond adequately over a 12-week escalation period, increasing the EPOGEN® 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 EPOGEN® 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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EPOGEN® (EPOETIN ALFA) RECOMBINANT

Indication

EPOGEN® (epoetin alfa) is indicated for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis to decrease the need for red blood cell (RBC) transfusion.

Limitations of Use:

- EPOGEN® has not been shown to improve quality of life, fatigue, or patient well-being.
- EPOGEN® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

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, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest EPOGEN® 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.**

Perisurgery:

- **Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended.**

- EPOGEN® is contraindicated in patients with:
  - Uncontrolled hypertension
  - Pure red cell aplasia (PRCA) that begins after treatment with EPOGEN® or other erythropoietin protein drugs
  - Serious allergic reactions to EPOGEN®
- EPOGEN® from multidose vials contains benzyl alcohol and is contraindicated in neonates, infants, pregnant women, and lactating women.
- 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 EPOGEN®.
- EPOGEN® 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 EPOGEN®, 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 EPOGEN®.
  - 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 EPOGEN® is not approved).
  - If severe anemia and low reticulocyte count develop during treatment with EPOGEN®, withhold EPOGEN® and evaluate patients for neutralizing antibodies to erythropoietin.
  - Permanently discontinue EPOGEN® in patients who develop PRCA following treatment with EPOGEN® 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 EPOGEN®. Immediately and permanently discontinue EPOGEN® if a serious allergic reaction occurs.

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

Important Safety Information (cont'd)

- 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 EPOGEN®) in the postmarketing setting. Discontinue EPOGEN® therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.
- Serious and fatal reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including EPOGEN® multiple-dose vials. There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
- Adverse reactions (≥ 5%) in EPOGEN® clinical studies in patients with CKD were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection.

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* In the postmarketing setting from launch through December 31, 2020. Data on incident and prevalent number of patients on dialysis and market share are used to estimate number of patients exposed.
† Based upon 99.9% of product shipped to Amgen Authorized Distributors of Record only.

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IMPORTANT SAFETY INFORMATION

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

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