

Epoetins ⊗

Epoetinas.

ATC — B03XA01.

ATC Vet — QB03XA01.

Description. Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor produced primarily in the kidneys.

Erythropoietin for clinical use is produced by recombinant DNA technology and the name epoetin is often applied to such material. Epoetin alfa, epoetin beta, epoetin gamma, epoetin omega, and epoetin zeta are recombinant human erythropoietins derived from a cloned human erythropoietin gene. All have the same 165 amino acid sequence but differ in the glycosylation pattern. Epoetin delta is a recombinant human erythropoietin derived from a genetically engineered continuous human cell line. It has the same amino acid sequence and glycosylation pattern as human erythropoietin.

Pharmacopoeias. *Eur.* (see p.vii) includes Erythropoietin Concentrated Solution.

Ph. Eur. 6.2 (Erythropoietin Concentrated Solution). A clear or slightly turbid colourless solution, containing 0.05 to 1% of glycoproteins indistinguishable from naturally occurring human erythropoietin in terms of amino acid sequence and glycosylation pattern. It has a potency of not less than 100 000 units per mg of active substance. Store in airtight containers below -20° and avoid repeated freezing and thawing.

Epoetin Alfa (BAN, USAN, rINN) ⊗

EPO; Epoetina alfa; Époétine Alfa; Epoetinum Alfa. I-165-Erythropoietin (human clone λ HEPOFL13 protein moiety), glycoform α .

Эпоэтин Альфа

CAS — 113427-24-0.

ATC — B03XA01.

ATC Vet — QB03XA01.

Epoetin Beta (BAN, USAN, rINN) ⊗

BM-06.019; EPOCH; Epoetina beta; Époétine Bêta; Epoetinum Beta. I-165-Erythropoietin (human clone λ HEPOFL13 protein moiety), glycoform β .

Эпоэтин Бета

CAS — 122312-54-3.

ATC — B03XA01.

ATC Vet — QB03XA01.

Epoetin Delta (USAN, rINN) ⊗

Epoetina delta; Époétine Delta; Epoetinum Delta; GA-EPO; HMR-4396. I-165-Erythropoietin (human HMR4396), glycoform δ .

Эпоэтин Дельта

CAS — 261356-80-3.

ATC — B03XA01.

ATC Vet — QB03XA01.

Epoetin Gamma (BAN, rINN) ⊗

BI-71.052; Epoetina gamma; Époétine Gamma; Epoetinum Gamma. I-165-Erythropoietin (human clone λ HEPOFL13 protein moiety), glycoform γ .

Эпоэтин Гамма

CAS — 130455-76-4.

ATC — B03XA01.

ATC Vet — QB03XA01.

Epoetin Omega (rINN) ⊗

Epoetina omega; Époétine Oméga; Epoetinum Omega. I-165-Erythropoietin (human clone λ HEPOFL13 protein moiety), glycoform ω .

Эпоэтин Омэга

CAS — 148363-16-0.

ATC — B03XA01.

ATC Vet — QB03XA01.

Epoetin Zeta (rINN) ⊗

Epoetina Zeta; Époétine Zêta; Epoetinum Zeta. I-165-Erythropoietin (human clone B03XA01), glycoform ζ .

Эпоэтин Цета

CAS — 604802-70-2.

ATC — B03XA01.

ATC Vet — QB03XA01.

Stability. Proprietary preparations of recombinant human erythropoietin may contain albumin or amino acids for stability. Use in neonates may necessitate making very dilute solutions. A study of the stability of epoetin alfa in various intravenous fluids¹ found that a minimum of 0.05% protein was required to prevent loss of drug from solutions containing epoetin alfa 0.1 units/mL. In another study,² 0.0125% albumin was sufficient to prevent loss of drug from a solution containing epoetin alfa 100 units/mL. Epoetin alfa was stable for up to 24 hours in a solution for enteral use in neonates, formulated to mimic amniotic

fluid, which also contained filgrastim and electrolytes.³ Epoetin alfa and filgrastim were stable for at least 24 hours when refrigerated and for at least 3 weeks when frozen. At room temperature epoetin alfa was stable for 24 hours and filgrastim was stable for 18 hours. Lowered epoetin alfa concentrations were thought to be due to adsorption to the plastic infusion bag or tubing, and this was overcome by priming the tubing.

- Ohls RK, Christensen RD. Stability of human recombinant epoetin alfa in commonly used neonatal intravenous solutions. *Ann Pharmacother* 1996; **30**: 466–8.
- Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. *Ann Pharmacother* 1996; **30**: 1501–2.
- Calhoun DA, et al. Stability of filgrastim and epoetin alfa in a solution designed for enteral administration in neonates. *Ann Pharmacother* 2000; **34**: 1257–61.

Adverse Effects and Treatment

Adverse effects of epoetins include flu-like symptoms such as fever, chills, headache, arthralgias, myalgias, asthenia, dizziness, and tiredness, which occur especially at the start of treatment. Other effects include rashes, urticaria, nausea and vomiting, diarrhoea, hyperkalaemia, and reactions at the injection site. Severe hypersensitivity reactions have been reported rarely. Pure red cell aplasia associated with neutralising antibodies has also been reported rarely in patients with chronic renal failure. Modest increases in the platelet count within the normal range may occur during epoetin therapy.

Hypertension is common with the use of epoetins, particularly in patients with renal failure, and is associated with a rapid rise in haematocrit. Hypertensive crisis with encephalopathy and seizures has been reported, even in patients with initially normal or low blood pressure.

Reports of thromboembolism include myocardial ischaemia and infarction, transient ischaemic attacks and cerebrovascular accidents, deep-vein thrombosis, and pulmonary embolism. Shunt thromboses may occur in the arteriovenous fistulae of dialysis patients, and occlusion of the dialysis system is possible, due to an increased haematocrit.

⊕ General references.

- Sowade B, et al. The safety of treatment with recombinant human erythropoietin in clinical use: a review of controlled studies. *Int J Mol Med* 1998; **1**: 303–14.
- Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis* 1999; **33**: 821–8.
- Smith KJ, et al. The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59**: 538–48.

Effects on the blood. The use of recombinant human erythropoietin has been associated with an increase in **thrombotic events**, including vascular access thrombosis in haemodialysis patients. A number of mechanisms have been proposed for this increase such as increased blood viscosity, effects on proteins involved in coagulation, activation of platelets and the endothelium, and a vasoconstrictor effect on vascular smooth muscle.¹

Pure red cell aplasia has been reported rarely in patients with chronic renal failure after months to years of treatment with epoetin alfa; most patients have been found to have antibodies to epoetins.² There have also been a few cases in patients treated with epoetin beta.^{3–5} A review⁶ of cases reported between January 1988 and April 2004 found that the number peaked in 2001 and 2002, and decreased rapidly when changes were made to recommendations for storage, handling, and use of epoetin alfa preparations. The effect appeared to be brand specific^{6–8} and associated particularly with the subcutaneous use of preparations containing polysorbate 80 as a stabiliser.⁹ Other possible causes have been proposed including contamination with silicone lubricant used in pre-filled syringes or release of organic compounds from rubber plungers.¹⁰ Subsequently, manufacturers have reported that cases of red cell aplasia with neutralising antibodies have also occurred in chronic renal failure patients treated with subcutaneous darbepoetin alfa.¹¹ They also warn that because of cross-reactivity, patients who develop antibody-mediated anaemia with either an epoetin or darbepoetin alfa should not be swapped to another erythropoietic protein.

Epoetin-induced red cell aplasia has been managed with withdrawal of the epoetin and treatment with immunosuppressants including corticosteroids, cyclophosphamide, and ciclosporin. Intravenous normal immunoglobulin has also been used. Kidney transplantation is reported to bring about a rapid recovery.^{10,12}

- Smith KJ, et al. The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59**: 538–48.
- Casadevall N, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; **346**: 469–75.
- Krueger A, et al. PRCA in a patient treated with epoetin beta. *Nephrol Dial Transplant* 2003; **18**: 1033–4.
- Tolman C, et al. Four cases of pure red cell aplasia secondary to epoetin β , with strong temporal relationships. *Nephrol Dial Transplant* 2004; **19**: 2133–6.

- Bennett CL, et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004; **351**: 1403–8.
- Gerston SK, et al. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346**: 1584–5.
- Casadevall N, Mayeux P. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346**: 1585. Correction. *ibid.*; **347**: 458.
- Macdougall IC. Pure red cell aplasia with anti-erythropoietin antibodies occurs more commonly with one formulation of epoetin alfa than another. *Curr Med Res Opin* 2004; **20**: 83–6.
- Janssen-Ortho. Important drug safety information: Eprex (epoetin alfa) sterile solution revised prescribing information for patients with chronic renal failure (January 13, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/eprex_3_hpc-cps-eng.pdf (accessed 29/08/08)
- Rossett J, et al. Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004; **15**: 398–406.
- Amgen USA. Aranesp (darbepoetin alfa), November 2005. Available at: http://www.fda.gov/medwatch/safety/2005/Aranesp_DHCP.pdf (accessed 11/04/06)
- Verhelst D, et al. Treatment of erythropoietin-induced pure red cell aplasia: a retrospective study. *Lancet* 2004; **363**: 1768–71.

Effects on electrolytes. Hyperkalaemia and hyperphosphataemia may occur in patients receiving recombinant human erythropoietin. However, hypophosphataemia has also been reported in cirrhotic patients given erythropoietin before autologous blood donation.¹

- Kajikawa M, et al. Recombinant human erythropoietin and hypophosphatemia in patients with cirrhosis. *Lancet* 1993; **341**: 503–4.

Effects on mental function. Visual hallucinations occurred in 4 patients during treatment with recombinant human erythropoietin, stopped when treatment was withdrawn, and recurred in 2 patients when erythropoietin was reinstated.¹ Commenting on these and a further 7 cases,² the manufacturers considered the reaction to be extremely rare and that the contribution of concurrent medication could not be discounted. In two groups of dialysis patients treated with recombinant human erythropoietin, 15 of 134 and 2 of 103 experienced visual hallucinations.³ Increasing age appeared to be a risk factor. Hallucination, associated with hypertension, has occurred during epoetin therapy in a patient with a history of bone marrow transplantation.⁴

- Steinberg H. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325**: 285.
- Stead RB. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325**: 285.
- Steinberg H, et al. Erythropoietin and visual hallucinations in patients on dialysis. *Psychosomatics* 1996; **37**: 556–63.
- van den Bent MJ, et al. Erythropoietin induced visual hallucinations after bone marrow transplantation. *J Neurol* 1999; **246**: 614–16.

Effects on the skin. Skin rashes may occur during treatment with recombinant human erythropoietin.

Pseudoporphyria cutanea tarda, a photosensitivity disorder, has been reported in 2 children undergoing peritoneal dialysis and receiving erythropoietin.¹ However, it was pointed out that this disorder has occurred in adults undergoing dialysis and the children were also receiving other potential photosensitisers.

- Harvey E, et al. Pseudoporphyria cutanea tarda: two case reports on children receiving peritoneal dialysis and erythropoietin therapy. *J Pediatr* 1992; **121**: 749–52.

Effects on the spleen. Aggravation of splenomegaly was reported in 2 patients with myeloproliferative disorders after use of recombinant human erythropoietin.¹ Splenic infarction has been reported in a patient with aplastic anaemia given erythropoietin,² and peliosis of the spleen was discovered at autopsy in a patient with end-stage renal failure who had been receiving erythropoietin.³

- Iki S, et al. Adverse effect of erythropoietin in myeloproliferative disorders. *Lancet* 1991; **337**: 187–8.
- Imashuku S, et al. Splenic infarction after erythropoietin therapy. *Lancet* 1993; **342**: 182–3.
- Lam KY, et al. Peliosis of the spleen: possible association with chronic renal failure and erythropoietin therapy. *Postgrad Med J* 1995; **71**: 493–6.

Effects of subcutaneous injection. Localised pain can occur on subcutaneous injection of human recombinant erythropoietin. In comparisons of preparations it has been suggested that different excipients may affect this.^{1–5} It has generally been reported that epoetin alfa preparations containing citrate buffer are more painful than those with phosphate buffer, and that epoetin beta preparations are less painful than epoetin alfa preparations.

- Frenken LAM, et al. Assessment of pain after subcutaneous injection of erythropoietin in patients receiving haemodialysis. *BMJ* 1991; **303**: 288.
- Lui SF, et al. Pain after subcutaneous injection of erythropoietin. *BMJ* 1991; **303**: 856.
- Yu AW, et al. Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alfa. *Int J Artif Organs* 1998; **21**: 341–3.
- Veys N, et al. Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. *Clin Nephrol* 1998; **49**: 41–4.
- Cumming MN, et al. Subcutaneous erythropoietin alpha (Eprex) is more painful than erythropoietin beta (Recormon). *Nephrol Dial Transplant* 1998; **13**: 817.

Treatment of adverse effects. Venesection¹ and erythropherisis² have been used to treat raised haematocrit and haemoglobin concentrations caused by recombinant human erythropoietin overdose. Venesection also successfully reduced the blood pressure in 4 patients with life-threatening hyperten-