Dextran 1 (p.1058) may be used to block the formation of dextran-reactive antibodies and hence the hypersensitivity reactions.

Effects on the blood. A syndrome of acute hypotension, pulmonary oedema, coagulopathy, and anaemia, has occurred after the intra-uterine instillation of 32% solution of dextran 70 for hysteroscopy.[1] The volumes of solution that were used in 10 reported cases ranged from 300 to 1200 mL, and these large volumes may have contributed to the intravascular absorption of dextran. The pathogenesis and role of dextran in this syndrome are unclear but suggestions have included acute volume overload, direct alveolar endothelial damage, and release of tissue factors that promote fibrinolysis and a consumptive coagulopathy.

1. Ellingson TL, Aboulafia DM. Dextran syndrome: acute hypotension, noncardiogenic pulmonary edema, anemia, and coagulopathy following hysteroscopic surgery using 32% dextran 70. *Chest* 1997; **111:** 513–18.

Effects on the kidneys. For a report of acute renal failure associated with use of dextran 70, see Dextran 40, above.

Hypersensitivity. In a retrospective study of allergic reactions to dextran 40 and dextran 70 reported in Sweden from 1970 to 1979,[1] there were 478 reports of reactions, 458 of which were considered to be due to dextran, out of 1 365 266 infusions given. There was a male to female ratio of 1.5 to 1 for all reactions and a ratio of 3 to 1 for the most severe reactions. The mean age of the patients was higher in those with severe reactions. Of the 28 fatal reactions, 27 occurred within 5 minutes of the start of the infusion and 25 when less than 25 mL had been infused. Three of the fatal reactions occurred after a test dose of only 0.5 to 1 mL and it was strongly recommended that such test doses should not be used.

An anaphylactic reaction has also been reported[2] more than 75 minutes after intraperitoneal instillation. After successful symptomatic treatment symptoms recurred 20 minutes later, due to slow absorption of dextran from the peritoneal cavity. No further reaction occurred after removal of 200 mL of intraperitoneal fluid by culdocentesis.

Anaphylactoid reactions after BCG vaccination have been attributed to hypersensitivity to dextran in the formulation.[3]

The use of dextran 1 for the prevention of hypersensitivity reactions is discussed under that monograph (p.1058).

1. Ljungström K-G, *et al.* Adverse reactions to dextran in Sweden 1970–1979. *Acta Chir Scand* 1983; **149:** 253–62.
2. Borten M, *et al.* Recurrent anaphylactic reaction to intraperitoneal dextran 75 used for prevention of postsurgical adhesions. *Obstet Gynecol* 1983; **61:** 755–7.
3. Rudin C, *et al.* Anaphylactoid reaction to BCG vaccine containing high molecular weight dextran. *Eur J Pediatr* 1995; **154:** 941–2.

Precautions

Dextran infusions produce a progressive dilution of oxygen-carrying capacity, coagulation factors, and plasma proteins and may overload the circulation. They are therefore contra-indicated in patients with severe heart failure, bleeding disorders such as hypofibrinogenaemia or thrombocytopenia, or renal failure and should be used with caution in patients with renal impairment, haemorrhage, chronic liver disease, or those at risk of developing pulmonary oedema or heart failure. Central venous pressure should be monitored during the initial period of infusion to detect fluid overload. Also patients should be watched closely during the early part of the infusion period, and the infusion stopped immediately if signs of anaphylactic reactions appear. Infusions should also be stopped if there are signs of oliguria or renal failure. The haematocrit should not be allowed to fall below 30% and all patients should be observed for early signs of bleeding complications. The bleeding time may be increased especially in patients receiving large volumes of dextrans. Deficiency of coagulation factors should be corrected and fluid and electrolyte balance maintained. Dehydration should be corrected before or at least during dextran infusions, in order to maintain an adequate urine flow.

The anticoagulant effect of heparin may be enhanced by dextran.

The higher molecular weight dextrans may interfere with blood grouping and cross-matching of blood, while the lower molecular weight dextrans may interfere with some methods. Therefore, whenever possible, a sample of blood should be collected before giving the dextran infusion and kept frozen in case such tests become necessary.

The presence of dextran may interfere with the determination of glucose, bilirubin, or protein in blood.

Pharmacokinetics

After intravenous infusion dextrans with a molecular weight of less than 50 000 are excreted unchanged by the kidney. Dextrans with a molecular weight greater than 50 000 are slowly metabolised to glucose. Small amounts of dextrans are excreted into the gastrointestinal tract and eliminated in the faeces.

About 50% of dextran 70 is excreted unchanged in the urine within 24 hours.

Uses and Administration

Dextran 70 is a plasma volume expander used in the management of hypovolaemic shock (p.1183). As a 6% solution dextran 70 exerts a colloidal osmotic pressure similar to that of plasma proteins and thus produces less expansion of plasma volume than dextrans of a lower molecular weight, although the expansion may have a longer duration because of less rapid renal excretion. Dextran 70 also reduces blood viscosity, interferes with fibrin polymerisation, has an antiplatelet effect, and inhibits sludging or aggregation of red blood cells. It may be used in the prophylaxis of postoperative thromboembolic disorders (p.1189).

Dextran 70 is given by intravenous infusion as a 6% solution, usually in sodium chloride 0.9% or glucose 5%.

Doses depend on the severity of the plasma loss and on the degree of haemoconcentration.

In **shock**, the usual initial dose for rapid expansion of plasma volume is 500 to 1000 mL infused at a rate of 20 to 40 mL/minute. A suggested maximum dose is 20 mL/kg during the first 24-hour period and 10 mL/kg per day thereafter; treatment should not continue for longer than 3 days. Patients may also require blood, coagulation factors, and electrolytes. A hypertonic solution of 6% dextran 70 in sodium chloride 7.5% is also available for use as a plasma expander, given in a single intravenous dose of 250 mL over 2 to 5 minutes, followed by isotonic fluids as required.

For the prophylaxis of pulmonary embolism or venous **thrombosis** in moderate- to high-risk patients undergoing surgery, a dose of 500 to 1000 mL may be given over 4 to 6 hours either during or immediately after surgery. A dose of 500 mL should be given on the next day and in high-risk patients on subsequent alternate days for up to 2 weeks after the operation.

A 32% solution of dextran 70 has been instilled into the uterus in a dose of 50 to 100 mL as a rinsing and dilatation fluid to aid **hysteroscopy**.

Dextran 70 is also an ingredient of artificial tears.

Hypertonic solutions. There is some evidence to suggest that hypertonic solutions of dextran 70 in sodium chloride 7.5% may be an effective treatment option for hypovolaemic shock resulting from trauma.[1,2]

1. Wade CE, *et al.* Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery* 1997; **122:** 609–16.
2. Alpar EK, Killampalli VV. Effects of hypertonic dextran in hypovolaemic shock: a prospective clinical trial. *Injury* 2004; **35:** 500–506.

Preparations

BP 2008: Dextran 70 Intravenous Infusion;
USP 31: Dextran 70 in Dextrose Injection; Dextran 70 in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Hyskon; ***Braz.:*** Volumax D 70†; ***Canad.:*** Gentran 70; ***Cz.:*** Tensiton†; ***Denm.:*** Macrodex; RescueFlow; ***Fin.:*** RescueFlow; ***Ger.:*** Longasteril 70†; RescueFlow†; ***Israel:*** Macrodex; ***Ital.:*** Plander; Solplex 70†; ***Mex.:*** Macrodex†; ***Neth.:*** RescueFlow; ***Norw.:*** Macrodex; RescueFlow; ***Port.:*** Neodextril 70; RescueFlow; ***S.Afr.:*** Macrodex; RescueFlow; ***Swed.:*** Macrodex; RescueFlow; ***Switz.:*** Dialens; Macrodex†; ***Turk.:*** Macrodex; ***UK:*** Gentran 70; RescueFlow; ***USA:*** Gentran 70; Hyskon; Macrodex; ***Venez.:*** Lacridos; Lacrimart; Lagrimas Artificiales.

Multi-ingredient: ***Arg.:*** Alcon Lagrimas; Kalopsis Lagrimas; Phoenix Lagrimas; Tears Naturale; Visine Plus; ***Austral.:*** Bion Tears; Opti-Free Comfort†; Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Belg.:*** Alcon Adequad; Lacrystat; Tears Naturale; ***Braz.:*** Lacribell; Lacrima Plus; Lacrima†; Trisorb; ***Canad.:*** Artificial Tears; Bion Tears; Tears Naturale; Tears Naturale Forte; Visine Advance Triple Action; ***Chile:*** Lagrimas Artificiales; Naphtears; Nico Drops; Nicotears; Tears Naturale; ***Cz.:*** Tears Naturale; ***Denm.:*** Dacriosol; ***Ger.:*** Isopto Naturale; ***Gr.:*** Tears Naturale; ***Hong Kong:*** Bion Tears; Tears Naturale Forte; ***Hung.:*** Dacrolux; Tears Naturale; ***Indon.:*** Isotic Tearin; Tears; Tears Naturale II; ***Irl.:*** Tears Naturale; ***Israel:*** Tears Naturale; ***Ital.:*** Dacriosol; ***Malaysia:*** Bion Tears; Dacrolux; Tears Naturale; ***Mex.:*** Lacrima Plus; Naphtears; Naturalag; Tears Naturale; Visine Extra; ***Neth.:*** Duratears; ***Norw.:*** Tears Naturale; ***NZ:*** Poly-Tears; Tears Naturale; Visine Advanced Relief; ***Philipp.:*** Gentle Tears; Tears Naturale; ***Pol.:*** Tears Naturale; ***Port.:*** Tears Naturale†; ***Rus.:*** Tears Naturale (Слеза Натуральная); ***S.Afr.:*** Tears Naturale; ***Singapore:*** Bion Tears; Dacrolux†; Tears Naturale; ***Spain:*** Dacrolux; Tears Humectante; ***Swed.:*** Bion Tears; ***Switz.:*** Tears Naturale; ***Thai.:*** Bion Tears; Tears Naturale; ***Turk.:*** Dacrolux; Tears Naturale; ***UK:*** Tears Naturale; ***USA:*** Advanced Relief Visine; Aquasite†; Bion Tears; Lacri-Tears; LubriTears; Moisture Drops; Nature's Tears; Ocucoat; Tears Naturale; Tears Renewed.

Dextran 75 *(BAN, USAN, rINN)* ⊗

Dextrán 75; Dextranum 75.

Декстран 75

CAS — 9004-54-0 (dextran).
ATC — B05AA05.
ATC Vet — QB05AA05.

Profile

Dextran 75 consists of dextrans (glucose polymers) of weight average molecular weight about 75 000 that are derived from the dextrans produced by the fermentation of sucrose by means of a certain strain of *Leuconostoc mesenteroides.*

Dextran 75 is a plasma volume expander with actions and uses similar to dextran 70 (p.1059). It is given by intravenous infusion as a 6% solution in sodium chloride 0.9% or glucose 5%.

Ecallantide *(USAN, rINN)*

DX-88; Ecalantida; Écallantide; Ecallantidum. Human plasma kallikrein-inhibitor (synthetic protein).

Экальлантид

CAS — 460738-38-9.

Profile

Ecallantide is a recombinant inhibitor of human plasma kallikrein. It is under investigation in the management of hereditary angioedema (p.1081).

◊ Reviews.

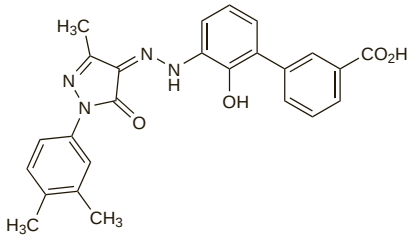
1. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Invest Drugs* 2006; **15:** 1077–90.

Eltrombopag *(rINN)*

Eltrombopagum. 3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid.

Элтромбопаг

$C_{25}H_{22}N_4O_4$ = 442.5.
CAS — 496775-61-2.



Eltrombopag Olamine *(USAN, rINNM)*

Eltrombopag olamina; Eltrombopagum Olaminum; SB-497115-GR. 3′-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3- methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl}-2′-hydroxybiphenyl-3-carboxylic acid compound with 2-aminoethanol (1:2).

Элтромбопаг Оламин

$C_{25}H_{22}N_4O_4.2(C_2H_7NO)$ = 564.6.
CAS — 496775-62-3.

Profile

Eltrombopag is a non-peptide thrombopoietin receptor agonist. It is under investigation as a platelet growth factor given orally for the management of thrombocytopenia in patients with hepatitis C infection, and in idiopathic thrombocytopenic purpura.

◊ References.

1. McHutchison JG, *et al.* Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; **357:** 2227–36.
2. Bussel JB, *et al.* Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; **357:** 2237–47.

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-