AUSTRALIAN PRODUCT INFORMATION – GRANOCYTE® (Lenograstim)

1. NAME OF THE MEDICINE

Lenograstim

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GRANOCYTE contains lenograstim, a recombinant glycoprotein equivalent to the human granulocyte colony stimulating factor (G-CSF).

GRANOCYTE 13 contains 105 µg (13.4 million International Units[#]) (IU) lenograstim in 1 mL of reconstituted product.

GRANOCYTE 34 contains 263 µg (33.6 million International Units[#]) (IU) lenograstim in 1 mL of reconstituted product.

The reconstituted product for both strengths of GRANOCYTE is formulated with a hydrochloric acid buffer at pH 6.5 and contains 2.5% mannitol, 1% arginine, 1% phenylalanine, 0.1% methionine and 0.01% polysorbate 20.

Excipient(s) with known effect

Phenylalanine

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

GRANOCYTE is presented as white cake of lyophilised powder for injection in a glass vial with a rubber stopper and a flip off cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

GRANOCYTE is indicated

- to reduce the duration of neutropenia and the severity of infections in patients with non-myeloid malignancy who have either undergone autologous or allogeneic bone marrow transplantation or undergone treatment with established cytotoxic chemotherapy.

[#] as measured by the GNFS-60 *in vitro* bioassay in comparison with the WHO International Standard for human G-CSF)

- to reduce the incidence of infection associated with established cytotoxic chemotherapy.
- to mobilise peripheral blood progenitor cells (PBPCs) either with GRANOCYTE alone, or after myelosuppressive chemotherapy, in order to accelerate haematopoietic recovery by infusion of such cells, after myelosuppressive or myeloablative therapy in patients with non-myeloid malignancies. GRANOCYTE is also indicated to accelerate the engraftment of these cells after their reinfusion.
- to mobilise peripheral blood progenitor cells (PBPCs) in healthy donors.
- in the treatment of severe congenital neutropenia.

4.2 Dose and Method of Administration

GRANOCYTE 13: 105 μg (13.4 million IU) per vial is used in patients with body surface area up to 0.7 m^2.

GRANOCYTE 34: 263 μg (33.6 million IU) per vial is used in patients with body surface area up to 1.8 m^2.

Dosage

In PBPC mobilisation following chemotherapy:

After myelosuppressive chemotherapy, GRANOCYTE should be administered daily at the recommended dose of 150 μg (19.2 million IU) per m^2 per day, clinically equivalent to 5 μg (0.64 million IU) per kg per day, as a subcutaneous (SC) injection starting on the day after completion of chemotherapy until the expected nadir has passed and neutrophil count returns to a normal range compatible with treatment discontinuation.

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

In PBPC mobilisation with GRANOCYTE alone:

GRANOCYTE should be administered daily at the recommended dose of 10 μg (1.28 million IU) per kg per day as a SC 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 of PBPC ($\geq 2.0 \times 10^6$ CD34+ cells/per kg).

In bone marrow transplantation (BMT) and post-PBPC reinfusion:

GRANOCYTE should be administered daily at the recommended dose of 150 μg/m^2/day, clinically equivalent to 5 μg/kg/day as a SC injection, starting the day following reinfusion of PBPC. In BMT, the recommended dose of GRANOCYTE can also be administered as a 30 minute intravenous (IV) infusion (see **Reconstitution and Administration** below).

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 BMT, 50% of patients will achieve neutrophil recovery. When given post-reinfusion of PBPCs, the first dose of GRANOCYTE should be administered at the recommended dose of 150 μg/m^2/day, clinically equivalent to 5 μg/kg/day, at least 24 hours after cytotoxic chemotherapy has ceased and at least 24 hours after reinfusion of PBPCs. The maximum duration of treatment with GRANOCYTE post-PBPC reinfusion should also be defined according to the period required for achievement of acceptable neutrophil counts (ie., >0.5 x 10^9/L for 3 consecutive days or > 1 x 10^9/L for 1 day).

In PBPC mobilisation in healthy donors

In healthy donors, a 10 μg/kg daily dose administered subcutaneously for 5-6 days allows a CD34+ cells collection ≥3.0 x 10^6/kg body weight with a single leukapheresis in 83% of subjects and with 2 leukaphereses in 97%.

In established cytotoxic chemotherapy:

The recommended dose of GRANOCYTE is 150 μg (19.2 million IU) per m^2 per day, clinically equivalent to 5 μg (0.64 million IU) per kg per day.

However, data from clinical studies suggest that a dose of 2 μg (0.256 million IU) per kg per day can reduce the days to neutrophil nadir, increase the total AUC value for neutrophils, and decrease the number of days with a neutrophil count < 1,000 x 10^6/L in patients. It is a matter of clinical judgement whether patients require this treatment.

GRANOCYTE at the recommended dose should be administered daily as a SC injection starting on the day following completion of chemotherapy. Daily administration of GRANOCYTE should continue until the expected nadir has passed and the neutrophil count returns to within the normal range, which usually occurs within 8 to 14 days after starting treatment.

Even if a transient increase of neutrophil takes place within the first 2 days of treatment, with continuation of treatment the subsequent nadir usually occurs earlier and recovers more quickly.

In severe congenital neutropenia:

GRANOCYTE at 150 μg/m^2/day, clinically equivalent to 5 μg/kg/day, should be administered as a SC injection. The initial evaluation period of neutrophil recovery should be 7 to 14 days. Induction doses up to 20 μg (2.56 million IU) per kg may be required. Once obtained, neutrophil recovery may be sustained by continuation of treatment; cautious dose tapering and/or alternate day treatment may be feasible in some patients based on their absolute neutrophil counts (ANC) counts.

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 for either strength of GRANOCYTE.

Children

Safety and efficacy of GRANOCYTE has been established in patients older than 2 years in BMT, after established cytotoxic chemotherapy and in patients older than 4.5 months, with severe congenital neutropenia.

Reconstitution and Administration

- GRANOCYTE vials contain no antimicrobial agent.
- Product is for single-dose use in one patient only.
- Discard any residue.
- Aseptically add 1.0 mL Water for Injections to the GRANOCYTE vial.
- Agitate gently until complete dissolution (about 5 seconds). Do not shake vigorously.
- Administer immediately by SC or IV route.

For SC administration, GRANOCYTE may be administered as a SC bolus or continuous infusion. The volume of SC injection should not exceed 1.0 mL and the site of injection should be alternated to avoid local bruising/bleeding.

For IV injection, dilution should be performed in 0.9% sodium chloride solution or 5% glucose. The solution is compatible with polyvinyl chloride bags and 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.

GRANOCYTE is compatible with the commonly used giving-sets for injection (polyvinyl chloride) when diluted in sodium chloride 0.9% solution.

4.3 Contraindications

GRANOCYTE should not be administered to patients with known hypersensitivity to the product or its constituents.

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

GRANOCYTE should not be administered concurrently with cytotoxic chemotherapy. GRANOCYTE should not be administered to patients suffering from myeloid malignancy.

4.4 Special Warnings and Precautions for Use

Patients with Severe Congenital Neutropenia

Acute myeloid leukaemia (AML) or abnormal cytogenetics have been reported to occur in the natural history of congenital neutropenia without cytokine treatment. Abnormal cytogenetics have been associated with the development of myeloid leukaemia. In patients with congenital neutropenia, it is unknown if therapy with lenograstim accelerates and/or transforms to the development of cytogenetic changes or myeloid leukaemia. Caution should, therefore, be exercised in using GRANOCYTE in patients with congenital neutropenia.

Care should be taken to confirm the diagnosis of severe congenital neutropenia before commencing therapy with GRANOCYTE as it may be difficult to distinguish the disease from myelodysplasia (MDS). The safety and efficacy of GRANOCYTE in the treatment of neutropenia, due to MDS or myeloid leukaemia, have not been established. It is important that serial full blood counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be done before commencement of therapy with GRANOCYTE. The use of GRANOCYTE before diagnostic confirmation of severe congenital neutropenia may mask neutropenia as a diagnostic sign of a disease process other than congenital neutropenia.

If a patient with severe congenital neutropenia develops abnormal cytogenetics, the risks and benefits of continuing GRANOCYTE should be carefully considered.

Malignant Cell Growth

G-CSF 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, acute myelogenous leukaemia (AML) or chronic myelogenous leukaemia have not been established. Therefore because of the possibility of tumour growth, GRANOCYTE should not be used in any myeloid malignancy.

Clinical trials have not established whether GRANOCYTE influences the progression of myelodysplastic syndromes to AML. Caution should be exercised in using GRANOCYTE 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 lenograstim therapy.

Leukocytosis

A leukocyte count greater than 50 x 10^9/L has been observed in none of the 174 patients treated with 5 µg/kg/day (0.64 million IU/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 IU/kg/day). No adverse events directly attributable to this degree of leukocytosis have been reported. In view of the potential risks associated with severe leucocytosis, a white blood cell count should, however, be performed twice weekly during GRANOCYTE therapy. If leukocyte counts exceed 10 x 10^9/L after the expected nadir, GRANOCYTE should be discontinued immediately.

However, during the period of administration of GRANOCYTE for PBPC mobilisation, GRANOCYTE should not be given if the leukocyte count rises to > 50 x 10^9/L.

Pulmonary Adverse Effects

The onset of pulmonary 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 adult respiratory distress syndrome (ARDS). GRANOCYTE should be immediately discontinued and appropriate treatment given.

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

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

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).

Splenic Rupture

Splenic rupture or splenomegaly have been reported during peripheral blood stem cell mobilisation with lenograstim and in patients who received lenograstim for neutropenia (see section 4.1) and the acceleration of haematopoietic recovery post PBPC reinfusion. Changes in haematological parameters and spleen size (e.g. by clinical examination, abdominal ultrasonography) should be monitored. If enlargement of the spleen is observed during therapy with GRANOCYTE, appropriate therapeutic measures should be taken, including discontinuing administration of GRANOCYTE.

A diagnosis of splenic rupture should be considered in donors or patients reporting left upper quadrant abdominal pain or shoulder tip pain.

In Bone Marrow Transplantation

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

With increased doses of chemotherapy

Safety and efficacy of GRANOCYTE have not been established in the context of intensified chemotherapy. GRANOCYTE should not be used to decrease beyond the established limits intervals between chemotherapy cycles and/or to increase single dosage chemotherapy. Indeed, non-myeloid toxicities have been limiting factors in a phase II chemotherapy intensification trial with GRANOCYTE.

In Autologous Peripheral Blood Progenitor Cell (PBPC) Mobilisation and Therapy

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 myelosuppressive 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 each individual patient.

Prior exposure to cytotoxic agents:

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

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

Assessment of progenitor cell yields:

Particular attention should be paid to the method of quantitation of progenitor cell yields as the results of flow cytometric analysis of CD34+ cell numbers vary among laboratories.

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. However, the minimum yield of CD34+ cells is not well defined. Yields higher than $\geq 2.0 \times 10^6$ CD34+ cells/kg are associated with more rapid recovery of haematopoiesis.

In healthy donors

PBPC mobilisation is a procedure without direct benefits for healthy donors and should only be performed in accordance with local regulations.

The efficacy and safety of GRANOCYTE has not been assessed in healthy donors aged over 60 years or below 18 years and therefore the procedure cannot be recommended in these subjects.

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 leucocytosis (WBC > 50×10^9/L) was observed in 24% of subjects studied.

There have been isolated cases of splenic rupture following administration of granulocyte-colony stimulating factors (G-CSFs) – see Section 4.4 Special warnings and precuations for use: Splenic Rupture.

Apheresis-related thrombocytopenia (platelets < 100×10^9/L) was observed in 42% of subjects studied and values < 50×10^9/L were occasionally noted following leukapheresis without related clinical adverse events. All subjects 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 < 100×10^9/L prior to apheresis; in general apheresis should not be performed if platelets < 75×10^9/L.

Insertion of a central venous catheter should be avoided if possible, and therefore consideration should be given to the adequacy of venous access when selecting donors.

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

Data on long term follow-up of donors are available on a small number of subjects. After a period of up to six years, no emerging long term sequelae adverse events have been reported. Nevertheless, a risk of promotion of a malignant myeloid clone is possible. 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. There have been rare reports of myeloproliferative disorder and acute myeloid leukaemia in PBPC donors who received a granulocyte colony-stimulating factor preparation, although a causal relationship has not been established. Therefore, it is recommended that systematic records and tracking of the stem-cell gifts be made by the apheresis centres.

In recipients of allogeneic peripheral blood progenitor cells mobilised with GRANOCYTE

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

In established cytotoxic chemotherapy

The use of GRANOCYTE is not recommended from 24 hours before, until 24 hours after chemotherapy ends.

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

In Peripheral Stem Cells or Bone Marrow Transplantation

Special attention should be paid to platelet recovery in patients recovering from chemotherapy-induced myelotoxicity or from bone marrow transplantation.

Other Precautions

- In patients with substantially reduced myeloid progenitor cells (e.g. due to prior extensive radiotherapy/chemotherapy), neutrophil response is sometimes diminished and the safety of GRANOCYTE has not been established.
- In patients receiving nitrosoureas without bone marrow rescue, efficacy and safety of GRANOCYTE have not been established.
- 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.
- 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.
- GRANOCYTE contains phenylalanine, which may be harmful for people with phenylketonuria.
- 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.
- Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and 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.

Use in hepatic impairment

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

Use in renal impairment

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

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

No data available

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 Interactions with Other Medicines and Other Forms of Interactions

The safety and efficacy of GRANOCYTE given on the same day as myelosuppressive cytotoxic chemotherapy have not been established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of GRANOCYTE should not precede or overlap the administration of cytotoxic chemotherapy. It is recommended that GRANOCYTE should start on the day following completion of chemotherapy.

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

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

Reproduction and fertility were unaffected by GRANOCYTE in mice at doses up to 1,000 μg/kg/day IV, and in rats at doses up to 100 μg/kg/day IV.

Use in pregnancy – Category B3

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

GRANOCYTE has been shown to have adverse effects in pregnant rabbits when given doses of 100 μg/kg/day IV. There are no adequate and well controlled studies in pregnant women.

In rabbits, increased abortion and embryolethality were observed in animals treated with GRANOCYTE at 100 μg/kg/day IV. Fetal weights were also reduced with this dose and to a lesser extent with 10 μg/kg/day. However, reductions in maternal weight gain and food

consumption were also seen with both doses. Similar adverse findings were not seen in a corresponding rat study, with the same doses, and there was no evidence for teratogenicity in either species.

Use in lactation

Studies in animals have shown that GRANOCYTE is excreted in the milk of lactating rats. It is not known whether GRANOCYTE is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if GRANOCYTE is administered to a nursing woman.

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 Adverse Effects (Undesirable Effects)

Frequency of adverse reactions issued from clinical trials and post-marketing surveillance data. Very common (≥ 10%); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Table 1

Medra System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Investigations	Elevated LDH					C-reactive protein increased
Blood and lymphatic system disorders	Leukocytosis 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	Pulmonary oedema[3] Interstitial pneumonia Pulmonary infiltrates Pulmonary fibrosis Pulmonary haemorrhage		
Gastrointestinal disorders		Abdominal pain				
Skin and subcutaneous tissue disorders					Cutaneous vasculitis Sweet's syndrome[4] Erythema nodosum Pyoderma gangrenosum Lyell's syndrome	

Medra System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[7]	Pain[1]				
General disorders and administration site condition		Injection site				
Immune system disorders					Allergic reaction Anaphylactic shock	
Hepatobiliary disorders	Elevated ASAT/ALAT[2] Elevated Alkaline-phosphatase					
Renal and urinary disorders:						Glomerulonephritis

[1] The risk of occurrence of pain is increased in subjects with high peak WBC values, especially when WBC ≥ 50 x 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 both healthy donors and patients receiving G-CSFs

[6] There have been post-marketing reports of life-threatening capillary leak syndrome

[7] Includes bone pain, back pain, arthralgia, myalgia and pain in extremity

In BMT

Special attention should be paid to platelet recovery since in double blind, placebo-controlled trials the mean platelet count may have been slightly lower in patients treated with GRANOCYTE as compared to placebo vehicle. However, this did not result in an increase in incidence of adverse experiences related to blood loss and the median number of days following BMT to last platelet infusion was similar in both GRANOCYTE and placebo groups.

In placebo-controlled trials, the most frequently reported side effects (> 15% in at least one treatment group), occurred with equal frequency in patients treated with GRANOCYTE or placebo. These were infection/inflammatory disorder of buccal cavity, fever, diarrhoea, rash, abdominal pain, vomiting, alopecia, sepsis and infection.

In placebo-controlled trials after BMT, the incidence of GVH disease was similar in patients treated with GRANOCYTE or placebo.

In PBPC Mobilisation and Therapy

In clinical practice, PBPCs are replacing BMT for a number of reasons including the reduction in time to platelet recovery. In the clinical trials carried out in patients and healthy volunteers undergoing PBPC mobilisation, as well as in patients undergoing PBPC reinfusion, GRANOCYTE was well tolerated. Side effects were generally mild. The most frequently encountered adverse events were bone pain, headache and malaise. There have been isolated cases of splenic rupture in subjects undergoing peripheral blood stem cell mobilisation with granulocyte-colony stimulating factors (G-CSFs) – see Section 4.4 Special warnings and precautions for use: Splenic Rupture.

In Chemotherapy-induced Neutropenia

In placebo-controlled trials, GRANOCYTE appeared safe with equal incidence of reported adverse experiences in patients treated with GRANOCYTE or placebo. The most commonly reported side effects were alopecia, nausea, vomiting, fever, headache, similar to that observed in cancer patients treated with chemotherapy.

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

A higher incidence of bone pain (about 10% higher) usually controlled with simple analgesics such as paracetamol, and injection site reaction (about 5% higher) was reported when patients were treated with GRANOCYTE.

In Severe Congenital Neutropenia

Special attention should be paid to the possible occurrence of any of the following during long term treatment:

- cutaneous rash/risk of vasculitis
- leukocytosis
- thrombocytopenia
- splenomegaly
- potential transformation to a myeloid malignancy

- risk of osteopenia.

Cytogenetic abnormalities, transformation to MDS and AML have been observed in patients treated with G-CSF preparations for congenital neutropenia.

Based on the analysis of long term data on patients treated with another brand of G-CSF, the greatest risk of developing these abnormalities (MDS, AML, cytogenetic abnormalities) seems to be in the subset of patients with congenital neutropenia. In patients with congenital neutropenia treated with G-CSF for up to 5 years, the rate of MDS and AML is reported to be fewer than 3 cases per 100 patient-years of exposure. In patients with non-congenital types of neutropenia (cyclic and idiopathic), the rate is fewer than 1 case per 100 patient-years of exposure. Leukaemic transformation has also been observed in congenital neutropenia patients prior to the use of G-CSF. In patients treated with G-CSF who had previously documented normal cytogenetic evaluations, cytogenetic abnormalities, including monosomy 7, have been reported.

It is unknown whether the development of abnormalities, such as MDS or AML, is related to chronic daily administration of G-CSF or to the natural history of congenital neutropenia. It is therefore recommended that an annual bone marrow and cytogenetic evaluation should be considered in patients with congenital neutropenia.

In healthy donors

There have been rare reports of myeloproliferative disorder and acute myeloid leukaemia in PBPC donors who received a granulocyte colony-stimulating factor preparation, although a causal relationship has not been established (see Section 4.4 Special warnings and precautions for use – 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 and LDH. Other adverse events reported in healthy donors, regardless of causality: cerebrovascular disorder, myocardial infarction, cardiac arrest, iritis, anaphylactoid reactions, gouty arthritis, and non-Hodgkins lymphoma.

Other Adverse Effects

Capillary leak syndrome which can be life-threatening if treatment is delayed has been reported uncommonly in the post-marketing setting following administration of granulocyte-colony-stimulating factors, mostly in cancer patients undergoing chemotherapy.

Pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or ARDS, which may be fatal. Pleural effusion has also been reported.

Arthralgia has been reported.

Post-Marketing Experience Relevant to All Indications

Cases of aortitis have been reported rarely (> 1/10,000 and < 1/1,000) in cancer patients and in healthy subjects treated with filgrastim.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

In animals, acute toxicity studies (up to 1,000 µg/kg/day in mice) and subacute toxicity studies (up to 100 µg/kg/day in monkeys) showed the effects of overdose were restricted to an exaggerated and reversible pharmacological effect.

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

The effects of GRANOCYTEoverdosage have not been established. 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 million IU/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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, ATC code: L03AA10

Mechanism of action

GRANOCYTE (lenograstim) belongs to the cytokine group of biologically active proteins which regulate cell differentiation and cell growth.

G-CSF is a factor which stimulates the neutrophil precursor cells as demonstrated by the CFU-S and CFU-GM cell count increases in peripheral blood in the mouse. GRANOCYTE induces a marked increase in peripheral blood neutrophil counts within 24 hours.

Elevations of neutrophil count are dose-dependent over the 1-10 µg/kg/day range. At the recommended dose (5 µg/kg/day) 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.

Use of GRANOCYTE in patients who have undergone bone marrow transplantation (BMT) or who are treated with cytotoxic chemotherapy leads to significant reductions in duration of neutropenia and severity of infections.

Clinical trials

In Peripheral Blood Progenitor Cell Mobilisation and Therapy

Use of GRANOCYTE, either alone or after chemotherapy mobilises haematopoietic progenitor cells into the peripheral blood. These peripheral blood progenitor cells (PBPCs) can be harvested and infused after 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 accelerate the reconstitution of haematopoiesis and reduce the time to engraftment, leading to a marked decrease in the number of days to platelet independence when compared to bone marrow transplantation.

In an open label phase II study, SC GRANOCYTE 10 μg/kg/day was administered to 24 patients after standard or intensified induction for advanced breast cancer. The level of granulocyte-monocyte colony forming cells (GM-CFC) was higher after one course of chemotherapy plus GRANOCYTE than after the initial lenograstim alone. Mobilisation was not affected by the chemotherapy dose levels used. Progenitor cell mobilisation was maximal between 6 and 7.5 days after GRANOCYTE alone and between 11 and 13 days after chemotherapy plus GRANOCYTE coinciding with the peak white cell counts obtained. The median number of GM-CFC collected in a single apheresis was 2.17×10^5/kg (n=9) after cycle 1, and 1.7×10^5/kg (n=13) after any cycle. This study demonstrated clearly the ability of GRANOCYTE to mobilise progenitor cells into the circulation, and showed that the combination of chemotherapy and GRANOCYTE mobilised more colony-forming cells than lenograstim alone. In another open label Phase II study, the ability of reinfused GRANOCYTE-primed PBPC together with GRANOCYTE post moderate intensity chemotherapy to facilitate platelet recovery in 21 advanced breast cancer patients, was investigated. Each patient received a 6-day course of SC GRANOCYTE 150 μg/m^2/day prior to commencing an intensified FAC regimen. One group of patients had GRANOCYTE only, a second group had GRANOCYTE plus PBPC collected after cycle 1, a third group had GRANOCYTE plus PBPC contained in 450 mL blood and collected after steady state and next 5 cycles and the fourth group had PBPC collected in the steady state after GRANOCYTE alone (no GRANOCYTE given after FAC chemotherapy). The peak levels of CD34+ cells and GM-CFC found in the blood after GRANOCYTE alone were 32×10^6/L and 7.2×10^5/L respectively and occurred around day 6. This study confirms that GRANOCYTE alone at a dose of 150 μg/m^2/day can mobilise progenitor cells; and chemotherapy plus GRANOCYTE yields higher progenitor cell levels although the levels decline after repeated administration of chemotherapy.

A Phase III multicentre study had been undertaken in 90 patients with Hodgkin's disease and non-Hodgkin's lymphoma treated with ablative chemotherapy (BEAM). The first part of the study was non-randomised where patients were mobilised with 1.5 g/m^2 cyclophosphamide followed by SC GRANOCYTE 263 μg per day from the day after cyclophosphamide (day 2) until day 10. PBPCs were harvested by leukapheresis on days 10 and 11. In the second part of the study, patients were randomised to receive SC GRANOCYTE 263 μg per day, or no growth factor, from day 1 post high dose therapy (BEAM) and PBPC reinfusion (day 0), until neutrophil recovery to $> 0.5 \times 10^9$/L for 3 days or $> 1 \times 10^9$/L for 1 day. Of the 62 evaluable patients, 34 received GRANOCYTE and 28 no growth factor. There was a significant difference observed between the treatment groups (p=0.0001) in the time to neutrophil recovery. The median time to neutrophil recovery was 9 days in the GRANOCYTE arm versus 13 days in the no growth factor arm. Similarly, there was a significant difference between the

treatment groups for days to hospitalisation (p=0.0002). Patients receiving GRANOCYTE stayed in hospital for a median of 13 days compared with patients receiving no GRANOCYTE who stayed in hospital a median of 15.5 days. The first part of the study confirmed that the combination of cyclophosphamide and GRANOCYTE 1 vial (263 μg) per day is an effective mobilisation regimen in most patients with lymphoma. The second part of the study indicates that the use of GRANOCYTE 1 vial (263 μg) per day post high dose chemotherapy, and reinfusion of PBPCs, shortens the period of neutropenia and decreases the number of days of hospitalisation.

In Healthy Donors

The efficacy of GRANOCYTE for PBPC mobilisation has been demonstrated in 4 studies involving a total of 124 healthy donors. In these studies, 106 subjects received the proposed dose of 10μg/kg/day subcutaneously for 5-6 days, 76 of whom underwent leukapheresis.

The minimum progenitor cell yield considered to be necessary for successful engraftment in autologous PBPC transplantation is 2.0 x 10^6 CD34+ cells/kg. The median yields obtained in all four studies in healthy donors were found to be well above this level. In the largest study, CSF-312, (n=62) GRANOCYTE was found to mobilise progenitor cells in the majority of normal individuals to a level such that > 3 x 10^6/kg CD34+ could be collected in one pheresis.

Study GCS-306, a Phase I randomised crossover study in 32 healthy male volunteers, investigated the ability of GRANOCYTE and NEUPOGEN® (filgrastim) to mobilise PBPCs when used at doses of 10 mcg/kg/day for five days. Although peak levels of white blood cell (WBC) counts were almost identical during the first period of therapy with either agent, peak PBPC values and leukapheresis yields were significantly higher in patients treated with GRANOCYTE, as demonstrated below:

Table 2

	GRANOCYTE	**NEUPOGEN**	**P value**
Mean peak values			
CD34+ cells (x10^6/L)	103.6 ± 38.2	82.2 ± 35.2	0.0001
GM-CFC (x 10^5/L)	14.6 ± 8.4	10.2 ± 4.6	0.0012
Leukapheresis yield			
CD34+ cells (x 10^6/kg)	5.4 ± 1.3	4.2 ± 0.8	0.05

In Established Cytotoxic Chemotherapy

A cross-over comparison of the efficacy of subcutaneously administered GRANOCYTE at 2 and 5 μg/kg/day during two consecutive cycles of a standard dose of myelosuppressive chemotherapy in patients with non-leukaemic malignancy has shown that both doses of GRANOCYTE provided similar levels of prophylaxis against the incidence, severity and duration of neutropenia and infectious complications.

In Severe Congenital Neutropenia

A European phase II, open label, multicentre study was conducted using lenograstim in 19 patients suffering from congenital agranulocytosis, a form of severe chronic neutropenia. The

patients were of both sexes ranging in age from 4.5 months to 23 years with a median of 5 years, and the disease was of sufficient severity as assessed by a recent history of infection, either recurrent under prophylactic antibiotic therapy or having led to hospitalisation. The treatment period ranged from 4 to 35 months (median duration of 27 months).

Induction doses of lenograstim 5 μg/kg/day by SC injection induced a significant increase in absolute neutrophil counts (ANC ≥ 1,000/μL) in 15 patients, the remaining 4 required doses of 10 – 20 μg/kg/day. Stable neutrophil counts above 0.5 x 10^9/L were achieved in 18 of the 19 patients and mostly obtained at a maintenance dose of 5 μg/kg/day. Intermittent treatment was possible in a minority of patients, usually those who achieved stable neutrophil counts at low dose levels, often below 5 μg/kg/day.

The frequency and severity of infections were markedly reduced in all but one patient. Growth and weight were seen to increase in line with observed prior growth rates. The number of curative antibiotic therapies and hospitalisations were reduced. Objective and subjective measurements of the quality of life also showed some improvement.

Despite prolonged lenograstim exposure, there were very few adverse events related to lenograstim administration. The main ones noted in this study were leucocytosis, mild hyperuricaemia, erythema at the site of injection, lumbar pain, splenomegaly and grade I thrombocytopenia. In only one patient was treatment with lenograstim discontinued; this patient, on three occasions, developed a rash which was thought to be vasculitis. However, the biopsy slide was subsequently re-examined and the diagnosis changed to acute suppurative pustulosis which subsequently recovered.

5.2 Pharmacokinetic Properties

The pharmacokinetics of GRANOCYTE show dose and time dependencies.

Following SC administration of GRANOCYTE 5 μg/kg/day to healthy volunteers, peak plasma concentrations are obtained at 6 ± 2.6 hours.

At the end of repeated dosing (IV and SC routes), peak serum concentrations are proportional to the injected dose. Repeated dosing with GRANOCYTE by both injection routes resulted in no evidence of drug accumulation.

The absolute bioavailability of SC GRANOCYTE decreases in a dose-dependent manner from approximately 62% to 24% in the 0.5 - 10 μg/kg dose range. At the recommended dose (5 μg/kg/day), the absolute bioavailability of GRANOCYTE is 30 ± 5% and the apparent distribution volume (Vd area) is approximately 52 ± 5 mL/kg body weight.

During multiple SC dosing, peak serum concentrations of GRANOCYTE 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 GRANOCYTE recovered in serum.

The pharmacokinetic profile of GRANOCYTE is similar in healthy volunteers and cancer patients with elimination half-life ($t_{1/2\beta}$) values of 2.3 - 3.3 hrs (volunteers); 2.8 - 7.5 hrs (cancer patients) following SC administration and 0.8 - 2.1 hrs (volunteers); 1.1 - 4.0 hrs (cancer patients) following IV administration.

Plasma clearance of lenograstim increased 3-fold (from 50 up to 150 mL/min) during repeated SC dosing. GRANOCYTE is poorly excreted in urine as intact compound (less than 1% of the dose) and is considered to be metabolised to peptides.

5.3 Preclinical Safety Data

Genotoxicity

Lenograstim was not mutagenic in *Salmonella typhimurium*, did not increase the frequency of chromosomal aberrations in cultured Chinese hamster lung cells, and was negative in a mouse micronucleus test.

Carcinogenicity

No carcinogenicity studies have been conducted with GRANOCYTE.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Arginine

Hydrochloric acid

Mannitol

Methionine

Phenylalanine

Polysorbate 20

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After reconstitution in 1.0 mL Water for Injections as recommended, the resultant solution is stable for 24 hours at 25°C. No decrease in activity was observed after dilution to a final concentration of not less than 0.26 million IU/mL (2 μg/mL) for GRANOCYTE 13 or 0.32 million IU/mL (2.5 μg/mL) for GRANOCYTE 34 when the dilution was stored at temperatures up to 30°C for 24 hours.

To reduce microbiological hazard, it is recommended to use reconstituted solutions as soon as practicable after dilution and if storage is necessary, to hold at 2-8°C for not more than 24 hours.

6.4 Special Precautions for Storage

GRANOCYTE vials should be stored below 30°C.

Short exposure of the vials to elevated temperatures (up to 4 weeks at 40°C) does not affect the product stability.

6.5 Nature and Contents of Container

GRANOCYTE is presented as a white cake (lyophilised powder) in a 5 mL Type I glass vial (single pack) with an elastomeric stopper, aluminium seal and flip-off top.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Lenograstim is expressed in a mammalian host cell system, Chinese hamster ovary (CHO) cells. Lenograstim has a molecular weight of about 20,000 Daltons and consists of 174 amino acids and approximately 4% carbohydrate. The amino acid sequence analysis of lenograstim reveals that it is identical to native G-CSF.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

14 December 2001

10. DATE OF REVISION

26 May 2021

Summary Table of Changes

Section changed	Summary of new information
Section 4.4	Addition of Venous and arterial thromboembolic events and Traceability statement
Section 4.8	Addition of post-marketing adverse effects under investigations (CRP increased) and under vascular disorders (venous thromboembolism, arterial thromboembolism)

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