2. Carless PA, *et al.* Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 03/06/05).
3. MacGillivray TE. Fibrin sealants and glues. *J Card Surg* 2003; **18:** 480–5.
4. Fattahi T, *et al.* Clinical applications of fibrin sealants. *J Oral Maxillofac Surg* 2004; **62:** 218–24.
5. Schexneider KI. Fibrin sealants in surgical or traumatic hemorrhage. *Curr Opin Hematol* 2004; **11:** 323–6.

Preparations

Ph. Eur.: Fibrin Sealant Kit.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Benplast P; ***Cz.:*** TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; TachoSil; Tissucol; ***Ger.:*** Beriplast; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; Tisseel; ***Hung.:*** Beriplast P; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; TachoSil; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** TachoSil; Tissucol Duo; ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Turk.:*** Beriplast P; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Fibrinogen

Factor I; Fibrinogène; Fibrinógeno; Fibrinogenum; Fibrinojen; Fibrynogen.

ATC — B02BB01; B02BC10.
ATC Vet — QB02BB01.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human Fibrinogen; Fibrinogenum Humanum). It contains the soluble constituent of human plasma that is transformed to fibrin on addition of thrombin. It is obtained from plasma for fractionation and the method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Stabilisers, including protein such as human albumin, salts, and buffers may be added. No antimicrobial preservative is added. When dissolved in the volume of solvent stated on the label, the solution contains not less than 10 g/litre of fibrinogen.

A white or pale yellow hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

Fibrinogen has been used to control haemorrhage associated with low blood-fibrinogen concentration in afibrinogenaemia or hypofibrinogenaemia although plasma or cryoprecipitate is usually preferred. Fibrinogen has also been used in disseminated intravascular coagulation (p.1048). It is a component of fibrin glue (see Fibrin, above). Recombinant human fibrinogen is under investigation.

Fibrinogen labelled with radionuclides has also been used in diagnostic procedures.

Preparations

Ph. Eur.: Fibrin Sealant Kit; Human Fibrinogen.

Proprietary Preparations (details are given in Part 3)
Austria: Haemocomplettan; ***Cz.:*** Haemocomplettan; ***Ger.:*** Haemocomplettan; ***Gr.:*** Haemocomplettan; ***Hung.:*** Haemocomplettan; ***Neth.:*** Haemocomplettan; ***Port.:*** Haemocomplettan; ***Switz.:*** Haemocomplettan; ***Thai.:*** Fibroraas.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; TachoSil; Tissucol; ***Ger.:*** Beriplast; Quixil; TachoComb†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; Quixil; TachoSil; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Quixil; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** TachoSil; Tissucol Duo; ***Rus.:*** TachoComb (ТахоКом6); ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Thai.:*** Fibrin Glue†; TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Filgrastim *(BAN, USAN, rINN)*

Filgrastiimi; Filgrastimum; r-metHuG-CSF. A recombinant human granulocyte colony-stimulating factor.

Филграстим

CAS — 121181-53-1.
ATC — L03AA02.
ATC Vet — QL03AA02.

Pegfilgrastim *(BAN, rINN)*

Pegfilgrastiimi; Pegfilgrastimum; Pegfilgrastimun. Filgrastim conjugated with monomethoxy polyethylene glycol.

Пегфильграстим

CAS — 208265-92-3.
ATC — L03AA13.
ATC Vet — QL03AA13.

Incompatibility. References.

1. Trissel LA, Martinez JF. Compatibility of filgrastim with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; **51:** 1907–13.

Stability. Solutions of filgrastim must not be diluted with sodium chloride solutions as precipitation will occur. Glucose 5% solution may be used if dilution is necessary. However, filgrastim in diluted solution may be adsorbed onto glass or plastic materials and so it should not be diluted below the recommended minimum concentration (2 micrograms/mL). Also, to protect from adsorption, solutions that are diluted to concentrations of filgrastim below 15 micrograms/mL must have albumin added to give a final concentration of 2 mg/mL. For mention of the stability of filgrastim in a solution intended for enteral use in neonates, see Stability under Epoetins, p.1061.

Adverse Effects

The main adverse effects of granulocyte colony-stimulating factors such as filgrastim during short-term treatment are musculoskeletal pain and dysuria. Hypersensitivity reactions have been reported rarely. In patients receiving long-term treatment the most frequent adverse effects are bone pain and musculoskeletal pain. Other adverse effects include splenic enlargement, thrombocytopenia, anaemia, epistaxis, headache, diarrhoea, and cutaneous vasculitis. There have been reports of pulmonary infiltrates leading to respiratory failure or acute respiratory distress syndrome, and rare reports of splenic rupture. Rises in lactate dehydrogenase, alkaline phosphatase, and uric acid, are usually mild to moderate, dose-dependent, and reversible.

Colony-stimulating factors are fetotoxic in *animal* studies.

◊ General references.

1. Vial T, Descotes J. Clinical toxicity of cytokines used as haemopoietic growth factors. *Drug Safety* 1995; **13:** 371–406.
2. Gutierrez-Delgado F, Bensinger W. Safety of granulocyte colony-stimulating factor in normal donors. *Curr Opin Hematol* 2001; **8:** 155–60.
3. Cottle TE, *et al.* Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. *Semin Hematol* 2002; **39:** 134–40.
4. Crawford J. Safety and efficacy of pegfilgrastim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2003; **23** (suppl): 15S–19S.

Disseminated intravascular coagulation. Long-term treatment with granulocyte colony-stimulating factor in a 7-year-old boy with HIV infection and zidovudine-induced neutropenia produced evidence of disseminated intravascular coagulation on 2 occasions.[1]

1. Mueller BU, *et al.* Disseminated intravascular coagulation associated with granulocyte colony-stimulating factor therapy in a child with human immunodeficiency virus infection. *J Pediatr* 1995; **126:** 749–52.

Effects on the bones. Bone mineral loss and osteoporosis have been reported in children with severe congenital neutropenia receiving granulocyte colony-stimulating factor for long periods.[1-3] However, the role of granulocyte colony-stimulating factor in producing this effect is uncertain since bone mineral loss may be a feature of the underlying disease.

1. Bishop NJ, *et al.* Osteoporosis in severe congenital neutropenia treated with granulocyte colony-stimulating factor. *Br J Haematol* 1995; **89:** 927–8.
2. Yakisan E, *et al.* High incidence of significant bone loss in patients with severe congenital neutropenia (Kostmann's syndrome). *J Pediatr* 1997; **131:** 592–7.
3. Sekhar RV, *et al.* Severe osteopenia in a young boy with Kostmann's congenital neutropenia treated with granulocyte colony-stimulating factor: suggested therapeutic approach. Abstract: *Pediatrics* 2001; **108:** 756–7. Full version: http://pediatrics.aappublications.org/cgi/content/full/108/3/e54 (accessed 27/10/05)

Effects on the eyes. Subretinal haemorrhage resulting in irreversible loss of vision in one eye occurred in a 4-year-old girl who received filgrastim and nartograstim for chemotherapy-induced neutropenia and for mobilising peripheral blood stem cells.[1] It was postulated that the colony-stimulating factor reactivated a primary ocular inflammation probably caused by an infection. Bilateral peripapillary and macular retinal haemorrhage occurred in an adult being treated for mantle cell lymphoma.[2] It was attributed to retinal leucostasis secondary to hyperleucocytosis resulting from the use of filgrastim for stem cell mobilisation. Vision improved after cessation of filgrastim and the use of leucapheresis.

1. Matsumura T, *et al.* Subretinal haemorrhage after granulocyte colony-stimulating factor. *Lancet* 1997; **350:** 336. Correction. *ibid.*; 1406.
2. Salloum E, *et al.* Hyperleukocytosis and retinal hemorrhages after chemotherapy and filgrastim administration for peripheral blood progenitor cell mobilization. *Bone Marrow Transplant* 1998; **21:** 835–7.

Effects on the lungs. There have been reports of exacerbation of chemotherapy-induced pulmonary toxicity in patients receiving granulocyte colony-stimulating factor (G-CSF) with bleomycin, cyclophosphamide, or methotrexate. A systematic review[1] of 73 cases noted that the doses of the antineoplastics were below the usual toxic cumulative dose, suggesting that G-CSF may have lowered the threshold for pulmonary toxicity of these drugs. It has been proposed that G-CSF has an activating effect on neutrophils that makes them toxic to the alveolar capillary wall. The review also included 2 cases of pulmonary toxicity in non-neutropenic patients treated with G-CSF alone. The circumstances of 9 other cases suggested that neutropenic patients with a recent history of pulmonary infiltrates may be at increased risk of acute respiratory distress syndrome during neutropenia recovery. The true role of G-CSF in these cases of pulmonary toxicity remains unclear, however.

1. Azoulay E, *et al.* Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001; **120:** 1695–1701.

Effects on the skin. Skin reactions may occur in patients given colony-stimulating factors. In a study in women with inflammatory breast cancer, a pruritic skin reaction developed at the subcutaneous injection site in all 7 given granulocyte-macrophage colony-stimulating factor.[1] A review[2] of 8 cases of generalised pruritic maculopapular rash associated with granulocyte or granulocyte-macrophage colony-stimulating factor found that in 6 of them the rash resolved in 4 to 17 days even though therapy was continued and half the patients did not receive any treatment for the rash. A localised lichenoid reaction has been described for granulocyte colony-stimulating factor.[3] Exacerbation of psoriasis[4] and precipitation or exacerbation of neutrophilic dermatoses including Sweet's syndrome,[5-7] pyoderma gangrenosum,[8] and neutrophilic eccrine hidradenitis[9] have been reported following use of granulocyte colony-stimulating factor.

1. Steger GG, *et al.* Cutaneous reactions to GM-CSF in inflammatory breast cancer. *N Engl J Med* 1992; **327**: 286.
2. Álvarez-Ruiz S, *et al.* Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol Venereol* 2004; **18:** 310–13.
3. Viallard AM, *et al.* Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (filgrastim). *Dermatology* 1999; **198:** 301–3.
4. Kavanaugh A. Flare of psoriasis and psoriatic arthritis following treatment with granulocyte colony-stimulating factor. *Am J Med* 1996; **101:** 567.
5. Petit T, *et al.* Lymphoedema-area-restricted Sweet syndrome during G-CSF treatment. *Lancet* 1996; **347:** 690.
6. Garty BZ, *et al.* Sweet syndrome associated with G-CSF treatment in a child with glycogen storage disease type Ib. *Pediatrics* 1996; **97:** 401–3.
7. Hasegawa M, *et al.* Sweet's syndrome associated with granulocyte colony-stimulating factor. *Eur J Dermatol* 1998; **8:** 503–5.
8. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors: a review of associated neutrophilic dermatoses and vasculitides. *Arch Dermatol* 1994; **130:** 77–81.
9. Bachmeyer C, *et al.* Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol* 1998; **139:** 354–5.

Effects on the thyroid. Reversible thyroid dysfunction has been reported in patients with pre-existing thyroid antibodies during treatment with granulocyte-macrophage colony-stimulating factor,[1] but not with granulocyte colony-stimulating factor.[2] However, clinical hypothyroidism has been reported in a patient with no history of thyroid dysfunction or thyroid antibodies during treatment with granulocyte colony-stimulating factor.[3]

1. Hoekman K, *et al.* Reversible thyroid dysfunction during treatment with GM-CSF. *Lancet* 1991; **338**: 541–2.
2. van Hoef MEHM, Howell A. Risk of thyroid dysfunction during treatment with G-CSF. *Lancet* 1992; **340:** 1169–70.
3. de Luis DA, Romero E. Reversible thyroid dysfunction with filgrastim. *Lancet* 1996; **348:** 1595–6.

Inflammatory disorders. Reactivation of various inflammatory disorders including rheumatoid arthritis[1] and pseudogout[2,3] has been reported after use of granulocyte colony-stimulating factors. For further reports of reactivation of sites of inflammation, see under Effects on the Eyes and Effects on the Skin, above.

1. Vildarsson B, *et al.* Reactivation of rheumatoid arthritis and development of leukocytoclastic vasculitis in a patient receiving granulocyte colony-stimulating factor for Felty's syndrome. *Am J Med* 1995; **98:** 589–91.
2. Sandor V, *et al.* Exacerbation of pseudogout by granulocyte colony-stimulating factor. *Ann Intern Med* 1996; **125:** 781.
3. Teramoto S, *et al.* Increased synovial interleukin-8 and interleukin-6 levels in pseudogout associated with granulocyte colony-stimulating factor. *Ann Intern Med* 1998; **129:** 424–5.

Precautions

Since granulocyte colony-stimulating factors such as filgrastim 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. Filgrastim and lenograstim should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy because of the sensitivity of rapidly dividing myeloid cells. Pegfilgrastim should not be used from 14

days before until 24 hours after chemotherapy. The safety and efficacy of granulocyte colony-stimulating factor therapy has not been established in patients receiving chemoradiotherapy, and concomitant use is generally avoided.

Granulocyte colony-stimulating factors should be used with caution in patients with sickle-cell disease. Preparations of filgrastim may contain sorbitol as an excipient; care is advisable in patients with hereditary fructose intolerance.

The complete blood count should be monitored regularly during therapy with granulocyte colony-stimulating factors. Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Transient positive changes in bone imaging findings have occurred with growth factor therapy, and should be considered when interpreting results. Bone density should be monitored in patients with osteoporosis who are receiving long-term treatment with filgrastim.

Sickle-cell disease. Granulocytosis occurs during sickle-cell crisis (p.1044) although the role of granulocytes in vaso-occlusion has not been established. Sickle-cell crisis has occurred in patients with sickle-cell disease who have been given granulocyte colony-stimulating factor.[1-3]

1. Abboud M, *et al.* Granulocytosis causing sickle-cell crisis. *Lancet* 1998; **351:** 959.
2. Adler BK, *et al.* Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. *Blood* 2001; **97:** 3313–14.
3. Wei A, Grigg A. Granulocyte colony-stimulating factor–induced sickle cell crisis and multiorgan dysfunction in a patient with compound heterozygous sickle cell/β thalassemia. *Blood* 2001; **97:** 3998–9.

Pharmacokinetics

After subcutaneous injection, peak serum concentrations of filgrastim occur within about 8 hours. The serum elimination half-life of filgrastim after intravenous or subcutaneous injection is about 3.5 hours. Pegfilgrastim peak concentrations occur later, at 16 to 120 hours after subcutaneous doses. Elimination of pegfilgrastim is non-linear and clearance becomes saturated and decreases with increasing dose. It is mainly eliminated by neutrophil-mediated clearance, such that the serum concentration of pegfilgrastim declines rapidly with neutrophil recovery. It has a half-life of 15 to 80 hours after subcutaneous injection.

◊ Reviews.

1. Zamboni WC. Pharmacokinetics of pegfilgrastim. *Pharmacotherapy* 2003; **23** (suppl): 9S–14S.

Uses and Administration

Filgrastim is a granulocyte colony-stimulating factor (G-CSF), a haematopoietic growth factor that stimulates the development of granulocytes (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. It is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation. Filgrastim is also used in the management of chronic neutropenia (congenital, cyclic, or idiopathic), and for persistent neutropenia in patients with advanced HIV infection.

Filgrastim may be given intravenously or subcutaneously. Doses may be expressed in micrograms or in units; 10 micrograms is equivalent to 1 million units.

As an **adjunct to antineoplastic therapy**, filgrastim is given in a dose of 5 micrograms/kg daily starting not less than 24 hours after the last dose of antineoplastic. It can be given as a single daily subcutaneous injection, as a continuous intravenous or subcutaneous infusion, or as a daily intravenous infusion over 15 to 30 minutes. Treatment is continued until the neutrophil count has stabilised within the normal range which may take up to 14 days or more. A formulation of filgrastim conjugated with monomethoxy polyethylene glycol (pegfilgrastim) may also be used to reduce the incidence of neutropenia associated with antineoplastic therapy; it is given by subcutaneous injection in a single dose of 6 mg, given not less than 24 hours after the last dose of antineoplastic.

The initial dose of filgrastim following **bone marrow transplantation** is 10 micrograms/kg daily, adjusted according to response. This may be given by intravenous infusion over 30 minutes or 4 hours, or by continuous intravenous or subcutaneous infusion over 24 hours.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 10 micrograms/kg daily of filgrastim may be given subcutaneously as a single daily injection or by continuous infusion for 4 to 7 days until the last leucapheresis procedure (usually performed on days 5 to 7 as required). If filgrastim is given after myelosuppressive chemotherapy, the dose is halved to 5 micrograms/kg daily by subcutaneous injection. It is given from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 4 or 5 days until leucapheresis (usually started on day 5).

In patients with **congenital neutropenia** the initial dose is 12 micrograms/kg daily and in patients with idiopathic or cyclic neutropenia the initial dose is 5 micrograms/kg daily. In these forms of neutropenia the dose is given subcutaneously in single or divided doses and should be adjusted according to response.

In patients with **HIV infection** and persistent neutropenia the initial dose is 1 microgram/kg daily by subcutaneous injection. The dose may be titrated up to a maximum of 4 micrograms/kg daily until a normal neutrophil count is achieved and then adjusted for maintenance according to response. Maintenance doses of 300 micrograms daily on 1 to 7 days a week have been used.

The filgrastim doses described above for patients receiving antineoplastic therapy and for chronic neutropenias may also be given to **children**. Pegfilgrastim should not be used in children or adolescents weighing less than 45 kg.

◊ Some reviews of filgrastim and pegfilgrastim.

1. Dale DC, ed. Filgrastim anniversary supplement: reviewing 10 years of clinical experience, a seminar-in-print. *Drugs* 2002; **62** (suppl 1): 1–98.
2. Curran MP, Goa KL. Pegfilgrastim. *Drugs* 2002; **62:** 1207–13.
3. Willis F, Pettengell R. Pegfilgrastim. *Expert Opin Biol Ther* 2002; **2:** 985–92.

Aplastic anaemia. Colony-stimulating factors, including granulocyte colony-stimulating factors, have been tried in patients with aplastic anaemia (p.1042).

Infections. As well as stimulating the development and maturation of haematopoietic precursors, granulocyte and granulocyte-macrophage colony-stimulating factors have been found to enhance neutrophil chemotaxis and phagocytosis, enhance oxidative activity, increase microbicidal activity and antibody-mediated cellular cytotoxicity, and delay neutrophil apoptosis. Granulocyte-macrophage colony-stimulating factor also modifies macrophage and monocyte functions in inflammation and cellular immune response.[1] It has therefore been suggested that colony-stimulating factors might be useful adjuncts in the treatment of infections in non-neutropenic patients, but their clinical role is yet to be established.

The use of granulocyte colony-stimulating factor was reported[2] to reduce mortality rates in patients with septic shock due to the bacterial infection melioidosis (p.178). In small placebo-controlled studies of patients with the protozoal infection cutaneous leishmaniasis (p.824), ulcers healed faster in those treated with granulocyte-macrophage colony-stimulating factor, as an adjunct to antimony therapy, by intralesional injection[3] and topical application.[4]

However, granulocyte colony-stimulating factor does not appear to be of benefit as an adjunct in the management of pneumonia[5] (p.186). In diabetic foot infections (see Diabetic Complications, p.433) granulocyte colony-stimulating factor does not appear to affect wound healing, although there is some suggestion that it may reduce the likelihood of surgical intervention.[6]

In HIV infection (p.856), granulocyte-macrophage colony-stimulating factor has been reported to improve CD4+ cell counts.[7]

Granulocyte-macrophage colony-stimulating factor has been investigated as an adjuvant for hepatitis B vaccination in healthy subjects, patients with chronic renal failure or on haemodialysis, and in HIV-infected patients. Overall, the colony-stimulating factor appears to improve seroconversion rates and antibody titres, but further study is needed.[8]

1. Root RK, Dale DC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in non-neutropenic patients. *J Infect Dis* 1999; **179** (suppl): S342–S352.
2. Cheng AC, *et al.* Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004; **38:** 32–7.
3. Almeida R, *et al.* Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony-stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. *J Infect Dis* 1999; **180:** 1735–7.
4. Santos JB, *et al.* Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *J Infect Dis* 2004; **190:** 1793–6.
5. Cheng AC, *et al.* Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 16/06/08).
6. Cruciani M, *et al.* Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care* 2005; **28:** 454–60.
7. Deresinski SC. Granulocyte-macrophage colony-stimulating factor: potential therapeutic, immunological and antiretroviral effects in HIV infection. *AIDS* 1999; **13:** 633–43.
8. Cruciani M, *et al.* Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination: a meta-analysis. *Vaccine* 2007; **25:** 709–18.

Ischaemia. Colony-stimulating factors have been investigated for their ability to mobilise stem cells and modulate inflammation in cardiovascular disorders characterised by ischaemia. In patients with atherosclerotic coronary artery disease (p.1159) filgrastim[1] and molgramostim[2] have been tried in an attempt to promote neovascularisation; there was no cardiac benefit with the former, and although the latter promoted collateral artery growth the balance of benefit to risk was questionable, since 2 of 7 actively treated patients developed an acute coronary syndrome. Benefit has been reported in 7 patients with acute ischaemic stroke (p.1185) given filgrastim 15 micrograms/kg subcutaneously daily for 5 days in addition to the usual care given to 3 controls.[3] There was a greater improvement in neurological function in filgrastim-treated patients on 12 months of follow-up, but larger studies are required to confirm the benefit.

1. Hill JM, *et al.* Outcomes and risks of granulocyte colony-stimulating factor in patients with coronary artery disease. *J Am Coll Cardiol* 2005; **46:** 1643–8.
2. Zbinden S, *et al.* Safety and efficacy of subcutaneous-only granulocyte-macrophage colony-stimulating factor for collateral growth promotion in patients with coronary artery disease. *J Am Coll Cardiol* 2005; **46:** 1636–42.
3. Shyu W-C, *et al.* Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial. *Can Med Assoc J* 2006; **174:** 927–33.

Neutropenia. Granulocyte colony-stimulating factors are used in the management of neutropenia. They may be used[1] long-term in the management of inherited forms of neutropenia (p.1051). They are used short-term[2-5] to treat or prevent antineoplastic-induced neutropenia (p.640) and have also been used in patients with neutropenia induced by a wide range of other drugs.[6-11] The use of colony-stimulating factors has been investigated[12] in the management of neutropenia in patients with HIV-associated infection (p.857). A controlled study[13] in 258 patients with advanced HIV infection found that prophylactic use of granulocyte colony-stimulating factor reduced the incidence of severe neutropenia and also suggested that the incidence and duration of bacterial infections was reduced.

Due to immature neutrophil production and function, neonates are susceptible to infection and preterm neonates are at particular risk. The use of colony-stimulating factors for prophylaxis or as adjuncts in the treatment of septicaemia (p.190) in neonates has been investigated in a few small trials but there is insufficient evidence of benefit to recommend the use of granulocyte or granulocyte-macrophage colony-stimulating factors in these patients. Although there is limited evidence to suggest that they may reduce mortality as adjuncts to treatment in patients with sepsis and severe neutropenia, further study is needed.[14,15] Granulocyte colony-stimulating factors have also been tried with mixed results in neonates with the rare condition of alloimmune neutropenia.[16,17]

1. Zeidler C, *et al.* Management of Kostmann syndrome in the G-CSF era. *Br J Haematol* 2000; **109:** 490–5.
2. Repetto L, *et al.* EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 2003; **39:** 2264–72.
3. 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.
4. Clark OAC, *et al.* Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol* 2005; **23:** 4198–4214.
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)

6. Wickramanayake PD, *et al*. Use of granulocyte colony-stimulating factor (filgrastim) in the treatment of non-cytotoxic drug-induced agranulocytosis. *Eur J Med Res* 1995; **1:** 153–6.
7. Murphy PT, Casey MC. Sulphasalazine induced agranulocytosis revisited. *Ir Med J* 1998; **91:** 216.
8. Bhidayasiri R, *et al*. Correction of mesalazine-induced neutropenia with high dose G-CSF. *Am J Gastroenterol* 2000; **95:** 3321–2.
9. Andrès E, *et al*. Nonchemotherapy drug-induced agranulocytosis in elderly patients: the effects of granulocyte colony-stimulating factor. *Am J Med* 2002; **112:** 460–4.
10. Andrès E, *et al*. Modern management of non-chemotherapy drug-induced agranulocytosis: a monocentric cohort study of 90 cases and review of the literature. *Eur J Intern Med* 2002; **13:** 324–8.
11. Hägg S, *et al*. Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol* 2003; **18:** 173–4.
12. Kuritzkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis* 2000; **30:** 256–60.
13. Kuritzkes DP, *et al*. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. *AIDS* 1998; **12:** 65–74.
14. Banerjea MC, Speer CP. The current role of colony-stimulating factors in prevention and treatment of neonatal sepsis. *Semin Neonatol* 2002; **7:** 335–49.
15. Carr R, *et al*. G-CSF and GM-CSF for treating or preventing neonatal infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/10/05).
16. Felix JK, Calhoun DA. Neonatal alloimmune neutropenia in premature monozygous twins. *Pediatrics* 2000; **106:** 340–2.
17. Maheshwari A, *et al*. Resistance to recombinant human granulocyte colony-stimulating factor in neonatal alloimmune neutropenia associated with anti-human neutrophil antigen-2a (NB1) antibodies. Abstract: *Pediatrics* 2002; **109:** 698. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/4/e64 (accessed 27/10/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Filgen; Neupogen; Neutrofil; Neutromax; ***Austral.:*** Neulasta; Neupogen; ***Austria:*** Neulasta; Neupogen; ***Belg.:*** Neulasta; Neupogen; ***Braz.:*** Filgrastine; Granulen; Granulokine; Leucin; Neulastim; ***Canad.:*** Neulasta; Neupogen; ***Chile:*** Neupogen; Neutromax; ***Cz.:*** Neulasta; Neupogen; Neupopeg; ***Denm.:*** Neulasta; Neupogen; ***Fin.:*** Neulasta; Neupogen; ***Fr.:*** Neulasta; Neupogen; ***Ger.:*** Neulasta; Neupogen; ***Gr.:*** Granulokine; Neulasta; ***Hong Kong:*** Neupogen; ***Hung.:*** Neulasta; Neupogen; ***India:*** Neupogen; ***Indon.:*** Neulastim; Neupogen; ***Irl.:*** Neulasta; Neupogen; ***Israel:*** Neupogen; ***Ital.:*** Granulokine; Neulasta; Neupogen; Neupopeg; ***Jpn:*** Gran; ***Malaysia:*** Neupogen; Peglasta; ***Mex.:*** Filatil; Neulastim; Neupogen; ***Neth.:*** Neulasta; Neupogen; Neupopeg; ***Norw.:*** Neulasta; Neupogen; ***NZ:*** Neupogen; ***Philipp.:*** Granulokine; ***Pol.:*** Neulasta; Neupogen; ***Port.:*** Neulasta; Neupogen; Neupopeg; ***Rus.:*** Neupogen (Нейпоген); ***S.Afr.:*** Neupogen; ***Singapore:*** Neulastim; Neupogen; ***Spain:*** Neulasta; Neupogen; ***Swed.:*** Neulasta; Neupogen; ***Switz.:*** Neulasta; Neupogen; ***Thai.:*** Neupogen; Neutromax; ***Turk.:*** Neupogen; ***UK:*** Neulasta; Neupogen; ***USA:*** Neulasta; Neupogen; ***Venez.:*** Neupogen.

Gelatin ⊗

Gelatina; Gélatine; Liivate; Modifiye Jelatin; Želatina; Želatyna; Zselatin.

ATC — B02BC01 (absorbable gelatin sponge); B05AA06 (gelatin).

ATC Vet — QB02BC01 (absorbable gelatin sponge); QB05AA06 (gelatin).

Grades. Gelling grades of gelatin are usually graded by gel strength, expressed as 'Bloom value', 'Bloom strength', or 'Bloom rating'.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.* Also in *USNF*.

The gelatin described in some pharmacopoeias is not necessarily suitable for preparations for parenteral use or for other special purposes.

Ph. Eur. 6.2 (Gelatin). A purified protein obtained either by partial acid hydrolysis (type A), by partial alkaline hydrolysis (type B), or by enzymatic hydrolysis of collagen from animals (including fish and poultry); it may also be a mixture of different types. The hydrolysis leads to gelling and non-gelling product grades. Gelling grades are characterised by the gel strength (Bloom value). It is not suitable for parenteral use or for other special purposes.

A faintly yellow or light yellowish-brown solid, usually occurring as translucent sheets, shreds, powder, or granules.

Gelling grades of gelatin swell in cold water and on heating give a colloidal solution which on subsequent cooling forms a more or less firm gel. Gelatin is practically insoluble in common organic solvents. Different gelatins form aqueous solutions that vary in clarity and colour. A 1% solution in water at about 55° has a pH of 3.8 to 7.6. Protect from heat and moisture.

USNF 26 (Gelatin). It is obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A, and gelatin derived from an alkali-treated precursor is known as Type B.

Faintly yellow or amber sheets, flakes, or shreds, or a coarse to fine powder, the colour varying in depth according to the particle size. A solution has a slight, characteristic, bouillon-like odour. It is stable in air when dry, but is subject to microbial decomposition when moist or in solution. Gelatin swells and softens when immersed in cold water, gradually absorbing 5 to 10 times its weight of water. Soluble in hot water, in 6N acetic acid, and in a hot mixture of glycerol and water; insoluble in alcohol, in chloroform, in ether, and in fixed and volatile oils.

Incompatibility. A white precipitate was formed immediately when vancomycin injection was infused through a giving set containing modified fluid gelatin solution.[1]

1. Taylor A, Hornbrey P. Incompatibility of vancomycin and gelatin plasma expanders. *Pharm J* 1991; **246:** 466.

Adverse Effects

Hypersensitivity reactions including anaphylactic reactions have occurred after the infusion of gelatin or its derivatives. Rapid infusion of gelatin derivatives may directly stimulate the release of histamine and other vasoactive substances.

For adverse reactions associated with the topical use of gelatin, see Haemostasis under Uses and Administration, below.

Hypersensitivity. Severe anaphylactoid reactions have been reported with infusion of modified fluid gelatin solutions.[1,2] As of June 2006, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[3] had also received 70 reports of hypotension or hypersensitivity reactions associated with succinylated gelatin. Although severe hypersensitivity reactions to gelatin-based plasma expanders appear to be rare, they may be underreported and fatalities have occurred.[2] The possibility of cross reactivity between succinylated gelatin and polygeline has also been considered; there are a few reports of patients who, after a reaction during clinical use with one plasma expander, have shown a positive skin test result to the other.[4,5] Some hypersensitivity reactions have been attributed to the use of gelatin as an excipient in vaccines[6-8] and other injectable drug products.[9] A haemostatic gelatin sponge put into place at the end of spinal surgery for a disc hernia was thought to be responsible for a delayed hypersensitivity reaction that caused oedema of the soft tissues and subsequent tingling and paresis of the lower limbs; removal of the sponge produced improvement.[10]

For reports of fatal reactions in asthmatic patients given gelatin derivatives, see Polygeline, p.1077.

1. Blanloeil Y, *et al*. Accidents anaphylactoïdes sévères après perfusion d'une gélatine fluide modifiée en solution équilibrée *Therapie* 1983; **38:** 539–46.
2. Walker SR, MacSweeney ST. Plasma expanders used to treat or prevent hypotension can themselves cause hypotension. *Postgrad Med J* 1998; **74:** 492–4.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Problems with colloids in fluid resuscitation. *Aust Adverse Drug React Bull* 2006; **25:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0606.pdf (accessed 07/12/06)
4. Russell WJ, Fenwick DG. Anaphylaxis to Haemaccel and cross reactivity to Gelofusin . *Anaesth Intensive Care* 2002; **30:** 481–3.
5. Russell WJ, Fenwick DG. Cross-reactivity between Gelofusin and Haemaccel. *Anaesth Intensive Care* 2003; **31:** 121–2.
6. Kelso JM. The gelatin story. *J Allergy Clin Immunol* 1999; **103:** 200–202.
7. Patja A, *et al*. Allergic reactions to measles-mumps-rubella vaccination. Abstract: *Pediatrics* 2001; **107:** 398. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/2/e27 (accessed 27/10/05)
8. Pool V, *et al*. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. Abstract: *Pediatrics* 2002; **110:** 1241. Full version: http://pediatrics.aappublications.org/cgi/content/full/110/6/e71 (accessed 27/10/05)
9. Sakaguchi M, *et al*. A case of anaphylaxis to gelatin included in erythropoietin products. *J Allergy Clin Immunol* 1999; **103:** 349–50.
10. Purello-D'Ambrosio F, *et al*. Allergy to gelatin. *Allergy* 2000; **55:** 414–15.

Precautions

When gelatin or its derivatives are used as plasma expanders the precautions under Dextran 70 (p.1060) should be considered. There does not appear to be any interference with blood grouping and cross-matching of blood.

When gelatin is used as an absorbable haemostatic the precautions under Oxidised Cellulose (p.1075) should be considered.

Pharmacokinetics

After infusion of modified fluid gelatin (succinylated gelatin), 75% of the dose is excreted in the urine in 24 hours. The half-life is about 4 hours.

Uses and Administration

Gelatin is a protein that has both clinical and pharmaceutical uses.

Gelatin is used as a haemostatic in surgical procedures as an absorbable film or sponge and can absorb many times its weight of blood. It is also employed as a plasma volume expander similarly to the dextrans in hypovolaemic shock (p.1183). A 4% solution of a modified fluid gelatin (succinylated gelatin) has been infused in doses of 500 to 1000 mL. It may also be used in the form of a gelatin-derived polymer, see Polygeline, p.1077.

Gelatin rods may be employed to temporarily block tear outflow in the diagnosis of dry eye (p.2140).

Gelatin is used in the preparation of pastes, pastilles, suppositories, tablets, and hard and soft capsule shells. It is also used for the microencapsulation of drugs and other industrial materials. It has been used as a vehicle for injections: Pitkin's Menstruum, which consists of gelatin, glucose, and acetic acid, has been used in a modified form for heparin while hydrolysed gelatin has been used for corticotropin. Gelatin is an ingredient of preparations used for the protection of stomas and lesions.

Haemostasis. Gelatin acts as a haemostatic (p.1045) by providing a physical meshwork within which clotting can occur.

Gelatin powder may be applied dry to wound beds and may be most useful when mixed with saline or thrombin and applied to bone. Gelatin sponge can be applied dry or soaked in saline or thrombin solutions. When applied to skin wounds the gelatin liquefies within 2 to 5 days; when implanted into tissues it is absorbed within 4 to 6 weeks. Adverse reactions include an increased incidence of infection, compression of surrounding tissue due to fluid absorption, granuloma formation, and fibrosis. Generally, gelatin sponges cause little tissue reaction and can be applied to bone, dura, and pleural tissue (but see also Hypersensitivity, above).

References.

1. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14:** 623–32.
2. Schonauer C, *et al*. The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *Eur Spine J* 2004; **13** (suppl): S89–S96.
3. Gabay M. Absorbable hemostatic agents. *Am J Health-Syst Pharm* 2006; **63:** 1244–53.

Neonatal intraventricular haemorrhage. Plasma volume expansion in preterm neonates has been thought to help prevent neonatal intraventricular haemorrhage (p.1050). However, a study using plasma or gelatin as plasma volume expanders,[1,2] found no evidence of a decreased risk of such haemorrhage or subsequent death or disability.

1. The Northern Neonatal Nursing Initiative Trial Group. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996; **155:** 580–8.
2. Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; **348:** 229–32.

Preparations

USP 31: Absorbable Gelatin Film; Absorbable Gelatin Sponge.

Proprietary Preparations (details are given in Part 3)
Arg.: Gelafundin; Geloplasma; Infukoll; ***Austral.:*** Gelfilm†; Gelfoam; Gelofusine; ***Austria:*** Gelofusin; ***Belg.:*** Gelfoam†; Gelofusine†; ***Braz.:*** Colagenan; Gelfoam; ***Canad.:*** Gelfilm; Gelfoam; ***Chile:*** Gelfoam; Gelofusine; Geloplasma; ***Cz.:*** Gelofusine; Geloplasma; ***Fin.:*** Gelofusine; ***Fr.:*** Bloxang; Gel-Phan; Gelodiet; Gelofusine†; Hydrocoll; ***Ger.:*** Gelafundin; Gelafusal; Gelaspon; Gelastypt; Spongostan; stypro; Thomaegelin†; ***Gr.:*** Gelofusine; ***Hong Kong:*** Gelfoam†; Gelofusine; ***Hung.:*** Gelaspon†; Gelofusine; ***India:*** Seraccel†; ***Indon.:*** Gelafundin; ***Israel:*** Gelfoam; ***Ital.:*** Cutanplast; Eufusin; Gelofusine; Spongostan; ***Malaysia:*** Gelfoam; ***Neth.:*** Gelfilm†; Gelfoam†; Gelofusine; Geloplasma; Willospon†; ***NZ:*** Gelfilm; Gelfoam; Gelofusine; ***Philipp.:*** Gelfoam; ***Pol.:*** Gelofusine; ***Port.:*** Gelafundina; Gelofusine; ***S.Afr.:*** Gelofusine; ***Singapore:*** Gelfoam; Gelofusine†; ***Switz.:*** Physiogel; ***Thai.:*** Gelafundin; Gelofusine; ***Turk.:*** Gelofusin; ***UK:*** Gelofusine; Geloplasma; Volplex; ***USA:*** Gelfilm; Gelfoam; ***Venez.:*** Gelfoam; Gelofusine.

Multi-ingredient: ***Arg.:*** Megaplus; Mucobase; ***Austral.:*** Orabase; Orahesive†; Stomahesive†; ***Austria:*** Gelacet; ***Canad.:*** Orabase†; Orahesive†; Tegasorb; ***Fr.:*** Plasmion; Rectopanbiline; ***Ger.:*** Gelacet N†; ***Irl.:*** Orabase; ***Israel:*** Orabase†; ***Ital.:*** Solecin; ***Mex.:*** Gelafundin; ***NZ:*** Orabase; Stomahesive; ***Port.:*** Dagragel; Varihesive†; ***S.Afr.:*** Granuflex; Orabase; ***Switz.:*** Gelacet†; ***UK:*** Orabase; Orahesive; Stomahesive; ***USA:*** Dome-Paste.

Haemoglobin ⊗

Hemoglobina.

Hemoglobin Glutamer *(rINN)* ⊗

Haemoglobin Glutamer; Hemoglobina glutámero; Hémoglobine Glutamère; Hemoglobinum Glutamerum.

Гемоглобин Глутамер

ATC — B05AA10 (bovine).

ATC Vet — QB05AA10 (bovine); QB05AA90.

NOTE. The species of origin and average molecular mass should be indicated (e.g. hemoglobin glutamer-250 (bovine) indicates a polymerised haemoglobin of bovine origin with an average mass of 250 kD).