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.
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8. Bhidayasiri R, *et al*. Correction of mesalazine-induced neutropenia with high dose G-CSF. *Am J Gastroenterol* 2000; **95:** 3321–2.
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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).

Profile
Haemoglobin has the property of reversible oxygenation and is the respiratory pigment of blood. Solutions of haemoglobin or modified haemoglobin are being investigated as blood substitutes.

Hemoglobin glutamer-250 (bovine) (HBOC-201; haemoglobin-based oxygen carrier-201) is a polymerised bovine haemoglobin that is used for the treatment of anaemia in surgical patients.

Hemoglobin glutamer-200 (bovine) (HBOC-301) is used in veterinary medicine for the treatment of anaemia in *dogs*.

Use. The structure of haemoglobin gives a non-linear oxygen dissociation curve; almost maximum oxygen saturation occurs in normal arterial blood without the need for oxygen-enriched air. Thus the use of haemoglobin solutions for emergencies appears logical. Initial *animal* experiments with haemoglobin from haemolysed erythrocytes resulted in serious renal damage but haemoglobin is not itself nephrotoxic and the development of stroma-free haemoglobin solutions reduced this toxicity. However, once released from the erythrocytes, haemoglobin loses its ability to hold 2,3-diphosphoglycerate, which is essential for the delivery of oxygen, and haemoglobin, being a small molecule, is rapidly excreted by the kidneys. Various methods have been tried to overcome these problems; formation of crosslinked haemoglobin restores the oxygen affinity to that of whole blood and conjugation, polymerisation, or microencapsulation in a lipid membrane extend the half-life. Although there is ongoing development of these preparations there are reservations concerning haemoglobin solutions as blood substitutes. Bovine blood is one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability. There is also concern about impairment of immune mechanisms. The development of recombinant human haemoglobin may overcome these problems and may allow further modification of the haemoglobin molecule.

References.

1. Farrar D, Grocott M. Intravenous artificial oxygen carriers. *Hosp Med* 2003; **64:** 352–6.
2. Creteur J, Vincent J-L. Hemoglobin solutions. *Crit Care Med* 2003; **31** (suppl): S698–S707.
3. Chang TMS. Hemoglobin-based red blood cell substitutes. *Artif Organs* 2004; **28:** 789–94.
4. Mackenzie CF, Bucci C. Artificial oxygen carriers for trauma: myth or reality. *Hosp Med* 2004; **65:** 582–8.
5. Awasthi V. Pharmaceutical aspects of hemoglobin-based oxygen carriers. *Curr Drug Deliv* 2005; **2:** 133–42.
6. Stowell CP. What happened to blood substitutes? *Transfus Clin Biol* 2005; **12:** 374–9.
7. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; **11:** 4099–4114.

Preparations
Proprietary Preparations (details are given in Part 3)
S.Afr.: Hemopure.

Multi-ingredient: ***India:*** Blosyn; Haem Up.

Interleukin-3
IL-3; Interleucina 3.

Profile
Interleukin-3 is a cytokine that acts as a colony-stimulating factor. It is under investigation in the management of myelosuppression associated with cancer chemotherapy and after bone marrow transplantation. A fusion molecule with granulocyte-macrophage colony-stimulating factor, known as milodistim (PIXY-321), has also been investigated but results have been disappointing.

Lenograstim *(BAN, USAN, rINN)*
Lenograstiimi; Lénograstim; Lenograstimum; rG-CSF. A recombinant human granulocyte colony-stimulating factor.

Ленограстим

CAS — 135968-09-1.
ATC — L03AA10.
ATC Vet — QL03AA10.

Stability. Solutions of colony-stimulating factors may be adsorbed onto glass or plastic materials. Solutions of lenograstim should not be diluted below the minimum recommended concentration for the formulation used.

Adverse Effects and Precautions
As for Filgrastim, p.1070.

Uses and Administration
Lenograstim is a granulocyte colony-stimulating factor with actions and uses similar to those of filgrastim (p.1071). 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 is also used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous or allogeneic peripheral blood stem cell transplantation.

Lenograstim may be given for **neutropenia** in a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily to patients after bone marrow transplantation and also to patients established on antineoplastic therapy; in post-transplant patients it is given by intravenous infusion over 30 minutes or by subcutaneous injection, and in patients on antineoplastics it is given subcutaneously. Treatment is given until the neutrophil count has stabilised within the normal range, but a maximum treatment period of 28 consecutive days should not be exceeded.

For **mobilisation** of peripheral blood progenitor cells for autologous peripheral blood stem cell transplantation, a dose of 150 micrograms/m^2 (19.2 million international units/m^2) daily may be given by subcutaneous injection. It is started the day after completion of chemotherapy and given until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range, so that leucapheresis can be performed. When used alone, a lenograstim dose of 10 micrograms/kg (1.28 million international units/kg) daily is given subcutaneously for 4 to 6 days, with leucapheresis usually performed between days 5 and 7. For mobilisation of cells in healthy donors, to use in allogeneic transplantation, a dose of 10 micrograms/kg daily may be given subcutaneously for 5 or 6 days before leucapheresis.

◊ References.

1. Frampton JE, *et al.* Lenograstim: a review of its pharmacological properties and therapeutic efficacy in neutropenia and related clinical settings. *Drugs* 1995; **49:** 767–93.
2. Dunn CJ, Goa KL. Lenograstim: an update of its pharmacological properties and use in chemotherapy-induced neutropenia and related clinical settings. *Drugs* 2000; **59:** 681–717.
3. Martino M, *et al.* Harvesting peripheral blood progenitor cells from healthy donors: retrospective comparison of filgrastim and lenograstim. *J Clin Apher* 2005; **20:** 129–36.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Granocyte†; Lenobio; Leumostin†; ***Austral.:*** Granocyte; ***Austria:*** Granocyte; ***Belg.:*** Granocyte; ***Braz.:*** Granocyte; ***Chile:*** Granocyte; ***Cz.:*** Granocyte†; ***Denm.:*** Granocyte; ***Fin.:*** Granocyte; ***Fr.:*** Granocyte; ***Ger.:*** Granocyte; ***Gr.:*** Granocyte; ***Hung.:*** Granocyte; ***Indon.:*** Granocyte; ***Irl.:*** Granocyte; ***Israel:*** Granocyte; ***Ital.:*** Granocyte; Myelostim; ***Jpn:*** Neutrogin; ***Malaysia:*** Granocyte; ***Neth.:*** Granocyte; ***Norw.:*** Granocyte; ***NZ:*** Granocyte; ***Philipp.:*** Granocyte; ***Pol.:*** Granocyte; ***Port.:*** Granocyte; ***Rus.:*** Granocyte (Граноцит); ***S.Afr.:*** Granocyte; ***Singapore:*** Granocyte; ***Spain:*** Euprotin; Granocyte; ***Swed.:*** Granocyte; ***Switz.:*** Granocyte; ***Thai.:*** Granocyte; ***UK:*** Granocyte; ***Venez.:*** Granocyte.

Leucocytes
Leucocitos.

Description. Preparations of leucocytes contain granulocytes with a variable content of red blood cells, lymphocytes, and platelets. Depending on the method of collection they may also contain dextran or hetastarch.

Adverse Effects and Precautions
Leucocyte transfusions may cause severe transfusion reactions and fever. As with other blood products, there is a risk of transmission of infection. Severe lung reactions, including fluid overload with pulmonary oedema, are a particular problem in patients with active pulmonary infections.

Red blood cell compatibility testing is necessary because of the content of red blood cells. Graft-versus-host disease may occur in immunosuppressed recipients, and can be avoided by irradiating the product before it is given.

Uses and Administration
Transfusion of leucocytes has been used in patients with severe granulocytopenia and infection which has not been controlled by treatment with appropriate antimicrobials. Transfusion of 1×10^{10} granulocytes once or twice daily has been suggested as an effective dose. Daily transfusions for at least 3 to 4 days are usually advised. Hydrocortisone and chlorphenamine may be given intravenously before transfusion to reduce the severity of adverse reactions.

◊ References.

1. Brozović B, *et al.* Platelet and granulocyte transfusions. In: Contreras M, ed. *ABC of transfusion.* 3rd ed. London: BMJ Books, 1998: 17–22.
2. Yeghen T, Devereux S. Granulocyte transfusion: a review. *Vox Sang* 2001; **81:** 87–92.
3. Hubel K, Engert A. Granulocyte transfusion therapy for treatment of infections after cytotoxic chemotherapy. *Onkologie* 2003; **26:** 73–9.
4. Briones MA, *et al.* Granulocyte transfusion: revisited. *Curr Hematol Rep* 2003; **2:** 522–7.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Immodin; ***Ger.:*** LeukoNorm.

Mirimostim *(rINN)*
Mirimostimum. A macrophage colony-stimulating factor; 1–214-Colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer.

Миримостим

CAS — 121547-04-4.

Profile
Mirimostim is a macrophage colony-stimulating factor (M-CSF). It promotes the differentiation and proliferation of monocytes and macrophage precursors, and stimulates secretion of granulocyte and granulocyte-macrophage colony-stimulating factors (see Haematopoiesis, p.1042). Mirimostim is used in the management of neutropenia in patients receiving myelosuppressive cancer chemotherapy.

Preparations
Proprietary Preparations (details are given in Part 3)
Jpn: Leukoprol.

Molgramostim *(BAN, USAN, rINN)*
Molgramostiimi; Molgramostimum; Sch-39300. A recombinant human granulocyte-macrophage colony-stimulating factor; Colony-stimulating factor 2 (human clone pHG_{25} protein moiety reduced).

Молграмостим

CAS — 99283-10-0.
ATC — L03AA03.
ATC Vet — QL03AA03.

Pharmacopoeias. *Eur.* (see p.vii) includes a concentrated solution.

Ph. Eur. 6.2 (Molgramostim Concentrated Solution; Molgramostimi Solutio Concentrata). A solution of a protein having the structure of the granulocyte-macrophage colony-stimulating factor which is produced and secreted by various human blood cell types. It contains not less than 2.0 mg of protein per mL. A clear, colourless liquid. Store in airtight containers at a temperature below –65°. Protect from light.

Stability. Solutions of molgramostim may be adsorbed onto glass and plastic materials and therefore should not be diluted below the recommended minimum concentration of 7 micrograms/mL.

Adverse Effects
Granulocyte-macrophage colony-stimulating factors such as molgramostim may cause transient hypotension and flushing, bone pain and musculoskeletal pain, fever and chills, dyspnoea, rash, fatigue, and gastrointestinal effects. Antibodies have been detected. Anaphylactic reactions, pleural and pericardial effusion, and cardiac arrhythmias have been reported rarely.

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. Moleski RJ. Comparison of G-CSF and GM-CSF adverse event profiles in office-based practices: preliminary study results. *Pharmacotherapy* 2000; **20** (suppl): 112S–117S.
3. Milkovich G, *et al.* Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. *Pharmacotherapy* 2000; **20:** 1432–40.

Antibodies. Antibodies can develop in patients given recombinant granulocyte-macrophage colony-stimulating factors. The antibodies have been reported to occur more commonly, and in higher titres, in patients who are not immunocompromised compared with those who are.[1,2] Although some binding antibodies are non-neutralising and have no apparent clinical effect,[3] neutralising antibodies can reduce the efficacy of the colony-stimulating factor in repeated treatment cycles.[1,2] However, antibodies have been reported to become undetectable after a number of weeks[2] and do not appear to have long-term effects.[1] Cross-reactivity between different granulocyte-macrophage colony-stimulating factors has been reported,[1-3] and antibody formation may also be product dependent.[2]

1. Ragnhammar P, *et al.* Induction of anti-recombinant human granulocyte-macrophage colony-stimulating factor (Escherichia coli-derived) antibodies and clinical effects in nonimmunocompromised patients. *Blood* 1994; **84:** 4078–87.
2. Wadhwa M, *et al.* Immunogenicity of granulocyte-macrophage colony-stimulating factor (GM-CSF) products in patients undergoing combination therapy with GM-CSF. *Clin Cancer Res* 1999; **5:** 1353–61.
3. Ullenhag G, *et al.* Incidence of GM-CSF antibodies in cancer patients receiving GM-CSF for immunostimulation. *Clin Immunol* 2001; **99:** 65–74.

Effects on the skin. See under Filgrastim, p.1070.

Effects on the thyroid. See under Filgrastim, p.1070.