Epoetin alfa

Renogen®

4000 I.U./mL vial
Solution for IV and SC Injection
Hematopoietic Agent

FORMULATION
Each mL solution contains:
Epoetin alfa (Recombinant Human Erythropoietin).....4,000 I.U.
Albumin (Human).....2.5 mg.
Sodium citrate.....5.88 mg
Citric acid.....0.06 mg
Sodium chloride.....5.80 mg
Water for Injection.....1 mL

PRODUCT DESCRIPTION
Epoetin Alfa (Renogen) is a sterile, clear, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution for intravenous (IV) or subcutaneous (SC) administration. It comes in a glass vial with aluminum seal and flip-off cap.

Epoetin Alfa (Renogen) is preservative-free and each vial is for single use only.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Epoetin Alfa is a glycoprotein manufactured by recombinant DNA technology. It stimulates the production of red blood cells in the bone marrow. Epoetin alfa has the same biological effects as endogenous erythropoietin.
Endogenous human erythropoietin is a glycosylated protein hormone secreted primarily by renal peritubular interstitial cells outside the tubular basement membrane in the cortex and outer medulla of the kidney. In adults, it is also produced in the liver (approximately 10%) and other extrarenal sites. Fetal erythropoietin production, on the other hand, occurs mainly in the liver.
Erythropoietin is secreted principally in response to reduction in arterial and/or venous oxygen tension and tissue oxygenation in the kidney. Hypoxia and anemia generally increase erythropoietin production. Erythropoietin in turn, induces erythrocyte production.
Low erythropoietin levels are seen in patients with chronic or end-stage renal disease and these patients develop normocytic, normochronic anemia and inappropriately low reticulocyte counts. The small amount erythropoietin produced by the diseased renal tissue, liver, and other extrarenal sites in patients with chronic or end-stage renal disease are usually not enough to maintain optimal erythropoiesis . Thus, these patients benefit from administration of a recombinant erythropoietin hormone such as Epoetin alfa especially during stress or acute blood loss.
Epoetin alfa may also treat anemia brought about by zidovudine treatment in patients with HIV and chemotherapy in cancer patients. It may also reduce blood transfusion requirement during surgery.
A clinically significant increase in hemoglobin is usually not observed in less than two weeks and may require up to 6 weeks in some patients because of the length of time required for erythropoiesis (several days for erythoid progenitors to be released into the circulation).

Pharmacokinetics
Absorption
Epoetin alfa is destroyed in the gastrointestinal tract and must be administered parenterally. Its systemic absorption is delayed and incomplete after subcutaneous (SC) injection or intraperitoneal instillation. Peak serum concentrations with the intravenous (IV) route are less sustained but are substantially higher than with SC injection. However, the IV route of administration generally offers no clinical advantage over the SC route except in patients with existing accessible IV sites (e.g., hemodialysis patients).

There is considerable interindividual variation in serum erythropoietin concentrations with a given epoetin alfa dose and route of administration. Reported peak serum concentrations of epoetin alfa are as follows:

Subjects	Route	Epoetin Alfa Dose (IU/kg)	Peak Serum Erythropoietin Concentration
Patients with renal Chronic Renal Failure	IV	80 12 150	1200 - 1800 U/mL 3200 - 4700 U/mL 3000 - 5000 U/mL
Healthy Individuals	IV	150 300	3500 mU/mL 7300 mU/mL
	SC	50 150 300	36 mU/mL (corrected for endogenous serum erythropoietin dose) 144 -226 mU/mL 285 -288 mU/mL

Serum concentration of erythropoietin after SC administration of usual therapeutic doses of epoetin alfa, peak within 4-24 hours and generally remain above baseline for 2-4 days.

After IV administration of 50-300 IU/kg of exogenous erythropoietin, serum erythropoietin concentrations generally decline to baseline levels within 1-3 days.

Multiple-dose SC administration of epoetin alfa reduces the first-dose peak by up to 40-70%

Distribution
Epoetin alfa's distribution in humans is not yet fully elucidated but it appears to distribute into a single compartment with an apparent volume of distribution that approximates or slightly exceeds plasma volume (about 4-5% of the body weight).

Extravascular distribution of the drug and endogenous hormone appear to be relatively minor. The volume of distribution in both healthy individuals and dialysis patients is estimated to be 21-80 mL/kg after a single IV dose, 57-107 mL/kg at the start of multi-dose therapy, and 42-70 mL/kg after normalization of hematocrit (98-378 days).

Drug accumulation may occur after multiple SC doses because of prolonged absorption, but little (if any) accumulation occurs at doses of 50-150 U/kg given IV or SC 3 times weekly or at 40,000 U weekly given SC.

It is not known whether epoetin alfa distributes into human milk

Elimination and Metabolism
Elimination of epoetin alfa and endogenous erythropoietin in humans is not yet fully elucidated but serum concentrations appear to decline principally in a first-order (monoexponential) fashion. However, bioexponential elimination from serum has been described in animals and occasionally in humans, particularly at relatively low doses. Epoetin alfa's elimination half-life after IV administration in healthy individuals and in adults and children with chronic renal failure ranges from 4-16 hours. Epoetin alfa's elimination half-life may increase with increasing dose but it may be reduced during continuous dosing. The elimination half-life does not appear to be affected by hemodialysis. Epoetin alfa's elimination characteristics appear to be similar in patients undergoing hemodialysis or peritoneal dialysis.

The metabolic fate of endogenous erythropoietin and the recombinant hormone is poorly understood. While *in vitro* and animal data suggest that the kidney may be involved in erythropoietin metabolism, limited evidence in humans suggests otherwise. It is said that the physicochemical characteristics of the glycoprotein would impede access to potential sites of renal metabolism, which thus limits any contribution of the kidney in the degradation of the endogenous and recombinant hormones.

Evidence from animal studies show that hepatic metabolism contributes only minimally to elimination of the intact hormone. Desialylated epoetin alfa (i.e., terminal sialic groups removed) appears to undergo substantial hepatic clearance via metabolic pathways and/or binding. Removal of the oligosaccharide side chains and/or desialylation of erythropoietin appear to occur principally in the liver and elimination of the desialylated drug by the kidneys, bone marrow, and spleen may also occur. The bone marrow may also play a role in the catabolism of erythropoietin.

About 10% or less of an administered recombinant epoetin alfa dose is excreted unchanged in the urine. The effect of hepatic impairment on elimination of erythropoietin is not known.

Epoetin alfa is predominantly eliminated through non-renal mechanisms and its elimination is similar in patients with varying degrees of renal failure.

Epoetin alfa is not removed by hemodialysis and removal of the hormone from the systemic circulation into peritoneal dialysate is small and contributes minimally to overall elimination of the drug.

INDICATIONS
- Treatment of anemia associated with renal insufficiency or chronic renal failure (CRF)
  - o In adult and pediatric patients on dialysis
  - o Treatment of severe anemia of renal origin accompanied by clinical symptoms in patients with renal insufficiency not yet undergoing dialysis

  Note: Epoetin alfa is **not** intended for patients who require immediate correction o f severe anemia
- Treatment of anemia in Zidovudine-treated HIV-infected patients to elevate or maintain the red blood cell (RBC) level (as shown by hematocrit or hemoglobin determinations) and to decrease the need for transfusions
- Treatment of anemia in cancer patients on chemotherapy
  - o Epoetin alfa is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy to reduce the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of two months

Note:
- Epoetin alfa is **not** indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy, unless receiving concomitant myelosuppressive chemotherapy
- Epoetin alfa is **not** indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure
- Epoetin alfa is **not** indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding
- Epoetin alfa has **not** been proven to improve symptoms of anemia, quality of life, fatigue, or patient well-being

- Reduction of allogeneic blood transfusion in adult surgery patients

o For the treatment of anemic patients (hemoglobin > 10 to < 13 g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusion and to facilitate erythropoietic recovery.
o To augment erythropoiesis in the perisurgical period to reduce allogeneic blood transfusions and correct postoperative anemia in adult non-iron deficient patients undergoing major elective orthopedic surgery. Restrict use to patients with moderate anemia (i.e., Hgb 10-13 g/dL) who do not have an autologous predonation program available and with expected moderate blood loss (900-1800 mL). Always use good blood management in the perisurgical setting.
o To augment autologous blood collection in a pre-deposit program and to limit the decline in hemoglobin in anemic patients scheduled for major elective surgery requiring a large volume of blood, i.e., ≥ 4 units for females and ≥ 5 units for males, who are not expected to pre-deposit their complete peri-operative blood needs.

Note: Epoetin alfa is **not** indicated for anemic patients who are willing to donate autologous blood.

DOSAGE AND ADMINISTRATION
General Dosing Recommendations
· ***Pretherapy Iron Evaluation***: Evaluate the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, before and during epoetin therapy. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by Epoetin alfa.
· Use the lowest dose of Epoetin alfa that will gradually increase the hemoglobin (Hgb) concentration to a level sufficient to avoid the need for RBC transfusion in order to reduce cardiovascular risks. Moreover, the rate of Hgb increase should not exceed 1 g/dL in any two week period and the Hgb concentration should not exceed 12 g/dL.
· Doses must be individualized to ensure that hemoglobin is maintained at an appropriate dose level for each patient.
· Administer Epoetin alfa under the guidance of a qualified physician.

1. Chronic Renal Failure (CRF)

DOSING IN CHRONIC RENAL FAILURE (CRF) PATIENTS	
Recommended Starting Dose: Adult Patients	50-100 IU/kg thrice a week; may be administered intravenously (IV) or subcutaneously (SC)
Pediatric Patients on Hemodialysis	50 IU/kg thrice a week; IV or SC
Reduce Dose When: Hgb approaches 12 g/dL OR Hgb increases by > 1 g/dL in any 2-week period	· Reduce dose by about 25% if the Hgb is increasing and approaching 12 g/dL. · If Hgb continues to increase, temporarily withhold dose until Hgb begins to decrease then reinitiate therapy at a dose about 25% lower than the previous dose. · Dose should also be reduced by about 25% if Hgb increases by more that 1 g/dL in a 2-week period.
Increase Dose If: Hgb does not increase by 2 g/dL after 8 weeks of therapy AND Hgb remains at a level not sufficient to avoid the need for RBC transfusion	· Dose may be increased by about 25% of the previous dose if the increase in Hgb is less than 1 g /dL over 4 weeks and iron stores are adequate. · Further increases may be made at 4 - week intervals until the specified Hgb is obtained. · Dose may also be increased if transferrin saturation is greater than 20% but increase should not be made more than once a month, unless clinically indicated since the response time of hemoglobin to a dose can be 2 to 6 weeks . · Measure Hgb twice weekly for 2 to 6 weeks after dose increases.
Adult Maintenance Dose	Individually titrate to achieve and maintain the lowest Hgb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL . · Increases in dose should not be made more than once a month. · Recommended Total Weekly Dose: 75-300 IU/kg
Pediatric Maintenance Dose	Adjust dosage to maintain Hgb values at the desired level (between 9.5-11 g/dL) Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults. Note the following maintenance doses in clinical trials after 6 months of treatment: Dose (IU/kg given 3 times a week) Weight (kg) / Median / Usual Maintenance Dose <10 / 100 / 75-150 10-30 / 75 / 60-150 >30 / 33 / 30-100 Data suggest that patients whose initial Hgb is very low (<6.8 g/dL) may require higher maintenance doses than those whose initial anemia is less severe (Hgb >6.8 g/dL)
· **The IV route is recommended in patients on hemodialysis**. (See WARNINGS : Pure Red Cell Aplasia) · Epoetin alfa administration is independent of the dialysis procedure but it may be administered into the venous line at the end of the dialysis procedure to avoid the need for additional venous access. · Epoetin alfa may be given either as an IV or SC injection in adult patient with CRF not on dialysis. · Epoetin alfa may be self-administered only by patients who have been judged competent by their physicians. · Monitor hematological parameters regularly. · Individualize dosing to ensure that Hgb is maintained at the appropriate level for each patient. · For patients whose Hgb does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate epoetin alfa dose titrations over a 12-week period :	
· ***Lack or Loss of Response:*** Evaluate causative factor if a patient fails to respond or maintain a response to treatment. (See WARNINGS: Pure Red Cell Aplasia, PRECAUTIONS: Lack or Loss of Response, Iron Evaluation) Administer supplemental iron if transferrin saturation is less than 20%.	
Or, as prescribed by a physician.	

2. Zidovudine-treated HIV-infected Patients

DOSING IN ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS	
Recommended Starting Dose in Adult Patients with serum erythropoietin levels < 500 mUnits/mL who are receiving Zidovudine ≤ 4200 mg/week	100 Units/kg thrice a week for 8 weeks; IV or SC · Determine endogenous serum erythropoietin level (prior to transfusion) before beginning Epoetin alfa therapy. Evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with Epoetin alfa.
Increase Dose If: The response is not satisfactory in terms of reducing transfusion requirements or increasing Hgb after 8 weeks or increasing Hgb after 8 weeks of therapy.	· Dose may be increased by 50 -100 IU/kg thrice a week. · Evaluate response every 4 to 8 weeks and adjust dose accordingly by 50 -100 IU/kg increments thrice a week. · If patients have not responded satisfactorily to a dose of 300 IU/kg thrice a week, it is unlikely that they will respond to higher doses of Epoetin alfa. · Monitor hemoglobin weekly during the dose adjustment phase.
Maintenance Dose:	· After attaining the desired response (i.e., reduced transfusion requirements or increased Hgb), titrate Epoetin alfa dose to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. · Discontinue Epoetin alfa if the hemoglobin exceeds 12 g/dL until the Hgb drops below 11 g/dL. Reduce dose by 25% when treatment is resumed and then titrate to maintain the desired hemoglobin.
Or, as prescribed by a physician.	

3. Cancer Patients on Chemotherapy
- Do not initiate therapy levels at Hg levels > 10g/dL
- Although no specific serum erythropoietin level has been established which predicts which patients would unlikely respond to Epoetin therapy, treatment of patients with grossly elevated serum erythropoietin levels (e.g., >200 mUnits/mL) is not recommended.
- Monitor Hgb weekly in patients receiving Epoetin alfa until hemoglobin becomes stable.
- Individualize titration of Epoetin alfa dosing for each patient to achieve and maintain the lowest Hgb level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL
- Discontinue Epoetin alfa after the completion of a course of chemotherapy

DOSING IN CANCER PATIENTS ON CHEMOTHERAPY (Thrice Weekly Dosing)	
Recommended Starting Dose (Adult Patients)	150 IU/kg SC thrice a week
Reduce dose by 25% When:	Hgb reaches a level needed to avoid transfusion OR Hgb increases to > 1 g/dL in any 2-week period
Withhold Dose If:	Hgb exceeds a level needed to avoid transfusion then restart dose at 25% below the previous dose when the Hgb approaches a level where transfusions may be required
Increase Dose If:	Increase dose to 300 IU/kg thrice a week if response is not satisfactory (i.e., no reduction in transfusion requirements or rise in hemoglobin) after 4 weeks to achieve and maintain the lowest Hgb level sufficient to avoid the need for RBC transfusion
Discontinue If :	After 8 weeks of treatment there is no response as measured by Hg levels or if transfusions are still required.
Or, as prescribed by a physician	

DOSING IN CANCER PATIENTS ON CHEMOTHERAPY (Once Weekly Dosing)	
Recommended Starting Dose Adults Children	 40,000 IU SC once a week 600 IU/kg IV (maximum 40,000 IU) once a week
Reduce dose by 25% When:	Hgb reaches a level needed to avoid transfusion OR Hgb increases to> 1 g/dL in any 2-week period
Withhold Dose If:	Hgb exceeds a level needed to avoid transfusion then restart dose at 25% below the previous dose when the Hgb approaches a level where transfusions may be required
Increase Dose If:	If response is not satisfactory (i.e., no increase in hemoglobin by ≥ 1 g/dL after 4 weeks of therapy, in the absence of RBC transfusion) to achieve and
Increase Dose If:	maintain the lowest Hgb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL , increase dose to : · Adults: 60,000 IU SC once a week · Children: 900 IU/kg IV (maximum 60,000 IU) once a week
Discontinue If :	After 8 weeks of treatment there is no response as measured by Hg levels or if transfusions are still required.
Or, as prescribed by a physician	

4. Adult Surgery Patients

DOSING IN ADULT SURGERY PATIENTS TO REDUCE ALLOGENIC BLOOD TRANSFUSION	
Recommended Dose	300 IU/kg/day SC for 10 days before surgery, on the day of surgery, and for 4 days after surgery **OR** 600 IU/kg SC once a week, 21, 14 and 7 days before surgery plus a fourth dose on the day of surgery.
· Obtain Hgb level to establish that it is > 10 to < 13 g/dL before starting treatment with Epoetin alfa. · Adequate iron supplementation is recommended for all patients. Initiate iron supplementation no later than the beginning of Epoetin treatment. Continue iron supplementation throughout the course of therapy. · Strongly consider antithrombotic prophylaxis.	
Or, as prescribed by a physician	

DOSING IN ADULT SURGERY PATIENTS IN AN AUTOLOGOUS PRE-DONATION PROGRAM	
Recommended Dose in Mildly Anemic Patients (hematocrit of 33-39% and/or Hgb 10-13 g/dL) requiring predeposit of > 4 units of blood;	600 IU/kg two times weekly for three weeks before surgery
Recommended Dose in Patients Requiring a Lesser Degree of Erythropoietic Stimulation	150 – 300 IU/kg administered twice weekly Note: This dose has been shown to augment autologous pre-donation and to decrease subsequent decline in hematocrit
In Adult Surgery Patients In An Autologous Pre-Donation Program: · Use the IV route; administer epoetin alfa after the completion of each blood donation procedure · Evaluate iron status of all patients before starting Epoetin alfa treatment. Correct iron deficiency before allowing a patient to enroll in an autologous blood donation program. Explore causes of anemia before starting Epoetin alfa treatment. · All patients being treated with Epoetin alfa should receive adequate iron supplementation (i.e. 200 mg oral elemental iron daily) throughout the course of Epoetin alfa treatment . Start iron supplementation as soon as possible to achieve high iron stores before starting Epoetin alfa therapy.	
Or, as prescribed by a physician	

Preparation and Administration of Epoetin Alfa:
1. Do not shake. Prolonged vigorous shaking may denature any glycoprotein (including Epoetin alfa), rendering it biologically inactive.
2. Inspect visually for particulate matter and discoloration before administration. Do not use any vial with particulate matter or discoloration.
3. Follow strict aseptic conditions. Attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing Epoetin alfa then wipe the septum with a disinfectant. Insert the needle into the vial and withdraw into the syringe an appropriate volume of solution.
4. Epoetin alfa (Renogen) vials contain no preservatives and are intended for single-use only. Do not extract more than one dose from the vial.
5. Do not dilute or administer with other drug solutions.

CONTRAINDICATIONS
· Uncontrolled hypertension
· Hypersensitivity to mammalian cell-derived products
· Hypersensitivity to Albumin (human) and other ingredients in the product

WARNINGS AND PRECAUTIONS

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOTIC EVENTS, and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE

Renal Failure: Epoetin alfa dosage should be individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. There is greater risk of death and serious cardiovascular events when patients are administered Erythropoiesis-Stimulating Agents (ESA), including epoetin alfa, to target higher versus lower hemoglobin levels (i.e., 13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in clinical studies

Cancer:
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head, and neck, lymphoid, and cervical cancers
- Use the lowest dose needed to avoid red blood cell transfusion to minimize these risks, as well as the risk of serious cardio- and thrombovascular events
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure
- Discontinue following the completion of a chemotherapy course

Perisurgery: Consider deep venous thrombosis prophylaxis in patients receiving Epoetin alfa. The rate of deep venous thrombosis is increased in patients not receiving prophylactic anticoagulation.

(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Tumor Progression or Recurrence, INDICATIONS, and DOSAGE AND

Increased Mortality, Serious Cardiovascular and Thromboembolic Events
ESAs, including epoetin alfa, when administered to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) increases the risk of death and serious cardiovascular events in patients with chronic renal failure. There may be greater risk for cardiovascular events (including myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis) and mortality in patients with chronic renal failure and in patients with insufficient response to ESA therapy. Hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

Cancer patients treated with erythropoietic agents have increased risk of thrombotic events.

An increased incidence of deep vein thrombosis is also seen in patients receiving Epoetin alfa undergoing surgical orthopedic procedures. Strongly consider antithrombotic prophylaxis when ESAs are used for the reduction of allogeneic red blood cell (RBC) transfusions in surgical patients. (See BOXED WARNINGS)

ESAs, including Epoetin alfa, are not approved for reduction of allogeneic RBC transfusions in patients scheduled for cardiac surgery.

Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence
ESAs, including Epoetin alfa, decreased locoregional control/progression-free and/or overall survival in patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

ESA's should only be used to treat cancer patients where anemia has arisen as a result of concomitant chemotherapy.

Pure Red Cell Aplasia
Pure Red Cell Aplasia (PRCA) and severe anemia with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with Epoetin alfa, predominantly in patients with chronic renal failure (CRF) receiving Epoetin alfa subcutaneously. Evaluate any patient who develops a sudden loss of response to Epoetin alfa accompanied by severe anemia and low reticulocyte count for the etiology of loss of effect including the presence of neutralizing antibodies to erythropoietin. Withhold Epoetin alfa and other erythropoietic proteins if anti-erythropoietin antibody-associated anemia is suspected. Permanently discontinue Epoetin alfa in patients with antibody-mediated anemia. Do not switch patients to other erythropoietic proteins because of cross reactivity.

Albumin (Human)
Epoetin alfa contains albumin, a derivative of human blood and may carry an extremely remote risk for transmission of viral diseases based on effective donor screening and product manufacturing processes. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases of CJD have ever been identified for albumin.

Hypertension
Do not use Epoetin alfa in patients with uncontrolled hypertension. Control blood pressure adequately before starting Epoetin alfa therapy.

About 80% of patients with chronic renal failure (CRF) have a history of hypertension. Blood pressure may rise during therapy although Epoetin alfa has no direct pressor effect. Approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy during the early phase of treatment when the hematocrit is increasing. Hypertensive encephalopathy and seizures have been reported in patients with CRF treated with Epoetin alfa.

Closely monitor and aggressively control blood pressure in patients treated with Epoetin alfa. Advise patients on the importance of compliance with antihypertensive therapy and dietary restriction. Reduce hemoglobin (Hgb) by decreasing by decreasing or withholding the dose of Epoetin alfa if blood pressure is difficult to control by initiation of appropriate measures. Clinically significant decrease in Hgb may not be observed for several weeks.

Decrease recommended Epoetin alfa dose if the Hgb increase exceed 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of Hgb with an exacerbation of hypertension. Manage the hemoglobin carefully, not to exceed 12 g/dL in CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure.

Although exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with Epoetin alfa, withhold Epoetin alfa treatment in these patients if pre-existing hypertension is uncontrolled. Do not start Epoetin alfa therapy until blood pressure is controlled.

Hypertension associated with a significant increase in hemoglobin has been reported rarely in cancer patients on chemotherapy treated with Epoetin alfa. Carefully monitor blood pressure, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Carefully monitor blood pressure in surgery patients being treated with Epoetin alfa since blood pressure may rise in the perioperative period.

Seizures
Seizures may occur in patients treated with Epoetin alfa usually during the first 90 days of treatment. Closely monitor blood pressure and premonitory neurological symptoms. Caution patients to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Thrombotic Events
During hemodialysis, patients treated with Epoetin alfa may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Other thrombotic events such as myocardial infarction, cerebrovascular accident, and transient ischemic attack have also been reported with Epoetin therapy in CRF patients. The risk of thrombotic events, including vascular access thrombosis is significantly higher in adult patients with ischemic heart disease or congestive heart failure receiving Epoetin alfa therapy with the goal of reaching a normal hematocrit (42%) compared to a target hematocrit of 30%. Closely monitor patients with pre-existing cardiovascular disease.

Zidovudine-treated HIV-infected Patients
Although Epoetin alfa has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients, clinical data do not rule out an increased risk for serious cardiovascular events.

General Precautions
> Apply appropriate precautions in the parenteral administration of any biologic product, including Epoetin alfa, in case allergic or other untoward reactions occur
> Efficacy and safety of Epoetin alfa have not been established in patients with known history of seizure disorder or underlying hematologic disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).
> Menses may resume in some female patients after Epoetin alfa therapy. Discuss the possibility of pregnancy and evaluate the need for contraception

Hematology
Exacerbation of porphyria has been rarely observed in patients with CRF treated with Epoetin alfa but Epoetin alfa has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Use Epoetin alfa with caution in patients with known porphyria.

Subclinical bone marrow fibrosis has also been associated with Epoetin alfa in preclinical studies in dogs and rats but not in monkeys. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. In clinical studies, incidence of bone marrow fibrosis was not increased in adult patients on dialysis treated with Epoetin alfa for 12-19 months compared with a matched group of patients who have not been treated with Epoetin alfa.

Measure hemoglobin twice a week in patients with CRF and once a week in zidovudine-treated HIV-infected and cancer patients until hemoglobin has stabilized; measure hemoglobin periodically thereafter.

Lack or Loss of Response
Consider and evaluate the following etiologies if the patient fails to respond or maintain a response to doses within the recommended dosing range:
- Iron deficiency. (see Iron Evaluation)
- Underlying infectious, inflammatory or malignant processes.
- Occult blood loss.
- Underlying hematologic diseases (i.e., thalassemia, refractory anemia or other myelodysplastic disorders).
- Folic Acid or Vitamin B_{12} deficiencies
- Hemolysis
- Aluminum intoxication
- Osteitis fibrosa cystica
- Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody-associated anemia: Evaluate patients for evidence of PRCA in the absence of another etiology. Test sera for the presence of antibodies to erythropoietin. (See WARNINGS: Pure Red Cell Aplasia)

(See Also: DOSAGE AND ADMINISTRATION: Chronic Renal Failure Patients-Lack or Loss of Response)

Iron Evaluation
Absolute or functional iron deficiency may develop during Epoetin alfa therapy. Functional iron deficiency with normal ferritin levels but low transferrin saturation is presumed to be caused by the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Evaluate the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, before and during Epoetin alfa therapy. Practically all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by Epoetin alfa. All surgery patients being treated with Epoetin alfa should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

INTERACTION WITH OTHER MEDICAMENTS
Evidence of interaction between Epoetin alfa and other drugs has not been observed in clinical trials.

STATEMENT OF USAGE FOR HIGH-RISK GROUPS
Pregnancy and Lactation
Pregnancy Category C. Adverse effects such as decreases in body weight gain, delays in appearance of abdominal hair, delayed vaginal opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses have been observed in rats when Epoetin alfa was given in doses 5 times the human dose (500 Units/kg).

Use Epoetin alfa in pregnancy only if the potential benefit justifies the potential risk to the fetus. IV administration of Epoetin alfa to lactating rats at 500 IU/kg caused retardation of growth and development of the offspring.

It is not known whether Epoetin alfa is excreted in human milk. Exercise caution when Epoetin alfa is administered to a breastfeeding woman since many drugs are excreted in human milk.

Geriatrics
No overall differences in safety or effectiveness were observed in geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit. (See DOSAGE AND ADMINISTRATION).
Careful monitoring of blood chemistry and blood pressure may be necessary because of a general increased risk of renal and/or cardiovascular complication in geriatric patients.

Infants and Children
Safety and effectiveness in pediatric patients less than 1 month old have not been established.
Epoetin alfa is indicated in pediatric patients (1 month to 16 years) for the treatment of anemia associated with CRF requiring dialysis. There is no increased risk to pediatric CRF patients on dialysis when compared with the safety profile of Epoetin alfa in adult CRF patients.
Epoetin alfa has also been used in pediatric patients for the treatment of anemia in CRF patients not requiring dialysis, in HIV-infected patients, and in cancer patients on chemotherapy.

ADVERSE EVENTS/UNDESIRABLE EFFECTS
Immunogenicity
There is a potential for immunogenicity with all therapeutic proteins. Neutralizing antibodies to erythropoietin, in association with pure red cell aplasia or severe anemia (with or without other cytopenias), have been reported in patients receiving Epoetin alfa.

Chronic Renal Failure (CRF) Patients
Hypertension, headache, arthralgia, nausea, edema, fatigue, diarrhea, vomiting, chest pain, skin reaction at the administration site, asthenia, dizziness, and clotted access have been reported in greater than 5% of patients with CRF in clinical trials. Significant adverse events of concern in patients with CRF such as seizures, cerebrovascular accident CVA/transient ischemic attack (TIA), myocardial infarction, and death have also been reported in clinical trials but the incidence is equal or less than that in placebo-treated patients.
In adult patients on dialysis, the most frequent adverse event reported include hypertension, headache, tachycardia, nausea/vomiting, clotted vascular access, shortness of breath, hyperkalemia and diarrhea. Rare, mild, and transient adverse events including injection site stinging and flu-like symptoms (i.e., arthralgias and myalgias) have been reported to occur within several hours of Epoetin alfa administration.
Adverse events in pediatric patients with CRF are similar to that in adults. Other adverse events in pediatric patients which have been seen in more than 10% of patients in clinical trials include abdominal pain, dialysis access complication (including access infections and peritonitis in those receiving peritoneal dialysis), fever, upper respiratory infection, cough, pharyngitis and constipation.
Thrombotic events (including clotting of the vascular access, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) have occurred in patients taking Epoetin alfa. Although casual relationship has not been established, rare cases of serious or unusual thromboembolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins have also been reported. No reports of serious allergic reactions or anaphylaxis have been seen during clinical trials although skin rashes and urticaria (generally mild and transient) have been rarely reported. Rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone, has also been observed, but causal relationship could not be established. Allergic reactivity may be occasionally associated with Epoetin alfa use since symptoms recurred with rechallenge in few instances. Immediately discontinue Epoetin alfa use and initiate appropriate therapy when an anaphylactoid reaction occurs.

Zidovudine-treated HIV-infected Patients
Adverse events reported in ≥ 10% of patients in clinical trials (both in the treatment and placebo groups) include pyrexia, fatigue, headache, cough, diarrhea, rash, respiratory congestion, nausea, shortness of breath, asthenia, skin reaction at the medication site, and dizziness. Urticarial reactions and seizures have also been reported. Seizures reported have generally been related to underlying pathologies such as meningitis or cerebral neoplasma.

Cancer Patients on Chemotherapy
Adverse events reported in more than 10% of patients in clinical trials (both in the treatment and placebo groups) include pyrexia, diarrhea, nausea, vomiting, edema, asthenia, fatigue, shortness of breath, paresthesia, upper respiratory infection, dizziness and trunk pain. Of these reported events, only the incidence of diarrhea and edema were significantly greater than those reported in the placebo groups.

Surgery Patients
Adverse events reported in ≥ 10% of patients in clinical trials include pyrexia, nausea, constipation, skin reaction at the medication site, vomiting, skin pain, pruritus, insomnia, headache, dizziness, urinary tract infection, hypertension, diarrhea, deep venous thrombosis, dyspepsia, anxiety, and edema.

OVERDOSAGE AND MANAGEMENT
Overdosage with Epoetin alfa manifest as signs and symptoms associated with excessive and/or rapid increase in hemoglobin concentration. These signs and symptoms include any cardiovascular event listed in WARNINGS AND PRECAUTIONS and ADVERSE EVENTS/UNDESIRABLE EFFECTS. Closely monitor patients for cardiovascular events and hematologic abnormalities. Acutely manage polycythemia with phlebotomy, as clinically indicated. After resolution of the effects of Epoetin alfa overdosage, closely monitor rapid increases in hemoglobin concentration (>1 g/dL per 14 days) when Epoetin alfa therapy is reintroduced. Reduce Epoetin alfa dose according to the recommendations described in DOSAGE AND ADMINISTRATION in patients with excessive hematopoietic response.

AVAILABILITY: Epoetin Alfa (Renogen) 4,000 I.U./mL vial in box of 1's

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

STORAGE: Store between 2° to 8°C. Do not shake or freeze. Single use only. Discard unused portion.

Manufactured by
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