Epoetin alfa

Brand Name: Epogen, Procrit
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Erythropoietin is a glycoprotein produced in the kidney that stimulates red blood cell production. Epoetin alfa, a biosynthetic form of erythropoietin, is a hematopoietic agent that principally affects erythropoiesis. The drug is prepared from cultures of genetically modified mammalian cells using recombinant DNA technology. [1]

HIV/AIDS-Related Uses

Epoetin alfa was approved by the FDA on December 31, 1990, for the treatment of anemia associated with zidovudine therapy in HIV infected adults and children. Epoetin alfa is not approved for the treatment of anemia due to other factors in HIV infected patients.[2]

Non-HIV/AIDS-Related Uses

Epoetin alfa is approved for the treatment of anemia associated with chronic renal failure (CRF) in adults and children. Epoetin alfa is used for both patients receiving dialysis (continuous peritoneal dialysis, high-flux short-time hemodialysis, or conventional hemodialysis) and patients who do not require dialysis.

Epoetin alfa is also indicated for the treatment of anemia in patients with nonmyeloid malignancies in which anemia is due to concomitantly administered chemotherapy. Epoetin alfa can be used to correct anemia in patients who are scheduled to undergo elective, noncardiac nonvascular surgery, reducing the need for allogeneic blood transfusions. Epoetin alfa is not a substitute for blood transfusions; however, with chronic use, epoetin alfa reduces the need for repeated maintenance blood transfusions.[3]

Pharmacology

Recombinant epoetin alfa has the same biological activity as the endogenous hormone, which induces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells, including burst-forming units-erythroid, colony-forming units-erythroid, erythroblasts, and reticulocytes in bone marrow. Erythropoietin also induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature into erythrocytes (red blood cells). Administration of epoetin alfa apparently does not induce antibody formation, because antibodies have not been detected in the blood of patients treated with the recombinant hormone for up to 12 months. Endogenous erythropoietin production, which occurs primarily in the kidney, may be suppressed by chronic administration of recombinant epoetin alfa.[4]

Epoetin alfa corrects the erythropoietin deficiency in patients with CRF. Epoetin alfa also stimulates red blood cell production in patients who do not have a documented erythropoietin deficiency. However, it may not be effective in patients who are anemic despite having significantly elevated concentrations of erythropoietin.[5]

Because of its protein nature, epoetin alfa is degraded in the gastrointestinal tract and must be administered parenterally. Serum concentrations peak significantly sooner and are substantially higher with IV administration as compared to subcutaneous injection; however, the concentrations of epoetin alfa are less sustained with IV administration. After a single IV dose, serum concentration peaks at 15 minutes; after a single subcutaneous dose, serum concentration peaks between 5 to 24 hours. However, with subcutaneous dosing, peak concentrations may be maintained for 12 to 16 hours, and detectable quantities are present for at least 24 hours after administration.[6]

Epoetin alfa's distribution in the human body is unknown. Epoetin alfa appears to distribute into a single compartment with an apparent volume of distribution that approximates or slightly exceeds plasma volume (about 4% to 5% of body weight); thus, extravascular distribution of epoetin alfa and endogenous hormone appears to be minimal.[7]

Epoetin alfa is in Pregnancy Category C. There have been no adequate and well-controlled studies of epoetin alfa in pregnant women. Adverse effects have been seen in rats given five times the human

Epoetin alfa

Pharmacology (cont.)

dose of epoetin alfa.[8] It is not known whether epoetin alfa is excreted into human breast milk; however, in animal studies, administration of up to 500 units per kg of body weight to female rats during lactation produced no adverse effects in their pups. Epoetin alfa should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.[9] [10]

IV-administered epoetin alfa is eliminated at a rate consistent with first-order kinetics. The half-life in healthy volunteers is approximately 20% shorter than the half-life of epoetin in CRF patients. The elimination half-life of epoetin averages 4 to 13 hours following IV or subcutaneous administration and is generally higher after the first few doses than after 2 or more weeks of treatment.[11]

Increase in reticulocyte count is appreciable within 7 to 10 days of administration. Clinically significant increases in red blood cell count, hemoglobin, and hematocrit generally occur in 2 to 6 weeks. The rate and extent of the response are dependent on dosage and availability of iron stores. In a series of clinical trials enrolling anemic cancer patients who received epoetin alfa three times weekly, the response over a 2-week period was as follows: administration of 50 units per kg of body weight three times weekly increases the hematocrit by an average of 1.5 points; administration of 100 units per kg of body weight three times weekly increases the hematocrit by an average of 2.5 points; and administration of 150 units per kg of body weight three times weekly increases the hematocrit by an average of 3.5 points.[12]

Adverse Events/Toxicity

Common adverse effects seen with the use of epoetin alfa include chest pain, edema, headache, hypertension (which can lead to cerebral ischemia or hypertensive encephalopathy), polycythemia (which may lead to peripheral vascular resistance, hypertension, and thrombotic complications), fever, hyperkalemia, shortness of breath, tachycardia, upper respiratory infection, seizures, deep venous thrombosis, skin rash or hives, urinary tract infection, diarrhea, dizziness, nausea, and vomiting.[13]

Unlike in patients with CRF, epoetin alfa therapy has not been linked to the exacerbation of hypertension, seizures, and thrombotic events in HIV infected patients.[14]

As with all therapeutic proteins, there is the potential for immunogenicity.[15] Seizures and pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, have occurred in patients with CRF while taking epoetin.[16] During hemodialysis, patients treated with epoetin may require anticoagulation with heparin to prevent clotting of the artificial kidney.[17]

Drug and Food Interactions

While systematic drug interaction studies have not been performed, epoetin alfa used in clinical trials with other drugs or biologics has shown no evidence of clinically important interactions.[18]

Androgens increase the sensitivity of erythroid progenitors; they have been used as an adjunct to epoetin alfa to decrease the total amount of epoetin alfa therapy needed to ameliorate anemia. However, controlled studies are needed to establish potential benefits and risks of such combination therapies. Concurrent therapy with epoetin alfa and desmopressin has resulted in an additive effect on reduction of bleeding time in a patient with end-stage renal disease who was receiving epoetin for correction of uremia-induced increased bleeding time and epistaxis. Probenecid has been shown to inhibit the renal tubular secretion of endogenous erythropoietin in animals. While the relevance to humans of this interaction is not known, it should be considered when these two substances are given concomitantly.[19]

Iron requirements may be raised as existing iron stores are used for erythropoiesis. Iron supplementation may be necessary for some patients, especially those who undergo frequent blood transfusions. In some patients, oral iron supplementation may be insufficient and IV iron dextran may be required.[20]

Epoetin alfa

Contraindications

Epoetin alfa is contraindicated in patients with uncontrolled hypertension and known hypersensitivity to mammalian cell-derived products or human albumin. The multidose, preservative-containing formulation contains benzyl alcohol and should not be used in neonates. Benzyl alcohol has been associated with an increased incidence of neurologic and other complications that are sometimes fatal in premature infants. Epoetin alfa should be used with caution in patients at risk for thrombosis, and the anticipated benefits of epoetin alfa treatment should be weighed against the potential for increased risks associated with therapy.[21]

Risk-benefit should be considered in patients with aluminum intoxication, Vitamin B12 or folic acid deficiency, hemolysis, infection, inflammation, iron deficiency (virtually all patients will eventually require supplemental iron therapy), malignancy (the possibility that epoetin can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded), osteitis fibrosa cystica, occult blood loss, controlled hypertension, hypercoagulable disorders, myelodysplastic syndromes, sickle cell anemia, peripheral vascular disease, porphyria, and history of seizure disorders.[22]

Clinical Trials

For information on clinical trials that involve Epoetin alfa, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Epoetin alfa AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous injection.[23]

Subcutaneous injection.[24]

Dosage Form: 1 ml single-dose vials containing preservative-free solutions (epoetin alfa 2,000, 3,000, 4,000, 10,000, and 40,000 units/ml); 2 ml multidose vials containing preservative-containing solutions (epoetin alfa 10,000 and 20,000 units/ml).[25]

Storage: Store vials between 2 C and 8 C (36 F to 46 F). Do not freeze.[26]

Chemistry

CAS Name: 1-165-Erythropoietin (human clone lambda HEPOFL13 protein moiety), glycoform alpha[27]

CAS Number: 113427-24-0[28]

Molecular formula: C809-H1301-N229-O240-S5[29]

C53.28%, H7.19%, N17.58%, O21.06%, S0.089%[30]

Molecular weight: 30,000 kDa[31]

Physical Description: Sterile, coloress liquid.[32]

Stability: Shaking may denature the glycoprotein and render it biologically inactive. Single dose injection should be used to administer only one dose and any unused portion should be discarded. Multidose vials should be discarded 21 days after initial entry.[33]

Other Names

EPO[34]

Erythropoietin-alfa, recombinant[35]

r-HuEPO[36]

Epoetin alpha[37]

Epoetina alfa[38]

Eprex[39]

Further Reading

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Epoetin alfa

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Manufacturer Information

Epoetin alfa
Ortho Biotech
P.O. Box 6914
430 Rt. 22 East
Bridgewater, NJ 08807-0914
(800) 682-6532

Procrit
Ortho Biotech
P.O. Box 6914
430 Rt. 22 East
Bridgewater, NJ 08807-0914
(800) 682-6532

Epogen
Amgen Inc
1840 Dehavilland Dr
Thousand Oaks, CA 91320-1799
(800) 772-6436

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

Epoetin alfa

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