SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GRANOCYTE 13 million IU/mL, powder and solvent for solution for injection/infusion.

GRANOCYTE 13 million IU/mL, powder and solvent for solution for injection/infusion in a pre-filled syringe.

GRANOCYTE 34 million IU/mL, powder and solvent for solution for injection/infusion.

GRANOCYTE 34 million IU/mL, powder and solvent for solution for injection/infusion in a pre-filled syringe.

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lenograstim* (rHuG-CSF) 13.4 million International Units (equivalent to 105 micrograms) per mL after reconstitution

Lenograstim* (rHuG-CSF) 33.6 million International Units (equivalent to 263 micrograms) per mL after reconstitution

*Produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

Excipients with known effect:

Phenylalanine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

Powder and solvent for solution for injection/infusion in a pre-filled syringe.

- White powder

- *Solvent*: clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GRANOCYTE is indicated in adults, adolescents and children aged older than 2 years for:

- The reduction of the duration of neutropenia in patients (with non myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation (BMT) and considered to be at increased risk of prolonged severe neutropenia.
- The reduction of the duration of severe neutropenia and its associated complications in patients undergoing established cytotoxic therapy associated with a significant incidence of febrile neutropenia.
- The mobilisation of peripheral blood progenitor cells (PBPCs), for patients as well as healthy donors.

4.2 Posology and method of administration

Method of administration

GRANOCYTE can be administered by sub-cutaneous injection or by intravenous infusion. Particular handling of the product or instructions for preparation are given in sections 6.6.

Posology

Therapy should only be given in collaboration with an experienced oncology and/or haematology centre.

The recommended dose of GRANOCYTE is 19.2 MIU (150 µg) per m^2 per day, therapeutically equivalent to 0.64 MIU (5 µg) per kg per day for:

- Peripheral Stem Cells or bone marrow transplantation,
- established cytotoxic chemotherapy
- PBPC mobilisation after chemotherapy.

GRANOCYTE 13 million IU/mL can be used in patients with body surface area

up to 0.7 m^2.

GRANOCYTE 34 million IU/mL can be used in patients with body surface area up to 1.8 m^2.

For PBPC mobilisation with GRANOCYTE alone, the recommended dose is 1.28 MIU (10 µg) per kg per day.

Adults

- In Peripheral Stem Cells or Bone Marrow Transplantation

  GRANOCYTE should be administered daily at the recommended dose of 19.2 MIU (150 µg) per m^2 per day as a 30-minute intravenous infusion diluted in isotonic saline solution or as a subcutaneous injection. The first dose should not be administered within 24 hours of the bone marrow infusion. Dosing should continue until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, with, if necessary, a maximum of 28 consecutive days of treatment.

  It is anticipated that by day 14 following bone marrow transplantation, 50% of patients will achieve neutrophil recovery.

- In Established Cytotoxic Chemotherapy

  GRANOCYTE should be administered daily at the recommended dose of 19.2 MIU (150 µg) () per m^2 per day as a subcutaneous injection. The first dose should not be administered less than 24 hours following cytotoxic chemotherapy (see 4.4 and 4.5). Daily administration of GRANOCYTE should continue until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, with, if necessary, a maximum of 28 consecutive days of treatment.

  A transient increase in neutrophil count may occur within the first 2 days of treatment, however GRANOCYTE treatment should not be stopped, since the subsequent nadir usually occurs earlier and recovers more quickly if treatment continues.

- In Peripheral Blood Progenitor Cells (PBPCs) Mobilisation

  After chemotherapy, GRANOCYTE should be administered daily, at the recommended dose of 19.2 MIU (150 µg) per m^2 per day as a subcutaneous injection starting within 1 to 5 days after completion of chemotherapy, according to the chemotherapy regimen administered for mobilisation.

  GRANOCYTE should be maintained until the last leukapheresis.

  Leukapheresis should be performed when the post nadir leukocyte count is rising or after assessment of $CD34^+$ cells in blood with a validated method. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient to obtain the acceptable minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells per kg).

In PBPC mobilisation with GRANOCYTE alone, GRANOCYTE should be administered daily at the recommended dose of 1.28 MIU (10 µg) per kg per day as a subcutaneous injection for 4 to 6 days. Leukapheresis should be performed between day 5 and 7.

In patients who have not had extensive chemotherapy one leukapheresis is often sufficient to obtain the acceptable minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells per kg).

In healthy donors, a 10µg/kg daily dose administered subcutaneously for 5-6 days allows a $CD34^+$ cells collection $\geq 3 \times 10^6$ /kg body weight with a single leukapheresis in 83% of subjects and with 2 leukapheresis in 97%.

Elderly

Clinical trials with GRANOCYTE have included a small number of patients up to the age of 70 years but special studies have not been performed in the elderly and therefore specific dosage recommendations cannot be made.

Children

The dose in children older than 2 years and adolescent is the same as in adults when used to reduce the duration of neutropenia after myeloablative therapy followed by BMT or after cytotoxic chemotherapy.

Very limited data are available for mobilisation of peripheral blood progenitor cells at the adult dose.

Paediatric population

The safety and efficacy of GRANOCYTE in children aged less than 2 years have not been established.

GRANOCYTE 13 million IU/mL may be the more appropriate dosage for administration in children with body surface area up to 0.7 m².

GRANOCYTE 34 million IU/mL can be used in patients with body surface area up to 1.8 m².

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

GRANOCYTE should not be used to increase the dose intensity of cytotoxic chemotherapy beyond established doses and dosage regimens since the drug could reduce myelo-toxicity but not overall toxicity of cytotoxic drugs.

It should not be administered concurrently with cytotoxic chemotherapy.

It should not be administered to patients

- with myeloid malignancy other than *de novo* acute myeloid leukaemia,
- with *de novo* acute myeloid leukaemia aged below 55 years, and/or
- with *de novo* acute myeloid leukaemia with good cytogenetics, i.e. t(8 ;21), t(15 ;17) and inv (16).

4.4 Special warnings and precautions for Use

- Malignant Cell Growth

  Granulocyte colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

  The safety and efficacy of GRANOCYTE administration in patients with myelodysplasia or secondary AML or chronic myelogenous leukaemia have not been established. Therefore, it should not be used in these indications. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

  Clinical trials have not established whether GRANOCYTE influences the progression of myelodysplastic syndrome to acute myeloid leukaemia. Caution should be exercised in using it in any pre-malignant myeloid condition. As some tumours with non-specific characteristics can exceptionally express a G-CSF receptor, caution should be exerted in the event of unexpected tumour regrowth concomitantly observed with rHuG-CSF therapy

- In children with ALL

  An increased risk for secondary myeloid leukaemia or myelodysplastic syndrome associated with CSFs has been reported in children with ALL. A comparable risk has been established by a systematic review of 25 randomized controlled trials in 12.804 adult patients with solid tumors or lymphomas, a risk, however, without negative impact on long term outcome in the adults investigated. Therefore, GRANOCYTE 13 million IU/mL and GRANOCYTE 34 million IU/ml should be used in children, in particular with favorable long term prognosis, only after careful weighting of short term benefits versus long term risks.

- Leukocytosis

  A leukocyte count greater than 50 x 10^9/L has not been observed in any of the 174 clinical trials patients treated with 5 µg/kg/day (0.64 million units/kg/day) following bone marrow transplantation. White blood cell counts of 70 x 10^9/L or greater have been observed in less than 5% of patients who received cytotoxic chemotherapy and were treated by GRANOCYTE at 5 µg/kg/day (0.64 million units/kg/day). No adverse events directly attributable to this degree of leukocytosis have been

reported. In view of the potential risks associated with severe leukocytosis, a white blood cell count should, however, be performed at regular intervals during GRANOCYTE therapy.

If leukocyte counts exceed 50 x 10^9/L after the expected nadir, GRANOCYTE should be discontinued immediately.

During PBPC mobilisation, GRANOCYTE should be discontinued if the leukocyte counts rise to > 70 x 10^9/L.

- Pulmonary adverse effects

  Rare (>0.01% and <0.1%) pulmonary adverse effects, in particular interstitial pneumonia, have been reported after G-CSFs administration.

  Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

  The onset of pulmonary symptoms or signs, such as cough, fever and dyspnoea, in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of acute respiratory distress syndrome (ARDS).

  GRANOCYTE should be immediately discontinued and appropriate treatment given.

  In donors and patients, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates, dyspnoea and hypoxia) have been reported in post marketing experience. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with Granocyte should be considered and appropriate medical care given.

- Venous and arterial thromboembolic events

  Cases of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (such as myocardial infarction and cerebrovascular event) have been reported in donors treated with lenograstim. Close monitoring is recommended in donors and patients with known risk factors for thrombosis (see section 4.8).

- In Peripheral Stem Cells or Bone Marrow Transplantation

  Special attention should be paid to platelet recovery since in double-blind placebo-controlled trials the mean platelet count was lower in patients treated with GRANOCYTE as compared with placebo.

  The effect of GRANOCYTE on the incidence and severity of acute and chronic graft-versus-host disease has not been accurately determined.

- In Established Cytotoxic Chemotherapy

  The use of GRANOCYTE is not recommended from 24 hours before, until 24 hours after chemotherapy ends (see section 4.5).

The safety of the use of GRANOCYTE with antineoplastic agents characterized by cumulative or predominant platelet lineage myelotoxicity (nitrosurea, mitomycin) has not been established. Administration of GRANOCYTE might enhance the toxicity of these agents, particularly to the platelets.

- Risks Associated with Increased Doses of Chemotherapy

  The safety and efficacy of GRANOCYTE have yet to be established in the context of intensified chemotherapy. It should not be used to decrease, beyond the established limits, intervals between chemotherapy courses and/or to increase the doses of chemotherapy. Non-myeloid toxicities were limiting factors in a phase II chemotherapy intensification trial with GRANOCYTE.

- Special precautions in Peripheral Blood Progenitor Cells mobilisation.

  Choice of the mobilisation method

  Clinical trials carried out among the same patient population have shown that PBPC mobilisation, as assessed within the same laboratory, was higher when GRANOCYTE was used after chemotherapy than when used alone. Nevertheless the choice between the two mobilisation methods should be considered in relation to the overall objectives of treatment for an individual patient.

  Prior exposure to radiotherapy and/or cytotoxic agents

  Patients, who have undergone extensive prior myelosuppressive therapy and/or radiotherapy, may not show sufficient PBPC mobilisation to achieve the acceptable minimum yield ($\geq 2 \times 10^6$ $CD34^+$ /kg) and therefore adequate haematological reconstitution.

  A PBPC transplantation program should be defined early in the treatment course of the patient and particular attention should be paid to the number of PBPC mobilised before the administration of high-dose chemotherapy. If yields are low, other forms of treatment should replace the PBPC transplantation program.

  Assessment of progenitor cell yields

  Particular attention should be paid to the method of quantification of progenitor cell yields as the results of flow cytometric analysis of $CD34^+$ cell number vary among laboratories.

  The minimum yield of $CD34^+$ cells is not well defined. The recommendation of a minimum yield of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg is based on published experience in order to achieve adequate haematological reconstitution. Yields higher than $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg are associated with more rapid recovery, including platelets, while lower yields result in slower recovery.

- In healthy donors

The PBPC mobilisation, which is a procedure without direct benefit for healthy people, should only be considered through a clear regular delimitation in accordance with local regulations as for bone marrow donation when applicable.

The efficacy and safety of GRANOCYTE has not been assessed in donors aged over 60 years, therefore the procedure cannot be recommended. Based on some local regulations and lack of studies, minor donors should not be considered.

PBPC mobilisation procedure should be considered for donors who fit usual clinical and laboratory eligibility criteria for bone marrow donation especially normal haematological values.

Marked leukocytosis (WBC $\geq 50 \times 10^9$/L) was observed in 24% of subjects studied.

Apheresis-related thrombocytopenia (platelets $< 100 \times 10^9$/L) was observed in 42% of subjects studied and values $< 50 \times 10^9$/L were occasionally noted following leukapheresis without related clinical adverse events, all recovered. Therefore leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. If more than one leukapheresis is required particular attention should be paid to donors with platelets $< 100 \times 10^9$/L prior to apheresis ; in general apheresis should not be performed if platelets $< 75 \times 10^9$/L.

Insertion of a central venous catheter should be avoided if possible with consideration given to venous access in selection of donors.

Transient cytogenetic modifications have been observed in normal donors following G-CSF use. The significance of these changes is unknown.

Long-term safety follow up of donors is ongoing. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

- In recipients of allogeneic peripheral stem-cells mobilised with GRANOCYTE

  Allogeneic stem-cell grafting may be associated with an increased risk for chronic GVH (Graft Versus Host Disease), and long-term data of graft functioning are sparse.

- Other Special Precautions

  In patients with severe impairment of hepatic or renal function, the safety and efficacy of GRANOCYTE have not been established.

  In patients with substantially reduced myeloid progenitor cells (e.g. due to prior intensive radiotherapy/chemotherapy), neutrophil response is sometimes diminished and the safety of GRANOCYTE has not been

established.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in either healthy donors or patients following administration of Granulocyte-colony stimulating factors (G-CSFs) including lenograstim (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). If enlargement of the spleen is observed during lenograstim therapy, appropriate therapeutic measures should be taken including discontinuing administration of the product. A diagnosis of splenic rupture should be considered when left upper abdominal pain or shoulder tip pain is reported.

Capillary leak syndrome has been reported after G-CSF administration, and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Lenograstim should be discontinued if patients develop symptoms of capillary leak syndrome, and appropriate symptomatic treatment, which may include a need for intensive care, should be given (see section 4.8).

Sickle cell crisis may be potentially associated with the use of lenograstim in patients with sickle cell trait or sickle cell disease. Therefore, physicians should use caution when prescribing Granocyte in patients with sickle cell trait or sickle cell disease.

Glomerulonephritis has been reported in patients and donors receiving lenograstim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of G-CSF. Urinalysis monitoring is recommended.

GRANOCYTE contains phenylalanine, which may be harmful for people with phenylketonuria.

Aortitis has been reported after G-CSF administration in healthy donors and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

Traceability:
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

In view of the sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of GRANOCYTE is not recommended from 24 hours before until 24 hours after chemotherapy ends (see section 4.4).

Possible interactions with other haematopoietic growth factors and cytokines have yet to be investigated in clinical trials.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of lenograstim in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

GRANOCYTE should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether lenograstim is excreted in human milk. The excretion of lenograstim in milk has not been studied in animals. Breast-feeding should be discontinued during therapy with GRANOCYTE.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety profile in children, adolescents, and adults is comparable.

- In Peripheral Stem Cells or Bone Marrow Transplantation

  In double-blind placebo-controlled trials the mean platelet count was lower in patients treated with GRANOCYTE as compared with placebo without an increase in incidence of adverse events related to blood loss and the median number of days following BMT to last platelet infusion was similar in both groups (see section 4.4).

- In Peripheral Stem Cells or Bone Marrow Transplantation and Chemotherapy-Induced Neutropenia

  In clinical trials, the most frequently reported adverse events (15%) were the same in patients treated with either GRANOCYTE or placebo. These adverse events were those usually encountered with conditioning regimens and those observed in cancer patients treated with chemotherapy. The most

commonly reported adverse events were infection/inflammatory disorder of the buccal cavity, sepsis and infection, fever, diarrhoea, abdominal pain, vomiting, nausea, rash, alopecia, and headache.

- In PBPC mobilisation in healthy donors

  The most frequently reported undesirable effects were transient and mild to moderate: pain, bone pain, back pain, asthenia, fever, headache and nausea, increased ALAT, ASAT, blood alkaline phosphatise and LDH.

  Apheresis-related thrombocytopenia and leukocytosis were observed in 42% and 24% respectively in study subjects.

  Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported.

  Allergic reactions including anaphylaxis have been reported very rarely after the first subcutaneous administration of lenograstim.

- Post-marketing life-threatening Adverse Drug Reaction (ADR)

  Capillary leak syndrome which can be life-threatening if treatment is delayed has been reported uncommonly (≥ 1/1000 to < 1/100) in the post-marketing setting following administration of granulocyte-colony-stimulating factors, mostly in cancer patients undergoing chemotherapy (see section 4.4).

<u>Frequency of adverse reactions issued from clinical trials and post-marketing surveillance data.</u> Very common (≥ 10%); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10000); not known (cannot be estimated from the available data).

Medra System Organ Class	Very common	Common	Uncommon	Rare	Very rare	<u>Not known</u>
Investigations	Elevated LDH					C-reactive protein increased
Blood and lymphatic system disorders	Leucocytosis Thrombocytopenia	Enlarged spleen size			Splenic rupture (5)	
Nervous system disorders	Headache Asthenia					
Vascular Disorders			Capillary leak syndrome[6]	Aortitis		Venous thromboembolism Arterial thromboembolism

Respiratory, thoracic and mediastinal disorders			Haemoptysis (8)	Pulmonary edema Interstitial pneumonia (3) Pulmonary infiltrates Pulmonary fibrosis Pulmonary haemorrhage (8)		
Gastrointestinal disorders		Abdominal pain				
Skin and subcutaneous tissue disorders					Cutaneous vasculitis Sweet's syndrome (4) Erythema nodosum Pyoderma gangrenosum Lyell's syndrome	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain (7)	Pain (1)				
Renal and urinary disorders						Glomerulonephritis
General disorders and administration site condition		Injection site reaction				
Immune system disorders					Allergic reaction Anaphylactic shock	
Hepatobiliary disorders	Elevated ASAT/ALAT (2) Elevated Alkaline-phosphatase					

1 / The risk of occurrence of pain is increased in subjects with high peak WBC values, especially when WBC $\geq 50 \times 10^9$/L

2 / Transient increase of ASAT and/or ALAT was observed. In most cases, liver function abnormalities improved after lenograstim discontinuation.

3 / Some of the respiratory reported cases have resulted in respiratory failure or acute respiratory distress syndrome (ARDS) which may be fatal.

4 / Sweet's syndrome, erythema nodosum and pyoderma gangrenosum were mainly described in patients with hematological malignancies, a condition known to be associated with neutrophilic dermatosis, but also in non-

malignant related neutropenia.

5 / Splenic ruptures have been reported in either healthy donors or patients receiving G-CSFs (see section 4.4)

6 / There have been post-marketing reports of life-threatening capillary leak syndrome (see section 4.4)
7 / includes bone pain, back pain, arthralgia, myalgia and pain in extremity
8 / Pulmonary adverse reactions have been reported like dyspnoea, hypoxia or haemoptysis, including very rarely Acute Respiratory Distress Syndrome (ARDS) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard).

4.9. Overdose

The effects of Granocyte overdose have not been established (see section 5.3). Discontinuation of Granocyte therapy usually results in a 50% decrease in circulating, neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

A white blood cell count of approximately 50 x 10^9/L was observed in one patient out of three receiving the highest Granocyte dose of 40 µg/kg/day (5.12 MIU/kg/day) on the 5th day of treatment.

In humans, doses up to 40 µg/kg/day were not associated with toxic side effects except musculoskeletal pain.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, ATC code: L03AA10

Lenograstim (rHuG-CSF) belongs to the cytokine group of biologically active proteins which regulate cell differentiation and cell growth.

Mechanism of action and Pharmacodynamic effects

rHuG-CSF is a factor that stimulates neutrophil precursor cells as demonstrated by the CFU-S and CFU-GM cell count which increases in peripheral blood.

GRANOCYTE induces a marked increase in peripheral blood neutrophil counts within 24 hours of administration.

Elevations of neutrophil count are dose-dependent over the 1-10 µg/kg/day range. At the recommended dose, repeated doses induce an enhancement of the neutrophil response. Neutrophils produced in response to GRANOCYTE show normal chemotactic and phagocytic functions.

As with other hematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells.

Clinical efficacy and safety

Use of GRANOCYTE in patients who underwent Bone Marrow Transplantation or who are treated with cytotoxic chemotherapy leads to significant reductions in duration of neutropenia and its associated complications.

Use of GRANOCYTE either alone or after chemotherapy mobilises haematopoietic progenitor cells into the peripheral blood. These autologous Peripheral Blood Progenitor Cells (PBPCs) can be harvested and infused after high dose cytotoxic chemotherapy, either in place of, or in addition to bone marrow transplantation.

Reinfused PBPCs, as obtained following mobilisation with GRANOCYTE have been shown to reconstitute haemopoiesis and reduce the time to engraftment, leading to a marked decrease of the days to platelets independence when compared to autologous bone marrow transplantation.

A pooled analysis of data from 3 double-blind placebo-controlled studies conducted in 861 patients (n=411 ≥ 55 years) demonstrated a favourable benefit/risk ratio of lenograstim administration in patients over 55 years of age undergoing conventional chemotherapy for *de novo* acute myeloid leukaemia, in the exception of AML with good cytogenetics, i.e. t(8 ;21), t(15 ;17) and inv (16).

The benefit in the sub-group of patients over 55 years appeared in terms of lenograstim-induced acceleration of neutrophil recovery, increase in the percentage of patients without infectious episode, reduction in infection duration, reduction in the duration of hospitalisation, reduction in the duration of IV antibiotherapy. However, these beneficial results were not associated with decreased severe or life-threatening infections incidence, nor with decreased infection-related mortality.

Data from a double-blind placebo-controlled study conducted in 446 patients with *de novo* AML showed that, in the 99 patients subgroup with good cytogenetics, the event-free survival was significantly lower in the lenograstim arm than in the placebo arm, and there was a trend towards a lower overall survival in the lenograstim arm when compared to data from the not good

cytogenetics subgroup.

5.2 Pharmacokinetic properties

Absorption and Distribution

The pharmacokinetics of GRANOCYTE are dose and time dependent.

During repeated dosing (IV and SC routes), peak serum concentration (immediately after IV infusion or after SC injection) is proportional to the injected dose. Repeated dosing with GRANOCYTE by the two administration routes showed no evidence of drug accumulation.

At the recommended dose, the absolute bioavailability of GRANOCYTE is 30%. The apparent volume of distribution (Vd) is approximately 1 L/kg body weight and the mean residence time close to 7 h following subcutaneous dosing.

Elimination

The apparent serum elimination half-life of GRANOCYTE (S.C. route) is about 3-4 h, at steady state (repeated dosing) and is shorter (1-1.5 h) following repeated IV infusion.

Plasma clearance of rHuG-CSF increased 3-fold (from 50 up to 150 mL/min) during repeated S.C. dosing. Less than 1% of lenograstim is excreted in urine unchanged and it is considered to be metabolised to peptides. During multiple S.C. dosing, peak serum concentrations of lenograstim are close to 100 pg/mL/kg body weight at the recommended dosage. There is a positive correlation between the dose and the serum concentration of GRANOCYTE and between the neutrophil response and the total amount of lenograstim recovered in serum.

5.3 Preclinical safety data

In animals, acute toxicity studies (up to 1000µg/kg/day in mice) and sub-acute toxicity studies (up to 100 µg/kg/day in monkey) showed the effects of overdose were restricted to an exaggerated and reversible pharmacological effect.

There is no evidence from studies in rats and rabbits that **GRANOCYTE** is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen.

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder

Arginine

Phenylalanine

Methionine

Mannitol (E421)

Polysorbate 20

Diluted Hydrochloric acid (for pH adjustment)

Solvent

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above + 30°C.

Do not freeze.

For storage conditions after reconstitution/dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

105 micrograms of powder in vial (type I glass) with a rubber stopper (type I

butyl rubber) + 1 mL of solvent in pre-filled syringe (type I glass) with a tip cap + 2 needles (19G and 26G); pack size of 1 or 5.

263 micrograms of powder in vial (type I glass) with a rubber stopper (type I butyl rubber) + 1 mL of solvent in pre-filled syringe (type I glass) with a tip cap + 2 needles (19G and 26G); pack size of 1 or 5.

or

105 micrograms of powder in vial (type I glass) with a rubber stopper (type I butyl rubber) + 1 mL of solvent in ampoule (type I glass); pack size of 1 or 5.

263 micrograms of powder in vial (type I glass) with a rubber stopper (type I butyl rubber) + 1 mL of solvent in ampoule (type I glass); pack size of 1 or 5.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product/solution or waste material should be disposed of in accordance with local requirements.

In view of the possible risk of microbial contamination, pre-filled syringe with solvent is for single use only.

Instructions for preparation

GRANOCYTE vials are for single-dose use only.

GRANOCYTE must be reconstituted before sub-cutaneous or intravenous administration.

Preparation of the reconstituted GRANOCYTE solution

Using a graduated syringe fitted with a needle, aseptically withdraw the entire extractable contents of one ampoule of solvent for GRANOCYTE. Inject the entire contents of the syringe into the corresponding GRANOCYTE vial.

Using the 19G needle provided in the pack, and the pre-filled disposable syringe with the solvent for GRANOCYTE ready for immediate use aseptically add the extractable contents of one pre-filled syringe of solvent for GRANOCYTE to the GRANOCYTE vial.

Agitate gently until completely dissolved. Do not shake vigorously.

The reconstituted parenteral solution appears transparent and free of particles. The reconstituted solution should preferably be used immediately after preparation. For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

Preparation for the subcutaneous administration

Prepare a reconstituted GRANOCYTE solution as described above.

Keeping the needle and the syringe attached to the vial, withdraw the required volume of reconstituted solution from the vial. Replace the needle used for reconstitution and fit the syringe with an appropriate needle for subcutaneous injection.

Keeping the needle 19G and the syringe attached to the vial , withdraw the required volume of reconstituted solution from the vial. Replace the needle used for reconstitution and fit the syringe with the 26G needle provided for subcutaneous injection.

Administer immediately by sub-cutaneous injection (refer to section 4.2 for administration requirements).

Preparation of the infusion solution for the intravenous administration:

When intravenous use GRANOCYTE has to be diluted after reconstitution.

Prepare a reconstituted GRANOCYTE solution as described above.

Keeping the needle and the syringe attached to the vial, withdraw the required volume of reconstituted solution from the vial.

Dilute the reconstituted GRANOCYTE solution to the required concentration by injecting the required volume into either 0.9% sodium chloride or 5% dextrose solution.

Administer by IV route (refer to section 4.2 for administration requirements)

GRANOCYTE is compatible with the commonly used administration sets for injection when diluted either in a 0.9% saline solution (polyvinyl chloride bags and glass bottles) or in a 5% dextrose solution (glass bottles)

Dilution of GRANOCYTE 13 million IU/mL to a final concentration of less than 0.26 million IU/mL (2 μg/mL) is not recommended. 1 vial of reconstituted GRANOCYTE 13 million IU/mL should not be diluted in more than 50 mL.

Dilution of GRANOCYTE 34 million IU/mL to a final concentration of less than 0.32 million IU/mL (2.5 μg/mL) is not recommended. 1 vial of reconstituted GRANOCYTE 34 million IU/mL should not be diluted in more than 100 mL.

7 MARKETING AUTHORISATION HOLDER

Chugai Pharma UK Ltd

Building 4

566 Chiswick High Road

London

W4 5YE

8. MARKETING AUTHORISATION NUMBER(S)

PL 12185/0002

PL 12185/0005 (Water for Injections in pre-filled syringe)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 1993

10 DATE OF REVISION OF THE TEXT

06/03/2026