to remove proteins, freezing and thawing, or rejuvenation using validated and approved procedures.

For preparations derived from whole blood, one unit (dose) of Red Blood Cells contains a minimum of 50 g of haemoglobin. One unit of Red Blood Cells, Leukocytes Reduced contains a minimum of 42.5 g of haemoglobin and has a residual leucocyte count of less than 5×10^6. One unit of Red Blood Cells, Deglycerolized contains a minimum of 40 g of haemoglobin. One unit of Red Blood Cells, Leukocytes Reduced and Deglycerolized contains a minimum of 34 g of haemoglobin and has a residual leucocyte count of less than 5×10^6.

For preparations derived by apheresis, one unit (dose) of Red Blood Cells, Pheresis contains a mean haemoglobin content of 60 g of haemoglobin. One unit of Red Blood Cells, Pheresis, Leukocytes Reduced contains a mean haemoglobin content of 51 g of haemoglobin and has a residual leucocyte count of less than 5×10^6.

Red blood cells should be stored in the original container, or transferred to an equivalent container using a technique that does not compromise sterility. An approved additive solution may be added after removal of the plasma. Liquid red blood cells is stored at 1° to 6°. Frozen red blood cells is stored at or below –65°.

Red blood cells in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at 1° to 6° after the blood has been drawn. Red blood cells in Anticoagulant Citrate Dextrose Phosphate Adenine Solution may be stored for up to 35 days at 1° to 6°. Red blood cells may be stored in an approved additive solution for up to 42 days at 1° to 6°.

Frozen red blood cells prepared with low glycerol content (20%) may be stored at or below –120° for not later than 10 years from years from the date of collection. Frozen red blood cells prepared with high glycerol content (40%) may be stored at or below –65° for not later than 10 years from years from the date of collection. If the frozen red blood cells is processed for freezing or for thawing, in an open system, the expiry date for the thawed red blood cells is 24 hours after removal from –65° storage, provided it is then stored at the temperature of unfrozen red blood cells.

Dark red in colour when packed and may show a slight creamy layer on the surface and a small supernatant layer of yellow or opalescent plasma.

Adverse Effects and Precautions

As for Blood, p.1056.

Antibody formation. Patients with sickle-cell anaemia frequently require repeated transfusions of red blood cells. Alloimmunisation is a common problem in these patients, and has the potential to cause haemolytic transfusion reactions.[1] Alloantibodies were detected in 32 of 107 black patients with sickle-cell anaemia who had received red cell transfusions compared with 1 of 19 non-black patients who had received transfusions for other chronic anaemias.[2] The incidence of antibody formation was related to the number of transfusions received. An analysis of the red cell phenotypes suggested that the high rate of alloimmunisation among patients with sickle-cell anaemia could be due to racial differences between donors and recipients. Alloimmunisation can also occur in thalassaemia patients who are given transfusions,[3] and the incidence in these patients may also be affected by racial differences between donors and recipients.[4] Erythrocyte autoantibody formation has also been reported.[1,3]

1. Aygun B, *et al.* Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion* 2002; **42:** 37–43.
2. Vichinsky EP, *et al.* Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990; **322:** 1617–21.
3. Singer ST, *et al.* Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. *Blood* 2000; **96:** 3369–73.
4. Ho H-K, *et al.* Alloimmunization in Hong Kong southern Chinese transfusion-dependent thalassemia patients. *Blood* 2001; **97:** 3999–4000.

Uses and Administration

Transfusions of red blood cells are given for the treatment of severe anaemia without hypovolaemia (p.1042).

Red blood cells are also used for exchange transfusion in babies with haemolytic disease of the newborn (p.2204). Red cells may be used with volume expanders for acute blood loss of less than half of the blood volume; if more than half of the blood volume has been lost, whole blood should be used.

Other red blood cell products are available. Concentrated red cells in an optimal additive solution containing sodium chloride, adenine, glucose, and mannitol has reduced viscosity and an extended shelf-life. Leucocyte-depleted red cells may be used in patients who have developed antibodies to previous transfusions or in whom development of antibodies is undesirable. Frozen, thawed, and washed red cell concentrates in which plasma proteins are removed in addition to leucocytes and platelets may be used in patients with rare antibodies.

◊ Reviews and guidelines.

1. Davies SC, Williamson LM. Transfusion of red cells. In: Contreras M, ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998: 10–16.
2. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines on the clinical use of leucocyte-depleted blood components. *Transfus Med* 1998; **8:** 59–71. Also available at: http://www.bcshguidelines.com/pdf/trans129.pdf (accessed 27/10/05)
3. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; **113:** 24–31. Also available at: http://www.bcshguidelines.com/pdf/bjh2701.pdf (accessed 27/10/05)
4. Hill SR, *et al.* Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 16/06/05).

Preparations

USP 31: Red Blood Cells.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Vulnofilin Compuesto†.

Romiplostim *(USAN, rINN)*

AMG-531; Romiplostimum. L-Methionyl[human immunoglobulin heavy constant gamma 1-(227 *C*-terminal residues)-peptide (Fc fragment)] fusion protein with 41 amino acids peptide, (7-7′:10,10′)-bisdisulfide dimer.

Ромиплостим

CAS — 267639-76-9.

Profile

Romiplostim is a protein that acts as an agonist at the thrombopoietin receptor to stimulate platelet production, although it has no sequence homology with endogenous thrombopoietin. It is under investigation in the treatment of chronic idiopathic thrombocytopenic purpura.

◊ References.

1. Bussel JB, *et al.* AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; **355:** 1672–81. Correction. *ibid.*; 2054.
2. Kuter DJ, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; **371:** 395–403.

Sargramostim *(BAN, USAN, rINN)*

BI-61.012; rhu GM-CSF; Sargramostimum. A recombinant human granulocyte-macrophage colony-stimulating factor; 23-L-Leucinecolony-stimulating factor 2 (human clone pHG_{25} protein moiety).

Сарграмостим

CAS — 123774-72-1.

ATC — L03AA09.

ATC Vet — QL03AA09.

Pharmacopoeias. In *US.*

USP 31 (Sargramostim). A single chain, glycosylated polypeptide of 127 amino acid residues expressed from *Saccharomyces cerevisiae*. The glycoprotein primarily consists of three molecular species having relative molecular weights of about 19 500, 16 800, and 15 500 due to different levels of glycosylation. Sargramostim has the property of generating granulocyte, macrophage, and mixed granulocyte macrophage colonies from haematopoietic progenitor cells found in bone marrow. Store in sealed containers at a temperature of –20° or below.

Stability. Solutions of sargramostim may be adsorbed onto glass or plastic materials and so albumin must be added to give a final concentration of 1 mg/mL to solutions that are diluted to concentrations of sargramostim below 10 micrograms/mL.

Adverse Effects and Precautions

As for Molgramostim, p.1073.

Uses and Administration

Sargramostim is a granulocyte-macrophage colony-stimulating factor with actions and uses similar to those of molgramostim (p.1074). 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 after bone marrow transplantation when engraftment is delayed or has failed. Sargramostim may be used to mobilise peripheral blood progenitor cells for collection and subsequent use in autologous peripheral blood stem cell transplantation, as well as after transplantation to improve engraftment.

As an **adjunct to antineoplastic therapy**, sargramostim is given by intravenous infusion over 4 hours in a dose of 250 micrograms/m^2 daily for up to 42 days as required.

After **bone marrow transplantation**, sargramostim may be given in a dose of 250 micrograms/m^2 daily by intravenous infusion over 2 hours. When engraftment is delayed or has failed, a course of sargramostim 250 micrograms/m^2 daily for 14 days may be used. The dose can be repeated after a 7-day interval if engraftment has not occurred. A third course of 500 micrograms/m^2 daily for 14 days may be tried after another 7-day interval if needed, but further dose escalation is unlikely to be of benefit.

For **mobilisation** of peripheral blood progenitor cells a dose of 250 micrograms/m^2 daily is given by continuous intravenous infusion over 24 hours or by subcutaneous injection, with leucapheresis usually starting on day 5. The same dosing regimen may be used after peripheral blood stem cell transplantation, until neutrophil recovery.

HIV infection and AIDS. Sargramostim has been evaluated in the management of HIV infection (p.856). There is some evidence to suggest that it might help to decrease and suppress viral load, and increase CD4+ cell counts, by enhancing the activity of antiretroviral drugs and increasing the resistance of monocytes to HIV infection.[1-3] However, in a study[4] of patients who were medically stable but had incompletely controlled HIV replication, sargramostim did not have a significant antiviral effect and there was only a trend towards increased CD4+ counts. The effect of molgramostim has been studied in a small trial[5] in which it was found to blunt viral rebound following interruption of HAART.

1. Skowron G, *et al.* The safety and efficacy of granulocyte-macrophage colony-stimulating factor (sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. *J Infect Dis* 1999; **180:** 1064–71.
2. Brites C, *et al.* A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. *J Infect Dis* 2000; **182:** 1531–5.
3. Angel JB, *et al.* Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. *AIDS* 2000; **14:** 387–95.
4. Jacobson JM, *et al.* Granulocyte-macrophage colony-stimulating factor induces modest increases in plasma human immunodeficiency virus (HIV) type 1 RNA levels and CD4+ lymphocyte counts in patients with uncontrolled HIV infection. *J Infect Dis* 2003; **188:** 1804–14.
5. Fagard C, *et al.* A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART. *AIDS* 2003; **17:** 1487–92.

Inflammatory bowel disease. A small dose-escalating study[1] reported a beneficial effect from the use of sargramostim in Crohn's disease (see Inflammatory Bowel Disease, p.1697). A subsequent larger placebo-controlled study[2] in moderate to severe active disease found that the rate of response to sargramostim was not significantly different from that of placebo. Although disease severity and quality of life improved in the sargramostim group, later unpublished study results were said to be disappointing, and in June 2007 the manufacturer declared that it would not be investigating sargramostim any further in Crohn's disease.

1. Dieckgraefe BK, Korzenik JR. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; **360:** 1478–80.
2. Korzenik JR, *et al.* Sargramostim for active Crohn's disease. *N Engl J Med* 2005; **352:** 2193–2201.

Malignant neoplasms. It has been suggested that granulocyte-macrophage colony-stimulating factor may be able to increase antitumour immune activity. Sargramostim, given by nebuliser to stimulate a local response, has been investigated in patients with lung metastases.[1,2]

1. Anderson PM, *et al.* Aerosol granulocyte macrophage-colony stimulating factor: a low toxicity, lung-specific biological therapy in patients with lung metastases. *Clin Cancer Res* 1999; **5:** 2316–23.
2. Rao RD, *et al.* Aerosolized granulocyte macrophage colony-stimulating factor (GM-CSF) therapy in metastatic cancer. *Am J Clin Oncol* 2003; **26:** 493–8.

Wounds and ulcers. See under Molgramostim (p.1074) for mention of the use of sargramostim in the promotion of wound healing.

Preparations

USP 31: Sargramostim for Injection.

Proprietary Preparations (details are given in Part 3)

USA: Leukine.