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one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability.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.