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one source used for production but there are concerns about potential antigenicity or disease transmission; the use of outdated donated human blood is limited by availability.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

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

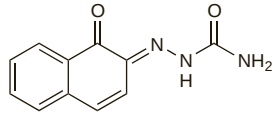
Proprietary Preparations (details are given in Part 3)
Arg.: Growgen-GM; Leucomax†; Molcass; ***Austria:*** Leucomax†; ***Belg.:*** Leucomax†; ***Braz.:*** Gramostim†; Leucocitim; Leucomax†; ***Chile:*** Leucomax†; ***Cz.:*** Leucomax†; ***Denm.:*** Leucomax†; ***Fin.:*** Leucomax†; ***Ger.:*** Leucomax†; ***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.