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. 1–165-Erythropoietin (human clone λHEPOFL13 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. 1–165-Erythropoietin (human clone λHEPOFL13 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. 1–165-Erythropoietin (human HMR4396), glycoform δ.

Эпоетин Дельта
CAS — 261356-80-3.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Gamma *(BAN, rINN)* ⊗

BI-71.052; Epoetina gamma; Époétine Gamma; Epoetinum Gamma. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform γ.

Эпоэтин Гамма
CAS — 130455-76-4.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Omega *(rINN)* ⊗

Epoetina omega; Époétine Oméga; Epoetinum Omega. 1–165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ω.

Эпоэтин Омега
CAS — 148363-16-0.
ATC — B03XA01.
ATC Vet — QB03XA01.

Epoetin Zeta *(rINN)* ⊗

Epoetina Dseta; Époétine Zêta; Epoetinum Zeta. 1–165-Erythropoietin (human clone B03XA01), glycoform ζ.

Эпоетин 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 fluids[1] 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.

1. Ohls RK, Christensen RD. Stability of human recombinant epoetin alfa in commonly used neonatal intravenous solutions. *Ann Pharmacother* 1996; **30:** 466–8.
2. Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. *Ann Pharmacother* 1996; **30:** 1501–2.
3. Calhoun DA, *et al.* Stability of filgrastim and epoetin alfa in a system 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.

1. 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.
2. Vaziri ND. Mechanism of erythropoietin-induced hypertension. *Am J Kidney Dis* 1999; **33:** 821–8.
3. 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 review[5] 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]

1. Smith KJ, *et al.* The cardiovascular effects of erythropoietin. *Cardiovasc Res* 2003; **59:** 538–48.
2. 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.
3. Krüger A, *et al.* PRCA in a patient treated with epoetin beta. *Nephrol Dial Transplant* 2003; **18:** 1033–4.
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.
5. Bennett CL, *et al.* Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004; **351:** 1403–8.
6. Gershon SK, *et al.* Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346:** 1584–5.
7. Casadevall N, Mayeux P. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; **346:** 1585. Correction. *ibid.*; **347:** 458.
8. 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.
9. 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)
10. Rossert J, *et al.* Anti-erythropoietin antibodies and pure red cell aplasia. *J Am Soc Nephrol* 2004; **15:** 398–406.
11. Amgen USA. Aranesp (darbepoetin alfa), November 2005. Available at: http://www.fda.gov/medwatch/safety/2005/Aranesp_DHCP.pdf (accessed 11/04/06)
12. 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]

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 reinstituted.[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]

1. Steinberg H. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
2. Stead RB. Erythropoietin and visual hallucinations. *N Engl J Med* 1991; **325:** 285.
3. Steinberg H, *et al.* Erythropoietin and visual hallucinations in patients on dialysis. *Psychosomatics* 1996; **37:** 556–63.
4. 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.

1. 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]

1. Iki S, *et al.* Adverse effect of erythropoietin in myeloproliferative disorders. *Lancet* 1991; **337:** 187–8.
2. Imashuku S, *et al.* Splenic infarction after erythropoietin therapy. *Lancet* 1993; **342:** 182–3.
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.

1. Frenken LAM, *et al.* Assessment of pain after subcutaneous injection of erythropoietin in patients receiving haemodialysis. *BMJ* 1991; **303:** 288.
2. Lui SF, *et al.* Pain after subcutaneous injection of erythropoietin. *BMJ* 1991; **303:** 856.
3. 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.
4. 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.
5. 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. Venesection[1] and erythropheresis[2] 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-

sion associated with recombinant human erythropoietin treatment.[3] None of the patients had a raised haematocrit and the hypertension had been unresponsive to antihypertensive therapy.

1. Brown KR, *et al.* Recombinant erythropoietin overdose. *Am J Emerg Med* 1993; **11:** 619–21.
2. Hoffman RS, *et al.* Erythropoietin overdose treated with emergent erythropheresis. *Vet Hum Toxicol* 2002; **44:** 157–9.
3. Fahal IH, *et al.* Phlebotomy for erythropoietin-associated malignant hypertension. *Lancet* 1991; **337:** 1227.

Precautions

Epoetins should be used with caution in patients with hypertension, a history of seizures, thrombocytosis, chronic hepatic impairment, ischaemic vascular disease, or in patients with malignant tumours. Hypertension should be well controlled before treatment is started and blood pressure monitored during treatment.

Response to epoetins may be diminished by iron deficiency, infection or inflammatory disorders, haemolysis, or aluminium intoxication. Anaemia due to folic acid and vitamin B_{12} deficiencies should also be excluded, since these may also reduce the response. Patients developing sudden lack of efficacy should be investigated. If pure red cell aplasia is diagnosed treatment should be stopped and testing for epoetin antibodies considered; patients should not be transferred to another epoetin.

Patients undergoing dialysis may require increased doses of heparin in view of the increase in packed cell volume.

Platelet counts, haemoglobin concentrations, and serum-potassium concentrations should be monitored regularly.

Dosage must be carefully controlled to avoid too fast an increase in haematocrit and haemoglobin, and recommended values should not be exceeded because of the increased risks of hypertension and thrombotic events.

For reference to the uncertainty of the effect of epoetins on tumour progression and progression-free survival when used in patients with cancer, see under Anaemias in Uses and Administration, p.1063.

Abuse. The potential dangers from abuse of recombinant human erythropoietin by athletes have been reviewed.[1] Normally, optimal athletic conditioning leads to little change in red cell volume but a significant increase in plasma volume and total blood volume. In contrast, the artificial increase in the red cell mass induced by epoetin is usually accompanied by a decrease in plasma volume and no change in total blood volume. Lack of medical supervision and fluid loss during endurance events increase the risk of serious adverse consequences of these changes in blood viscosity produced by such misuse of epoetin. In one case,[2] cerebral sinus thrombosis in a cyclist was attributed to the combined use of epoetin, human growth hormone, and high doses of vitamins A and E.

1. Spivak JL. Erythropoietin use and abuse: when physiology and pharmacology collide. *Adv Exp Med Biol* 2001; **502:** 207–24.
2. Lage JMM, *et al.* Cyclist's doping associated with cerebral sinus thrombosis. *Neurology* 2002; **58:** 665.

Haematocrit and haemoglobin. A study[1] involving 1233 patients undergoing haemodialysis and suffering from heart failure or ischaemic heart disease found that erythropoietin in doses sufficient to increase haematocrit to 42% (within the normal range) was associated with lack of benefit and a trend towards increased mortality when compared with doses sufficient to maintain a lower haematocrit of around 30%. However, these results are difficult to interpret, since within each group, increased haematocrit was associated with lower mortality, despite the between-group differences. The possibility that intravenous iron supplementation might have contributed to these adverse results was considered, but commentators suggested that until further data were available aiming for a haematocrit of 33 to 36%, and using intravenous iron supplementation where necessary, was still appropriate.[2]

Two studies have looked at the effects of adjusting haemoglobin to different concentrations in patients with chronic renal impairment who did not yet need dialysis. In the CHOIR study[3] of 1432 patients, epoetin alfa was used to adjust haemoglobin to either 11.3 or 13.5 g per 100 mL. The risk of cardiovascular complications, particularly death and hospitalisation for congestive heart failure, was increased in the group with the higher haemoglobin target, without any additional improvement in quality of life. The CREATE study[4] included 603 patients who were treated with epoetin beta to adjust haemoglobin to either 13.0 to 15.0 g per 100 mL or 10.5 to 11.5 g per 100 mL. Although the measures for quality of life were better in the group adjusted to the higher target and there was no statistically significant difference between the groups in the risk of cardiovascular complications, there was a trend towards a more favourable outcome in the low-target group. The FDA subsequently issued a reminder[5] that in patients receiving epoetins or darbepoetin alfa, a target haemoglobin range of 10 to 12 g per 100 mL is recommended, and that haemoglobin concentrations and blood pressure should be monitored.

1. Besarab A, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584–90.
2. Adamson JW, Eschbach JW. Erythropoietin for end-stage renal disease. *N Engl J Med* 1998; **339:** 625–7.
3. Singh AK, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085–98.
4. Drüeke TB, *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355:** 2071–84.
5. FDA. Information for healthcare professionals: erythropoiesis stimulating agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)] (issued 16/11/06). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE_HCP.htm (accessed 20/11/06)

Resistance. Many factors may contribute to a poor response to recombinant human erythropoietin (see Precautions, above). A study in patients with anaemia of end-stage renal disease[1] found that inadequate dialysis was associated with a reduced response to erythropoietin treatment. The dialysis time and mode of dialysis may also influence response to erythropoietin therapy.[2] Antibodies to recombinant human erythropoietin have also been reported.[3,4] Delayed clinical response to recombinant human erythropoietin in a patient[5] could have been due to an inherited subclinical pyruvate kinase deficiency.

1. Ifudu O, *et al.* The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996; **334:** 420–5.
2. Locatelli F, *et al.* The modality of dialysis treatment: does it influence the response to erythropoietin treatment? *Nephrol Dial Transplant* 2001; **16:** 1971–4.
3. Peces R, *et al.* Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; **335:** 523–4.
4. Viron B, *et al.* Anticorps anti-érythropoïétine humaine recombinante: une cause exceptionnelle de résistance à l'érythropoïétine. *Nephrologie* 2002; **23:** 19–22.
5. Zachée P, *et al.* Pyruvate kinase deficiency and delayed clinical response to recombinant human erythropoietin treatment. *Lancet* 1989; **i:** 1327–8.

Pharmacokinetics

Epoetins exhibit some differences in their pharmacokinetics, possibly due to differences in glycosylation and in the formulation of the commercial preparations.

Epoetin alfa is slowly and incompletely absorbed after subcutaneous injection, and a relative bioavailability of about 10 to 20% has been reported. Peak concentrations after epoetin alfa intravenously are attained within 15 minutes, and within 5 to 24 hours after subcutaneous injection.

The elimination half-life of epoetin alfa after intravenous doses has been reported to be 4 to 13 hours in patients with chronic renal failure; the half-life is generally less in patients with normal renal function. An estimated elimination half-life of about 24 hours has been reported for epoetin alfa given subcutaneously.

Epoetin beta is similarly slowly and incompletely absorbed after subcutaneous injection, and its absolute bioavailability has been reported to be 23 to 42%. Peak serum concentrations are attained within 12 to 28 hours of subcutaneous doses. An elimination half-life of 4 to 12 hours has been reported after intravenous doses and a terminal half-life of 13 to 28 hours after subcutaneous doses.

Epoetin delta has a bioavailability after subcutaneous injection of between 26 and 36%, the peak serum concentration occurs after 8 to 36 hours, and the half-life in patients is about 27 to 33 hours. After intravenous injection, it has an elimination half-life of about 4 to 13 hours in patients with chronic renal failure, which is about double that measured in healthy subjects.

Epoetin zeta has a bioavailability of about 20% after subcutaneous injection, and peak serum concentrations occur after about 12 to 18 hours. The half-life after subcutaneous injection has been estimated to be about 24 hours. After intravenous injection, a half-life of about 4 hours has been measured in healthy subjects, and about 5 hours in patients with chronic renal failure; the half-life in children is about 6 hours.

◊ References.

1. Macdougall IC, *et al.* Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). *Clin Pharmacokinet* 1991; **20:** 99–113.
2. Halstenson CE, *et al.* Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 1991; **50:** 702–12.
3. Gladziwa U, *et al.* Pharmacokinetics of epoetin (recombinant human erythropoietin) after long term therapy in patients undergoing haemodialysis and haemofiltration. *Clin Pharmacokinet* 1993; **25:** 145–53.
4. Montini G, *et al.* Pharmacokinetics and hematologic response to subcutaneous administration of recombinant human erythropoietin in children undergoing long-term peritoneal dialysis: a multicenter study. *J Pediatr* 1993; **122:** 297–302.
5. Brown MS, *et al.* Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. *J Pediatr* 1993; **122:** 655–7.
6. Reddingius RE, *et al.* Pharmacokinetics of recombinant human erythropoietin in children treated with continuous ambulatory peritoneal dialysis. *Eur J Pediatr* 1994; **153:** 850–4.
7. Chakraborty A, *et al.* Population pharmacokinetics of erythropoietin in critically ill subjects. *J Clin Pharmacol* 2005; **45:** 193–202.

Uses and Administration

Erythropoietin is a glycosylated protein hormone and a haematopoietic growth factor. It is secreted primarily by the kidneys, although a small amount is produced in extrarenal sites such as the liver. Erythropoietin regulates erythropoiesis by stimulating the differentiation and proliferation of erythroid precursors, the release of reticulocytes into the circulation, and the synthesis of cellular haemoglobin. The release of erythropoietin is promoted by hypoxia or anaemia, and up to 1000 times the normal serum-erythropoietin concentration may be reached under these conditions; this response may be impaired in some disease states such as chronic renal failure. The haematological response to erythropoietin is reduced if there is an inadequate supply of iron. For an outline of blood cell formation in general and average cell counts in adults see Haematopoiesis, p.1042.

Epoetins alfa, beta, delta, and zeta are recombinant human erythropoietins available for clinical use that have the same pharmacological actions as endogenous erythropoietin. They are used in the management of anaemia associated with chronic renal failure in dialysis and predialysis patients; they may reduce or obviate the need for blood transfusions in these patients. Epoetins alfa, beta, and zeta are also used in the management of chemotherapy-induced anaemia in patients with non-myeloid malignant disease. Epoetin alfa is used in zidovudine-related anaemia in HIV-positive patients. Epoetin beta is used in the management of anaemia of prematurity. Recombinant human erythropoietin is also being evaluated in the management of other types of normocytic-normochromic anaemias, including that associated with inflammatory disorders such as rheumatoid arthritis. In all patients, iron status should be monitored and supplementation provided if necessary.

Epoetins alfa, beta, and zeta may also be used in patients with moderate anaemia (but no iron deficiency) before elective surgery to increase the yield of blood collected for autologous blood transfusion. Epoetin alfa may also be used in such patients to reduce the need for allogeneic blood transfusion.

In the management of **anaemia of chronic renal failure** epoetin alfa, beta, or delta may be given intravenously or subcutaneously; epoetin zeta may only be given intravenously. For haemodialysis patients the dose of epoetin should be given intravenously because of the risk of pure red cell aplasia reported with subcutaneous use (see Effects on the Blood, above); it may be given during or at the end of the dialysis session using the dialysis vascular access. For predialysis and peritoneal dialysis patients, in whom intravenous access is not readily available, doses should be given subcutaneously. The aim of treatment in adults is to increase the haemoglobin concentration to 10 to 12 g per 100 mL or to increase the haematocrit to 30 to 36%. The rate of rise in haemoglobin should be gradual to minimise adverse effects such as hypertension; a rate not exceeding 2 g per 100 mL per month is suggested.

Epoetin alfa may be given subcutaneously or by intravenous injection over at least 1 minute; slow intravenous injection over 5 minutes may be used in patients who experience flu-like symptoms as adverse effects. ***Epoetin zeta*** may be given intravenously.

- In predialysis and haemodialysis patients, a recommended initial dose of epoetin alfa or zeta is 50 international units/kg three times weekly. For epoetin alfa, a higher initial dose of 50 to 100 units/kg three times weekly has been suggested in the USA.
- Doses may be increased at 4-week intervals in increments of 25 units/kg three times weekly until the target is reached.
- In patients on peritoneal dialysis an initial dose of 50 units/kg given twice weekly may be used.

Once the target is reached doses may need to be adjusted for maintenance therapy.

- The usual total weekly maintenance dose of epoetin alfa or zeta in predialysis patients is 50 to 100 units/kg given in three divided doses, and in haemodialysis patients it is about 75 to 300 units/kg given in three divided doses. In predialysis patients a total weekly dose of 600 units/kg should not be exceeded. In patients on peritoneal dialysis, the usual total weekly maintenance dose is 50 to 100 units/kg given in two divided doses.

In children, epoetin alfa or zeta may be given intravenously to those on haemodialysis.

- The initial dose is 50 units/kg three times weekly. The dose may be increased at 4-week intervals in increments of 25 units/kg three times weekly until a target haemoglobin concentration of 9.5 to 11 g per 100 mL is reached.

The usual total weekly maintenance dose given in three divided doses is:

- 225 to 450 units/kg for those weighing less than 10 kg
- 180 to 450 units/kg for those weighing 10 to 30 kg
- 90 to 300 units/kg for those weighing over 30 kg

Epoetin beta is used similarly in the management of anaemia of chronic renal failure in dialysis and predialysis patients. It may be given subcutaneously or by intravenous injection over 2 minutes. The following dosages may be used in adults and children:

- For subcutaneous injection the initial dose is 60 units/kg weekly for 4 weeks; the total weekly dose may be divided to be given in daily doses or three times a week
- For intravenous injection the initial dose is 40 units/kg three times weekly for 4 weeks; the dose may then be increased to 80 units/kg three times weekly
- Thereafter the dose of epoetin beta may be increased at 4-week intervals, for both subcutaneous and intravenous injection, in increments of 60 units/kg weekly in divided doses, until the target haemoglobin concentration or haematocrit is reached. A total weekly dose of 720 units/kg of epoetin beta should not be exceeded

For maintenance, the dose is halved initially and then adjusted every 1 to 2 weeks according to response. The weekly subcutaneous maintenance dose may be divided into 1, 3, or 7 doses; in patients stabilised on a once-weekly dose, it may be possible to adjust to a single dose every 2 weeks.

Epoetin delta is also used in the management of anaemia of chronic renal failure in dialysis and predialysis patients.

- For subcutaneous injection, the initial dose is 50 units/kg twice weekly.
- For intravenous injection, the initial dose is 50 units/kg three times weekly.
- Dosage may be adjusted by 25 to 50%, at intervals of at least 4 weeks, as required.

In adults receiving chemotherapy for **non-myeloid malignant disease**, epoetin alfa, beta, or zeta may be given by subcutaneous injection for symptomatic anaemia, usually when the haemoglobin concentration has fallen to 10 g or lower per 100 mL. The rise in haemoglobin should be gradual; a rate not exceeding 2 g per 100 mL per month, and a target haemoglobin concentration of not more than 12 g per 100 mL, are suggested.

- Epoetin alfa or zeta may be given in an initial dose of 150 units/kg three times weekly or 450 units/kg once weekly. The dose may be increased after 4 or 8 weeks, if necessary, to 300 units/kg three times weekly. If the response is still inadequate after 4 weeks at this higher dose, treatment should be stopped. Epoetin alfa may also be given in a once-weekly dose of 40 000 units, which may be increased to 60 000 units after 4 weeks if necessary.
- Epoetin beta may be given in an initial dose of 30 000 units (about 450 units/kg) weekly, as a single dose or divided into 3 to 7 doses. The dose may be doubled after 4 weeks if necessary, but treatment should be stopped if the response is still inadequate after 4 weeks at the higher dose. The total weekly dose should not exceed 60 000 units. Once the desired haemoglobin concentration has been reached, the dose should be reduced by 25 to 50% for maintenance therapy, and adjusted as necessary.

Epoetins should be stopped after the end of chemotherapy, but epoetin alfa, beta, or zeta may be continued for up to one month in the UK.

In children, epoetin alfa may be given intravenously in a single weekly dose of 600 units/kg (to a maximum of 40 000 units). The dose may be increased if necessary after 4 weeks to 900 units/kg (maximum 60 000 units).

In adult **HIV-positive patients** on zidovudine therapy, epoetin alfa may be beneficial if the endogenous serum-erythropoietin concentration is 500 milliunits/mL or less. Epoetin alfa is given by subcutaneous or intravenous injection in an initial dose of 100 units/kg three times weekly for 8 weeks. The dose may then be increased every 4 to 8 weeks by 50 to 100 units/kg three times weekly according to response. However, patients are unlikely to benefit from doses above 300 units/kg three times weekly if this dose has failed to elicit a satisfactory response.

In the management of **anaemia of prematurity** epoetin beta is given subcutaneously in a dose of 250 units/kg three times weekly. Treatment should be started as early as possible and continued for 6 weeks.

To increase the yield of **autologous blood** in adults, epoetin alfa, beta, or zeta may be used with iron supplementation. The dose depends on the volume of blood required for collection and on factors such as the patient's whole blood volume and haematocrit. Suggested regimens are:

- epoetin alfa or zeta 600 units/kg given intravenously twice weekly starting 3 weeks before surgery
- up to 800 units/kg of epoetin beta intravenously, or up to 600 units/kg subcutaneously, twice weekly for 4 weeks before surgery

To reduce the need for allogeneic blood transfusion in adults, epoetin alfa may be given in a dose of 600 units/kg subcutaneously once weekly starting 3 weeks before surgery, with a fourth dose given on the day of surgery. Alternatively, when the time before surgery is short, 300 units/kg subcutaneously daily may be given for 10 days before surgery, on the day of surgery, and for 4 days after.

◊ Reviews.

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2. Dunn CJ, Markham A. Epoetin beta: a review of its pharmacological properties and clinical use in the management of anaemia associated with chronic renal failure. *Drugs* 1996; **51:** 299–318.
3. Beguin Y. A risk-benefit assessment of epoetin in the management of anaemia associated with cancer. *Drug Safety* 1998; **19:** 269–82.
4. Cheer SM, Wagstaff AJ. Epoetin beta: a review of its clinical use in the treatment of anaemia in patients with cancer. *Drugs* 2004; **64:** 323–46.
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6. Corwin HL. The role of erythropoietin therapy in the critically ill. *Transfus Med Rev* 2006; **20:** 27–33.
7. Hasselblatt M, *et al*. The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. *J Neurosurg Anesthesiol* 2006; **18:** 132–8.

Administration in neonates. Recombinant human erythropoietin may be given to neonates for anaemia of prematurity (see Anaemias, below). It is usually given by subcutaneous injection. Intravenous infusion in total parenteral nutrition solutions produced satisfactory results in a group of 20 neonates.[1] Enteral dosage in one small study[2] increased plasma-erythropoietin concentrations and peak reticulocyte counts, but in another larger study[3] it had no effect.

For a warning about diluting recombinant human erythropoietin solutions, see Stability, above.

1. Ohls RK, *et al.* Pharmacokinetics and effectiveness of recombinant erythropoietin administered to preterm infants by continuous infusion in total parenteral nutrition solution. *J Pediatr* 1996; **128:** 518–23.
2. Ballin A, *et al.* Erythropoietin, given enterally, stimulates erythropoiesis in premature infants. *Lancet* 1999; **353:** 1849.
3. Juul SE. Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. *J Pediatr* 2003; **143:** 321–6.

Anaemias. Epoetins are used in normocytic-normochromic anaemias (p.1044) associated with low endogenous erythropoietin concentrations.

Anaemia associated with *chronic renal disease* is primarily a result of inadequate production of erythropoietin in the kidney. Other factors that can contribute to the anaemia include iron deficiency, blood loss associated with dialysis, and severe hyperparathyroidism. The use of epoetins in the management of renal anaemia is well established,[1,2] as consistently good results have been obtained not only for correction of anaemia but also for improvement in quality of life.[1,3] In predialysis patients, epoetins also correct anaemia, reduce the requirement for blood transfusions, and improve quality of life and exercise capacity, but there may be increased hypertension[2,4] and it is not known whether the need for dialysis is delayed.[4] Over 90% of patients with renal anaemia respond to treatment with epoetins.[1] Many factors can contribute to a poor response (see Precautions, above) and the patient should always be investigated and the cause corrected where possible. Common causes of inadequate response are iron deficiency, inflammatory disorders, chronic blood loss, hyperparathyroidism, and aluminium toxicity.[1,5]

Epoetins may be given intravenously or subcutaneously. Epoetin given subcutaneously produces lower but more sustained plasma concentrations and total weekly maintenance doses are reduced.[1,2,6] The subcutaneous route is generally used in predialysis patients and those on peritoneal dialysis,[1,2] partly because of the need to avoid venepuncture of veins that are likely to be needed for future haemodialysis access. While subcutaneous injection can also be used for haemodialysis patients, the intravenous route is preferred because of the rare risk of pure red cell aplasia reported with subcutaneous use[1] (see Effects on the Blood, above) and the ready availability of intravenous access. The dosage frequency may also be important in maximising the response to treatment, but may be influenced by the epoetin being used, route of administration, treatment phase, and patient preference. For example, giving epoetins 2 or 3 times a week may allow for a lower total weekly dose than once weekly, and may be more effective, but dosing once weekly may be more convenient for maintenance therapy.[1,2] A systematic review[7] concluded that there was no evidence to support one frequency over another in terms of maintaining target haemoglobin. See Uses and Administration, above, for examples of licensed doses, routes, and dose frequency for epoetins. Darbepoetin alfa (p.1058) is given at longer dosage intervals than epoetins and there is no difference in weekly dosage requirements between subcutaneous and intravenous routes.[2,6]

Intraperitoneal use of epoetins has also been proposed and investigated.[8,9] However, this route is rarely used because the doses must be given into a dry abdomen,[1] dose requirements are generally higher than those for intravenous or subcutaneous use, and there is the potential for more frequent episodes of peritonitis.[1,2]

Blood transfusions are often used to treat *anaemia of prematurity*, and epoetins have been investigated as a means of reducing transfusion requirements. A systematic review[10] found that although epoetin reduced transfusion needs, the effect was only modest and there was considerable variation between studies. More selective reviews of very-low-birth-weight infants (less than 1500 g) also found modest reductions in transfusion requirements, whether epoetin was started within the first week of life[11] or after one week,[12] although transfusion requirements were unlikely to be eliminated completely. Response to the late use of epoetin was also found to be dose-dependent.[12]

Factors contributing to *cancer-related anaemia* include chemotherapy, radiotherapy, and the malignancy itself. Epoetin therapy can reduce the need for blood transfusions in cancer patients[13,14] and may improve quality of life.[14,15] Guidelines for the use of epoetins in chemotherapy-induced anaemia have been issued (see Anaemia, under Bone-marrow Depression, p.639). There

has, however, been some concern raised about the effect of epoetin therapy on patient survival. A placebo-controlled study of epoetin alfa to maintain normal haemoglobin concentrations (12 to 14 g per 100 mL) in patients receiving chemotherapy for metastatic breast cancer was terminated early when an increase in death was found in the epoetin group.[16] In another placebo-controlled study[17] of patients with head and neck cancer undergoing radiotherapy, epoetin beta was associated with correction of anaemia but poorer locoregional progression-free survival. In contrast, analysis of a study[18] in patients with lymphoproliferative malignancies found no effect of epoetin beta on patient survival. Two meta-analyses[14,19] found no conclusive evidence that epoetins affected tumour response or survival, but pointed out that few studies were primarily designed to assess these outcomes. Subsequently, a study of the quality of life in anaemic patients with advanced non-small cell lung cancer was stopped early, when an unplanned safety analysis suggested a reduced overall survival in patients given epoetin alfa.[20] However, two later studies did aim to investigate whether epoetin therapy influenced cancer treatment outcome and survival. One study in women treated with radiochemotherapy for advanced cervical cancer reported no positive correlation between haemoglobin increase and improvement in clinical outcomes, and could not draw a definite conclusion as to whether epoetin beta had an effect on disease progression or survival.[21] Another study, in women given chemotherapy for metastatic breast cancer, found that epoetin beta had no significant effect on overall survival.[22] Nevertheless, a further meta-analysis[23] of studies in cancer patients found that epoetin or darbepoetin alfa therapy was associated with increased risks of venous thromboembolism and death. Studies to date have generally used haemoglobin targets of 12 g and above per 100 mL, and further information is needed on the benefits and risks associated with the lower targets now advised (see Uses and Administration, above). In response to these concerns, authorities have strengthened warnings in licensed product information regarding the use of epoetins and related products in patients with cancer. The MHRA has also advised[24] that blood transfusion should be the preferred option for the management of anaemia in patients with cancer, particularly in those receiving adjuvant chemotherapy or who are being treated with curative intent. They also suggest that transfusion may be preferable in patients with advanced or metastatic cancer who have a good survival prognosis.

Epoetins are sometimes used to treat *anaemias from other causes*. Potential applications include zidovudine-induced anaemia in AIDS patients (see Effects on the Blood under Zidovudine, p.914), postpartum anaemia,[25,26] anaemia in critically ill patients,[27-29] and anaemia of chronic diseases such as rheumatoid arthritis,[30,31] inflammatory bowel disease,[32-34] and chronic heart failure.[35]

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15. Jones M, *et al.* Epoetin alfa improves quality of life in patients with cancer: results of a metaanalysis. *Cancer* 2004; **101:** 1720–32.
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Cardiovascular diseases. There is some interest in the non-haematopoietic effects of erythropoietin, including protection from apoptosis, antoxidant activity, and pro-angiogenic effects. A possible role in the management of ischaemic stroke and myocardial infarction is under investigation.[1]

1. van der Meer P, *et al.* Erythropoietin in cardiovascular diseases. *Eur Heart J* 2004; **25:** 285–91.

Surgery. Concern over the safety of blood transfusions and the need to conserve blood supplies has led to interest in methods of reducing blood use in surgery. Recombinant human erythropoietin has been used to increase the number of units harvested for autologous transfusion[1] and to reduce transfusion requirements.[2-4] It has also been used as an alternative to blood transfusions in Jehovah's Witnesses.[5-8]

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Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Epogen; Eprex; Eritrogen; Hemax; Hypercrit; Pronivel; Recormon; ***Austral.:*** Eprex; NeoRecormon; ***Austria:*** Culat; Erypo; NeoRecormon; Recormon; ***Belg.:*** Eprex; NeoRecormon; ***Braz.:*** Eprex; Eritina; Eritromax; Hemax-Eritron; Hemoprex; Mepotin†; Recormon; Tinax; ***Canad.:*** Eprex; ***Chile:*** Epokine; Eprex; Hypercrit; Recormon; ***Cz.:*** Binocrit; Dynepo; Epomax†; Eprex; NeoRecormon; Recormon†; Retacrit; Silapo; ***Denm.:*** Eprex; NeoRecormon; ***Fin.:*** Eprex; NeoRecormon; ***Fr.:*** Eprex; NeoRecormon; ***Ger.:*** Eprex; Erypo; NeoRecormon; ***Gr.:*** Eprex; NeoRecormon; ***Hong Kong:*** Eprex; Recormon; ***Hung.:*** Eprex; NeoRecormon; ***India:*** Wepox; ***Indon.:*** Epotrex-NP; Eprex; Hemapo; Recormon; ***Irl.:*** Eprex; NeoRecormon; ***Israel:*** Eprex; Recormon; ***Ital.:*** Epoxitin†; Eprex; Globuren†; NeoRecormon; ***Jpn:*** Epogin; Espo; ***Malaysia:*** Eprex; Recormon; ***Mex.:*** Bioyetin; Epomax; Eprex; Erlan; Exetin-A; Hypercrit; Negortire; Recormon; Yepotin; ***Neth.:*** Dynepo; Eprex; NeoRecormon; ***Norw.:*** Eprex; NeoRecormon; ***NZ:*** Eprex; Recormon; ***Philipp.:*** Epokine; Eposino; Eprex; Recormon; Renogen; ***Pol.:*** Eprex; NeoRecormon; ***Port.:*** Dynepo; Eprex; NeoRecormon; Recormon†; Retacrit; Silapo; ***Rus.:*** Epocrin (Эпокрин); Eprex (Эпрекс); Erythrostim (Эритростим); Recormon (Рекормон); ***S.Afr.:*** Eprex; Recormon; Repotin; ***Singapore:*** Eprex; Recormon; ***Spain:*** Epopen; Eprex; NeoRecormon; ***Swed.:*** Eprex; NeoRecormon; ***Switz.:*** Eprex; Recormon; ***Thai.:*** Epokine; Eprex; Espogen; Hemax; Recormon; ***Turk.:*** Eprex; NeoRecormon; ***UAE:*** Epotin; ***UK:*** Binocrit; Dynepo; Eprex; NeoRecormon; Retacrit; ***USA:*** Epogen; Procrit; ***Venez.:*** Eprex; Hypercrit; Recormon.

Etamsylate *(BAN, rINN)*

Cyclonamine; E-141; Etamsilat; Etamsilatas; Etamsilato; Etamsylaatti; Etamsylát; Etamsylat; Étamsylate; Etamsylatum; Etamszilát; Ethamsylate *(USAN)*; MD-141. Diethylammonium 2,5-dihydroxybenzenesulphonate.

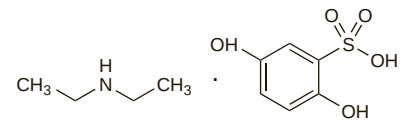
Этамзилат

$C_{10}H_{17}NO_5S$ = 263.3.

CAS — 2624-44-4.

ATC — B02BX01.

ATC Vet — QB02BX01.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Etamsylate). A white or almost white, crystalline powder. It shows polymorphism. Very soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 10% solution in water has a pH of 4.5 to 5.6. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Nausea, vomiting, diarrhoea, fever, headache, and skin rash have occurred after use of etamsylate. Headache and skin rashes may disappear on reduced dosage, and gastrointestinal disturbances are reduced by giving etamsylate after food. Transient hypotension has been reported following intravenous injection.

Porphyria. Etamsylate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pharmacokinetics

Etamsylate is absorbed from the gastrointestinal tract. It is excreted unchanged, mainly in the urine. Etamsylate is distributed into breast milk.

Uses and Administration

Etamsylate is a haemostatic that appears to maintain the stability of the capillary wall and correct abnormal platelet adhesion. It is given for the prophylaxis and control of haemorrhages from small blood vessels.

For short-term blood loss in menorrhagia a dose of 500 mg is given orally four times daily during menstruation. For the prophylaxis and treatment of periventricular haemorrhage in low birth-weight neonates 12.5 mg/kg is given by intramuscular or intravenous injection every 6 hours. For the control of haemorrhage after surgery etamsylate may be given orally to adults, or by intramuscular or intravenous injection in a dose of 250 to 500 mg; this dose may be repeated every 4 to 6 hours as necessary.

Menorrhagia. When given during menstruation to women with idiopathic menorrhagia (p.2126), etamsylate was as effective as mefenamic acid in reducing uterine blood loss in 1 study,[1] but was ineffective in another.[2] A review, which included published and unpublished results from these and 2 earlier studies, reported