

# 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

# Epoetin alfa

## 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 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.[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

# Epoetin alfa



## 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, colorless 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

---

Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human

# Epoetin alfa



## **Further Reading (cont.)**

---

immunodeficiency virus: a systematic review of the literature. *Am J Med.* 2004 Apr 5;116 Suppl 7A:27S-43S. Review. PMID: 15050884

Buskin SE, Sullivan PS. Anemia and its treatment and outcomes in persons infected with human immunodeficiency virus. *Transfusion.* 2004 Jun;44(6):826-32. PMID: 15157246

Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M; Anemia in HIV Working Group. Anemia in HIV infection: clinical impact and evidence-based management strategies. *Clin Infect Dis.* 2004 May 15;38(10):1454-63. Epub 2004 Apr 27. PMID: 15156485

Sullivan P. Associations of anemia, treatments for anemia, and survival in patients with human immunodeficiency virus infection. *J Infect Dis.* 2002 May 15;185 Suppl 2:S138-42. PMID: 12001035

## **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](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

# Epoetin alfa



## References

---

1. USP DI - 2004; p. 1235
2. AHFS Drug Information - 2004; p. 1468
3. USP DI - 2004; p. 1235
4. USP DI - 2004; p. 1235
5. USP DI - 2004; p. 1235
6. USP DI - 2004; p. 1235
7. AHFS Drug Information - 2004; p. 1467
8. USP DI - 2004; p. 1235
9. AHFS Drug Information - 2004; pp. 1467-1468
10. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 14. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
11. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 14. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
12. USP DI - 2004; p. 1236
13. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 3. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
14. USP DI - 2004; p. 1235
15. USP DI - 2004; p. 1235
16. USP DI - 2004; p. 1235
17. Ortho Biotech - Procrit Prescribing Information, April 2004, pp. 4-5. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
18. USP DI - 2004; p. 1237
19. USP DI - 2004; p. 1237
20. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 17. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
21. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 17. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
22. Ortho Biotech - Procrit Prescribing Information, April 2004, pp. 9-10. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
23. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 11. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
24. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 12. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
25. AHFS Drug Information - 2004; p. 1465
26. USP DI - 2004; p. 1236
27. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 9. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
28. USP DI - 2004; p. 1237
29. USP DI - 2004; p. 1238
30. USP DI - 2004; p. 1239

# ***Epoetin alfa***



- 31. USP DI - 2004; p. 1239
- 32. USPD - 2003; p. 320
- 33. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 34. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 35. Calculation. -
- 36. USP DI - 2004; p. 1235
- 37. Ortho Biotech - Procrit Prescribing Information, April 2004, p. 1. Available at: <http://www.orthobiotech.com/procrit.html>. Accessed 07/26/04.
- 38. USP DI - 2004; p. 1239
- 39. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 40. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 41. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 42. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 43. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.
- 44. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 07/26/04.