Epoetin alfa

Brand Name: Epogen, Procrit

Drug Description
Erythropoietin is a glycoprotein produced in the kidney that stimulates red blood cell production and the division and differentiation of committed erythroid progenitors of the bone marrow. [1] 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. [2]

HIV/AIDS-Related Uses
Epoetin alfa was approved by the FDA on December 31, 1990, for the treatment of anemia associated with zidovudine (AZT) 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. [3]

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 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 is also indicated for the treatment of anemia in patients with nonmyeloid malignancies in which anemia is due to concomitantly administered chemotherapy. Epoetin 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 is not a substitute for blood transfusions; however, with chronic use, epoetin reduces the need for repeated maintenance blood transfusions. [4]

Pharmacology
Recombinant epoetin 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. 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.[5]

Epoetin corrects the erythropoietin deficiency in patients with CRF. Epoetin 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. [6]

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. [7] 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 13 hours after administration. [8]

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. [9]

Epoetin alfa is in Pregnancy Category C. There have been no adequate and well-controlled studies of epoetin alfa in pregnant women. Adverse effects
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Pharmacology (cont.)

have been seen in rats given five times the human
dose of epoetin alfa.[10] 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 produce no adverse effects in their
pups. Epoetin alfa should be used during pregnancy
only if potential benefit justifies the potential risk to
the fetus.[11] [12]

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.[13]
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.[14]

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.[15] 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.[16] [17]

Adverse Events/Toxicity

Common adverse effects seen with the use of
epoetin alfa include chest pain, edema, headache,
hypertension (which can lead to hypertensive
encephalopathy), polycythemia (which may lead to
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.[18]

The most common adverse effects observed in
zidovudine-treated HIV infected patients include
fever, headache, shortness of breath, skin rash or
hives, and seizures (possibly relating to underlying
pathology).[19] Unlike patients with CRF, epoetin
alfa therapy has not been linked to the exacerbation
of hypertension, seizures, and thrombotic events in
HIV infected patients.[20]

As with all therapeutic proteins, there is the
potential for immunogenicity.[21] Seizures and
pure red cell aplasia (PRCA), in association with
neutralizing antibodies to native erythropoietin,
have occurred in patients with CRF while taking
epoetin.[22] During hemodialysis, patients treated
with epoetin may require anticoagulation with
heparin to prevent clotting of the artificial
kidney.[23]

Drug and Food Interactions

While systematic drug interaction studies have not
been performed, epoetin used in clinical trials with
other drugs or biologicals has shown no evidence of
clinically important interactions.[24]

Androgens increase the sensitivity of erythroid
progenitors; they have been used as an adjunct to
epoetin 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
erthropoietin in animals. While the relevance to
humans of this interaction is not known, it should
be considered when these two substances are given
concomitantly.[25]

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
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**Drug and Food Interactions (cont.)**

Blood transfusions. In some patients, oral iron supplementation may be insufficient and IV iron dextran may be required.[26]

**Contraindications**

Epoetin 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 neurological and other complications in premature infants that are sometimes fatal. Epoetin should be used with caution in patients at risk for thrombosis, and the anticipated benefits of epoetin treatment should be weighed against the potential for increased risks associated with therapy.[27]

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.[28]

**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; subcutaneous injection.[29]

Dosage Form: 1 ml single-dose vials containing preservative-free solutions (2,000, 3,000, 4,000, 10,000, and 40,000 units/ml); 2 ml multidose vials containing preservative-containing solutions (10,000 and 20,000 units/ml).[30]

Storage: Store at 2 C to 8 C (36 F to 46 F). Do not freeze.[31]

**Chemistry**

CAS Name: 1-165-Erythropoietin (human clone lambda HEPOFL13 protein moiety), glycoform alpha[32]

CAS Number: 113427-24-0[33]

Molecular formula: C809-H1301-N229-O240-S5[34]

C53.28%, H7.19%, N17.58%, O21.06%, S0.089%[35]

Molecular weight: 30,000 kDa[36]

Physical Description: Sterile, coloress liquid.[37]

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. Multi-dose vials should be discarded 21 days after initial entry.[38]

**Other Names**

EPO[39]

Erythropoietin-alfa, recombinant[40]

r-HuEPO[41]

Epoetin alpha[42]

Epoetina alfa[43]

Eprex[44]

**Further Reading**

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Further Reading (cont.)

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Sullivan P. Associations of anemia, treatments for
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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

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

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

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
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7. AHFS Drug Information - 2004; p. 1467
8. USP DI - 2004; p. 1235
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12. USP DI - 2004; p. 1236
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