Precautions

Since granulocyte-macrophage colony-stimulating factors such as molgramostim can promote growth of myeloid cells *in vitro* their use in myeloid malignancies has been contra-indicated, although recently colony-stimulating factors have been used in some patients with myeloid diseases without stimulation of malignant cells. However, caution is required when they are used in patients with any pre-malignant or malignant myeloid condition. They should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy or radiotherapy because of the sensitivity of rapidly dividing myeloid cells.

Granulocyte-macrophage colony-stimulating factors should be used with caution in patients with pulmonary disease as they may be predisposed to dyspnoea. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Caution is also necessary in patients with fluid retention or heart failure as fluid retention may be aggravated.

The complete blood count should be monitored regularly during therapy.

Uses and Administration

Molgramostim is a granulocyte-macrophage colony-stimulating factor (GM-CSF), a haematopoietic growth factor that stimulates the development of white blood cells, particularly granulocytes, macrophages, and monocytes (see Haematopoiesis, p.1042). It is used to treat or prevent neutropenia in patients receiving myelosuppressive cancer chemotherapy and to reduce the period of neutropenia in patients undergoing bone marrow transplantation (p.640). It has also been used to reduce ganciclovir-induced neutropenia (see Effects on the Blood, p.879).

As an **adjunct to antineoplastic therapy**, molgramostim is given by subcutaneous injection, starting 24 hours after the last dose of antineoplastic, in a dose of 5 to 10 micrograms/kg (60 000 to 110 000 international units/kg) daily. Treatment should be continued for 7 to 10 days.

Following **bone marrow transplantation**, molgramostim may be given by intravenous infusion over 4 to 6 hours in a dose of 10 micrograms/kg (110 000 international units/kg) daily. Treatment should be begun the day after bone marrow transplantation and continued for up to 30 days depending on the neutrophil count.

For the management of **ganciclovir-induced neutropenia**, molgramostim has been given by subcutaneous injection in a dose of 5 micrograms/kg (60 000 international units/kg) daily. After 5 doses have been given the dose of molgramostim should be adjusted according to the neutrophil count.

The maximum dose for any indication should not exceed 10 micrograms/kg (110 000 international units/kg) daily.

Granulocyte colony-stimulating factors such as filgrastim (p.1070) and macrophage colony-stimulating factors such as mirimostim (p.1073) are also used.

◊ General references.

1. Armitage JO. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1998; **92:** 4491–4508.
2. Mangi MH, Newland AC. Febrile neutropenia: prophylactic and therapeutic use of GM-CSF. *Eur J Cancer* 1999; **35** (suppl): S4–S7.
3. Croockewit S. GM-CSF in haematopoietic stem cell transplantation. *Eur J Cancer* 1999; **35** (suppl): S11–S13.
4. Sung L, *et al.* Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2004; **22:** 3350–6.
5. Smith TJ, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205. Also available at: http://www.jco.org/cgi/reprint/24/19/3187 (accessed 20/09/06)

Infections. See under Filgrastim, p.1071, and under HIV Infection and AIDS in Sargramostim, p.1079.

Ischaemia. For mention of the use of molgramostim in patients with atherosclerotic coronary artery disease see under Filgrastim, p.1071.

Respiratory disorders. Pulmonary alveolar proteinosis is a rare diffuse lung disease that may result from impaired alveolar macrophage function caused by neutralising autoantibodies. It is characterised by excessive surfactant accumulation, and is usually managed with whole-lung lavage. Several months of therapy with subcutaneous granulocyte-macrophage colony-stimulating factor, typically in doses of 5 or 6 micrograms/kg daily, has been reported to induce remission in a number of these patients.[1-6] There has also been a case report[7] of the effective use of inhaled granulocyte-macrophage colony-stimulating factor.

1. Barraclough RM, Gillies AJ. Pulmonary alveolar proteinosis: a complete response to GM-CSF therapy. *Thorax* 2001; **56:** 664–5.
2. Seymour JF, *et al.* Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am J Respir Crit Care Med* 2001; **163:** 524–31.
3. Schoch OD, *et al.* BAL findings in a patient with pulmonary alveolar proteinosis successfully treated with GM-CSF. *Thorax* 2002; **57:** 277–80.
4. Romero A, *et al.* GM-CSF therapy in pulmonary alveolar proteinosis. *Thorax* 2002; **57:** 837.
5. Khanjari F, *et al.* GM-CSF and proteinosis. *Thorax* 2003; **58:** 645.
6. Abdul Rahman JA, *et al.* Pulmonary alveolar proteinosis associated with psoriasis and complicated by mycobacterial infection: successful treatment with granulocyte-macrophage colony stimulating factor after a partial response to whole lung lavage. *Respirology* 2004; **9:** 419–22.
7. Arai T, *et al.* Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. *Respir Med* 2004; **98:** 1227–30.

Wounds and ulcers. Macrophages and granulocyte-macrophage colony-stimulating factors play important roles in several mechanisms essential to wound healing.[1] Recombinant granulocyte-macrophage colony-stimulating factors are being tried in non-healing wounds and ulcers (p.1585), particularly chronic venous leg ulcers. They have been given by perilesional subcutaneous injection and topical application in a few small studies and case reports with apparent promotion of wound healing.[1] In a study[2] of patients with pressure ulcers, healing was better during a 35-day period of treatment with granulocyte-macrophage colony-stimulating factor compared with placebo. However, a year after the treatment period there was no difference.[3] In a group of 3 patients with inherited disorders of neutrophil function, topical sargramostim was reported to be of benefit in wound healing.[4] In 1 case sargramostim was also given by continuous subcutaneous infusion for 72 hours into the surgical site of a gastrostomy closure. Topical molgramostim has also been used to promote healing of sickle-cell leg ulcers.[5] Molgramostim has been used as a mouthwash to relieve severe recurrent aphthous mouth ulcers in a small number of patients with AIDS.[6] There has also been some investigation of the use of granulocyte-macrophage colony-stimulating factor for oral mucositis in cancer patients, particularly those undergoing radiotherapy for head and neck cancers. Small studies of subcutaneous injection or topical application as a mouthwash have provided some optimistic results.[7,8] Comparative studies, however, have found molgramostim to be no better than hydrocortisone mouthwash[9] and perhaps only slightly better than sucralfate mouthwash.[10]

1. Groves RW, Schmidt-Lucke JA. Recombinant human GM-CSF in the treatment of poorly healing wounds. *Adv Skin Wound Care* 2000; **13:** 107–12.
2. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; **231:** 600–611.
3. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; **181:** 81–6.
4. De Ugarte DA, *et al.* Treatment of chronic wounds by local delivery of granulocyte-macrophage colony-stimulating factor in patients with neutrophil dysfunction. *Pediatr Surg Int* 2002; **18:** 517–20.
5. Méry L, *et al.* Topical effectiveness of molgramostim (GM-CSF) in sickle cell leg ulcers. *Dermatology* 2004; **208:** 135–7.
6. Herranz P, *et al.* Successful treatment of aphthous ulcerations in AIDS patients using topical granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2000; **142:** 171–6.
7. Fung SM, Ferrill MJ. Granulocyte macrophage-colony stimulating factor and oral mucositis. *Ann Pharmacother* 2002; **36:** 517–20.
8. Mantovani G, *et al.* Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy- and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: an evaluation of effectiveness, safety and costs. *Oncol Rep* 2003; **10:** 197–206.
9. Sprinzl GM, *et al.* Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. *Eur J Cancer* 2001; **37:** 2003–9.
10. Saarilahti K, *et al.* Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *Int J Radiat Oncol Biol Phys* 2002; **54:** 479–85.

Preparations

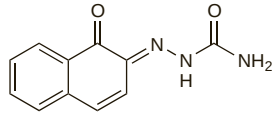
Proprietary Preparations (details are given in Part 3)
Arg.: Growgen-GM; Leucomax†; Molcass; ***Austria:*** Leucomax†; ***Belg.:*** Leucomax†; ***Braz.:*** Gramostim†; Leucocitim; Leucomax†; ***Chile:*** Leucomax†; ***Cz.:*** Leucomax†; ***Denm.:*** Leucomax†; ***Fin.:*** Leucomax†; ***Ger.:*** Leucomax†; ***Gr.:*** Leucomax; Mielogen; ***Hong Kong:*** Leucomax†; ***Hung.:*** Leucomax†; ***India:*** Leucomax; ***Irl.:*** Leucomax; ***Israel:*** Leucomax; ***Ital.:*** Leucomax†; Mielogen†; ***Malaysia:*** Leucomax†; ***Mex.:*** Gramal; Leucomax†; ***Neth.:*** Leucomax†; ***Norw.:*** Leucomax†; ***NZ:*** Leucomax; ***S.Afr.:*** Leucomax†; ***Spain:*** Leucomax†; ***Swed.:*** Leucomax†; ***Switz.:*** Leucomax†; ***Thai.:*** Leucomax†; ***UK:*** Leucomax†; ***Venez.:*** Leucomax†.

Naftazone *(BAN, rINN)*

Naftazona; Naftazonum. 1,2-Naphthoquinone 2-semicarbazone.

Нафтазон

$C_{11}H_9N_3O_2$ = 215.2.
CAS — 15687-37-3.



Profile

Naftazone is a haemostatic, and is reported to increase venous tone and have a capillary stabilising effect. It has been used in venous insufficiency of the lower limbs and diabetic retinopathy, in oral doses of 30 mg daily. It was formerly given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Mediaven; ***Fr.:*** Etioven; ***Switz.:*** Mediaven.

Nartograstim *(rINN)*

Nartograstimum. A recombinant human granulocyte colony-stimulating factor; *N*-L-Methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine colony-stimulating factor (human clone 1034).

Нартограстим

CAS — 134088-74-7.

Profile

Nartograstim is a granulocyte colony-stimulating factor with properties similar to those of filgrastim (p.1070). It has been given by intravenous or subcutaneous injection in the management of neutropenia.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Neu-Up.

Oprelvekin *(USAN, rINN)*

Oprelvekina; Oprelvékine; Oprelvekinum. 2-178-Interleukin 11 (human clone pXM/IL-11).

Опрельвекин

$C_{854}H_{1411}N_{253}O_{235}S_2$ = 19047.0.
CAS — 145941-26-0.
ATC — L03AC02.
ATC Vet — QL03AC02.

Adverse Effects and Precautions

Fluid retention may occur and lead to peripheral oedema, dyspnoea and pulmonary oedema, capillary leak syndrome, and exacerbation of pre-existing pleural effusions; caution is required when giving oprelvekin to patients with a history or signs of heart failure. Dilutional anaemia may occur. Fluid balance and electrolytes should be monitored in patients receiving long-term diuretic therapy. Transient atrial arrhythmias commonly occur; there have also been some reports of ventricular arrhythmias occurring within 2 to 7 days of starting oprelvekin. Other adverse effects include exfoliative dermatitis, blurred vision, and conjunctival injection. Hypersensitivity reactions, including anaphylaxis, have been reported with the use of oprelvekin. Papilloedema has been reported, and oprelvekin should be used with caution in patients with pre-existing papilloedema or tumours involving the CNS.

Use of oprelvekin after myeloablative chemotherapy and bone marrow transplantation is considered to be contra-indicated because of an increased incidence of adverse effects.

Fetotoxicity has been reported in *animals.*

◊ Reviews.

1. Smith JW. Tolerability and side-effect profile of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 41–7.

Effects on the eyes. Papilloedema has been reported in patients treated with oprelvekin,[1] and was found to be a dose-limiting adverse effect in a study of safety and pharmacokinetics in children.[2]

1. Peterson DC, *et al.* Oprelvekin-associated bilateral optic disk edema. *Am J Ophthalmol* 2005; **139:** 367–8.
2. Cairo MS, *et al.* Phase I/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. *Br J Haematol* 2005; **128:** 49–58.

Pharmacokinetics

The bioavailability of oprelvekin after subcutaneous injection is about 80%, peak serum concentrations are reached after about 3 hours, and it has a terminal half-life of about 7 hours. Oprelvekin is metabolised before excretion by the kidneys, and its clearance is reduced in renal impairment.

Uses and Administration

Oprelvekin, a recombinant human interleukin-11, is a platelet growth factor that stimulates the proliferation and maturation of megakaryocytes and thus increases the production of platelets. Oprelvekin is given by subcutaneous injection in a dose of 50 micrograms/kg daily to prevent severe thrombocytopenia and reduce the need for platelet transfusions in high-risk patients after myelosuppressive, but not myeloablative, chemotherapy for non-myeloid malignancies (see Thrombocytopenia under Treatment of Adverse Effects in Antineoplastics, p.640). The dose should be reduced in severe renal impairment (see below). The initial dose should be given 6 to 24 hours after the last dose of antineoplastic, and continued up to a maximum of 21 days. Treatment with oprelvekin should be stopped at least 2 days before starting the next planned cycle of chemotherapy.

Oprelvekin is under investigation for the treatment of Crohn's disease, rheumatoid arthritis, and chronic hepatitis C.

Administration in renal impairment. In severe renal impairment (creatinine clearance less than 30 mL/min) the recommended dose of oprelvekin is 25 micrograms/kg daily by subcutaneous injection.

Thrombocytopenia. References.

1. Tepler I, *et al.* A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood* 1996; **87:** 3607–14.
2. Isaacs C, *et al.* Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *J Clin Oncol* 1997; **15:** 3368–77.
3. Reynolds CH. Clinical efficacy of rhIL-11. *Oncology (Huntingt)* 2000; **14** (suppl 8): 32–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Neumega†; ***Braz.:*** Neumega; ***Chile:*** Neumega†; ***Mex.:*** Neumega†; ***USA:*** Neumega; ***Venez.:*** Neumega.

Oxidised Cellulose

Cellulosic Acid; Celulosa oxidada; Oxidized Cellulose.

CAS — 9032-53-5.
ATC — B02BC02.
ATC Vet — QB02BC02.

Description. Oxidised cellulose is a sterile polyanhydroglucuronic acid, prepared by the oxidation of a suitable form of cellulose.

Pharmacopoeias. In *US* which also includes Oxidized Regenerated Cellulose.
USP 31 (Oxidized Cellulose). It contains not less than 16% and not more than 24% of carboxyl groups, calculated on the dried basis. It is a slightly off-white gauze or lint with a slight, charred odour. Insoluble in water and in acids; soluble in dilute alkalis. Store at a temperature not exceeding 8°. Protect from direct sunlight.
USP 31 (Oxidized Regenerated Cellulose). It contains 18 to 24% of carboxyl groups calculated on the dried basis. It is a slightly off-white knit fabric, with a slight odour. Insoluble in water and in dilute acids; soluble in dilute alkalis. Store at a temperature between 15° and 30°. Protect from direct sunlight.

Adverse Effects and Precautions

Foreign body reactions may occur after the use of oxidised cellulose or oxidised regenerated cellulose. Headache, burning, and stinging have been reported and sneezing has been noted after use in epistaxis. Oxidised cellulose swells on contact with a bleeding surface; this could result in tissue necrosis, nerve damage, obstruction, or vascular stenosis if packed closely, especially into bony cavities, or if wrapped tightly around blood vessels. To minimise such complications the removal of excess material should be considered after haemostasis is achieved, and oxidised cellulose should always be removed after use near the spinal cord or optic nerve. Oxidised cellulose should not be used in packing or implantation for fractures since it may interfere with bone regeneration or cause cyst formation. It should not be used as a surface dressing, except for immediate control of haemorrhage, as it inhibits epithelialisation.

Oxidised cellulose should be used as the dry material since moistening will reduce its ability to absorb blood. Silver nitrate or other escharotic chemicals should not be applied before use as cauterisation might inhibit absorption of oxidised cellulose. Thrombin is inactivated by the low pH of oxidised cellulose; it is recommended that oxidised cellulose should not be impregnated with other haemostatics or antibacterials.

Uses and Administration

Oxidised cellulose and oxidised regenerated cellulose are absorbable haemostatics (p.1045). When applied to a bleeding surface, they swell to form a gelatinous mass which aids in the formation of a clot. It is gradually absorbed by the tissues, usually within 7 to 14 days. These materials also have a weak bactericidal action. They are used in surgery as adjuncts in the control of moderate bleeding where suturing or ligation is impracticable or ineffective; they should not be used to control haemorrhage from large arteries. The gauze, lint, or knitted material should be laid on the bleeding surface or held firmly against the tissues until haemostasis is achieved; removal should then be considered (see Adverse Effects and Precautions, above). Oxidised cellulose should be used as the dry material as moistening will reduce its ability to absorb blood.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Surgicel; ***Ger.:*** Tabotamp; ***Hong Kong:*** Seal On†; ***Irl.:*** Alltracel P†; Premdoc†; Seal-On; Traumacel P; ***Ital.:*** Tabotamp; ***UK:*** Oxycel; StopBleed; ***USA:*** Oxycel; Surgicel.

Multi-ingredient: ***Fr.:*** Promogran; ***Irl.:*** Alltracel S†; ***Ital.:*** Promogran; ***UK:*** Seal-On.

Oxypolygelatin ⊗

Oxipoligelatina.

Profile

Oxypolygelatin is a polymer derived from gelatin (p.1072). It is used as a 5.5% solution as a plasma volume expander. There have been reports of anaphylaxis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gelifundol†; ***Austria:*** Gelifundol; ***Cz.:*** Gelifundol†; ***Ger.:*** Gelifundol†; ***Hong Kong:*** Gelifundol†; ***Hung.:*** Gelifundol†; ***S.Afr.:*** Gelifundol†; ***Thai.:*** Gelifundol.

Pegzerepoetin Alfa ⊗

Methoxy Polyethylene Glycol-Epoetin Beta; Pegserepoetin Alfa; R-744; Ro-50-3821. 1-165-Erythropoietin (human) monoamide with α-(3-carboxypropyl)-ω-methoxypoly(oxy-1,2-ethanediyl).

CAS — 677324-53-7.
ATC — B03XA03.
ATC Vet — QB03XA03.

Adverse Effects and Precautions

As for Epoetins, p.1061.

Pharmacokinetics

In patients with chronic renal impairment, pegzerepoetin alfa is absorbed after subcutaneous injection with an absolute bioavailability of about 60%. It has a terminal elimination half-life of about 134 hours after intravenous injection and about 140 hours when given subcutaneously. Haemodialysis does not affect the pharmacokinetics of pegzerepoetin alfa.

Uses and Administration

Pegzerepoetin alfa is described as a continuous erythropoietin receptor activator (CERA). It has similar properties to the epoetins (p.1062), but a longer duration of action. Pegzerepoetin alfa is used in the treatment of anaemia associated with chronic renal failure (see Normocytic-normochromic Anaemia, p.1044). A starting dose of 600 nanograms/kg is given once every 2 weeks as a single intravenous or subcutaneous injection. The dose may be adjusted by about 25%, at monthly intervals, so that the rate of rise of haemoglobin is between 1 and 2 g per 100 mL each month. When the target haemoglobin concentration of between 11 and 12 g per 100 mL has been achieved, a maintenance dose of pegzerepoetin alfa may be given once monthly; this is equal to twice the dose that had been given once every 2 weeks.

Pegzerepoetin alfa is also under investigation in the treatment of anaemia in patients with non-myeloid malignant disease receiving chemotherapy.

◊ References.

1. de Francisco ALM, *et al.* BA16260 Study Investigators. Continuous Erythropoietin Receptor Activator (C.E.R.A.) administered at extended administration intervals corrects anaemia in patients with chronic kidney disease on dialysis: a randomised, multicentre, multiple-dose, phase II study. *Int J Clin Pract* 2006; **60:** 1687–96.
2. Sulowicz W, *et al.* PROTOS Study Investigators. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007; **2:** 637–46.
3. Levin NW, *et al.* MAXIMA study investigators. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet* 2007; **370:** 1415–21.
4. Österborg A, *et al.* Phase II study of three dose levels of continuous erythropoietin receptor activator (C.E.R.A.) in anaemic patients with aggressive non-Hodgkin's lymphoma receiving combination chemotherapy. *Br J Haematol* 2007; **136:** 736–44.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mircera; ***Fr.:*** Mircera; ***Port.:*** Mircera; ***UK:*** Mircera; ***USA:*** Mircera.

Plasma

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii).
Ph. Eur. 6.2 (Human Plasma for Fractionation; Plasma Humanum ad Separationem). The liquid part of human blood remaining after separation of the cellular elements from whole blood or collected in an apheresis procedure; it is intended for the manufacture of plasma-derived products. It is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.
A light yellow to green, clear or slightly turbid liquid, without visible signs of haemolysis. Frozen plasma should be stored at or below –20°; it may still be used for fractionation if the temperature is between –20° and –15° for not more than a total of 72 hours without exceeding –15° on more than one occasion as long as the temperature is at all times –5° or lower.
Ph. Eur. 6.2 (Human Plasma (Pooled and Treated for Virus Inactivation); Plasma Humanum Coagumentum Conditumque ad Exstinguendum Virum). A frozen or freeze-dried, sterile, non-pyrogenic preparation obtained from human plasma derived from donors belonging to the same ABO blood group. The plasma used complies with the requirements for Human Plasma for Fractionation (above). The method of preparation is designed to minimise activation of any coagulation factor and includes a step or steps that have been shown to inactivate known agents of infection.
The frozen preparation, after thawing, is a clear or slightly opalescent liquid free from solid and gelatinous particles. The freeze-dried preparation is an almost white or slightly yellow powder or friable solid.

Adverse Effects and Precautions

As for Blood, p.1056, though with a low risk of transmitting cell-associated viruses. However, the production of blood products using plasma from UK donors has been phased out due to the possible risk of transmission of Creutzfeldt-Jakob disease.

Uses and Administration

Fresh frozen plasma contains useful amounts of clotting factors. It should be reserved for patients with proven abnormalities in blood coagulation. Indications include congenital deficiencies in clotting factors for which specific concentrates are unavailable, severe multiple clotting factor deficiencies (for example in patients with liver disease), rapid reversal of the action of coumarin anticoagulants, and disseminated intravascular coagulation. It may be used after massive blood transfusion when there is evidence of coagulation deficiency but its value for routine prophylaxis against abnormal bleeding tendencies in patients receiving massive blood transfusions is contentious except where clotting abnormalities have been confirmed. It has also been used in the treatment of thrombotic thrombocytopenic purpura and as a source of plasma proteins.

The amount of fresh frozen plasma transfused depends on the required level of clotting factors. A unit of fresh frozen plasma refers to the quantity of plasma obtained from 1 unit of whole blood; this generally represents a volume of about 250 mL, including anticoagulant.

Fresh frozen plasma should not be used as a volume expander or as a nutritional source.

Therapeutic plasma exchange or plasmapheresis (see below) are used in a wide variety of disorders.

Plasma is used to prepare blood products including albumin, antithrombin III, blood clotting factors, immunoglobulins, and platelets. Other preparations include cryoprecipitate depleted plasma, which is deficient in fibrinogen, factor VIII, von Willebrand factor, cryoglobulin, and fibronectin, and single donor plasma, which is not frozen. A solvent-detergent-treated plasma preparation is available.

Guidelines and reviews. General references to the use of plasma.

1. Fresh-frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; **271:** 777–81.
2. Cohen H, *et al.* Plasma, plasma products, and indications for their use. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London; BMJ Books, 1998: 40–44.
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126:** 11–28. Also available at: http://www.bcshguidelines.com/pdf/freshfrozen_280604.pdf (accessed 27/10/05) Addenda, amendments, and corrections (4 sets) at http://www.bcshguidelines.com/pdf/Amendments_FFP_091205.pdf (issued 07/12/05), *ibid.* 2007; **136:** 514–16, at http://www.bcshguidelines.com/pdf/FFPAmendment_1_17_Oct_2007.pdf (issued 17/10/07), at http://www.bcshguidelines.com/pdf/FFPAmendment_2_17_Oct_2007.pdf (issued 17/10/07) (accessed 19/06/08)
4. Stanworth SJ, *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; **126:** 139–52.