Granocyte® 34
Lenograstim

Powder and solvent for solution for injection

SANOFI

IDENTIFICATION OF THE MEDICINAL PRODUCT

Name of Product

GRANOCYTE 34 (33.6 x 10^6 IU/ml) lyophilized powder in vial and solvent in prefilled syringe for injection or infusion (subcutaneous injection or intravenous infusion).

Qualitative and Quantitative composition

Lyophilisate :	per vial
Lenograstim* (INN) 33.6 x 10^6 IU**	263 micrograms
L-Arginine	10 mg
L-Phenylalanine	10 mg
L-Methonine	1 mg
Mannitol	25 mg
Polysorbate 20	0.1 mg
Hydrochloric acid	q.s pH 6.5
Solvent :	per pre-filled syringe
Water for injections	1 ml

* Recombinant glycoprotein (rHuG-CSF) equivalent to the human Granulocyte Colony Stimulating Factor isolated from CHU-2, a human cell line. Lenograstim is expressed and glycosylated in a mammalian host cell system, Chinese Hamster Ovary (CHO) cells.

** Measurement by the GNFS-60 *in vitro* bioassay in comparison with the WHO International Standard for human G-CFS.

Pharmaceutical form

Powder and solvent for solution for injection.

CLINICAL PARTICULARS

Therapeutic indications

- Reduction in the duration of neutropenia and associated complications in patients (with non-myeloid neoplasia) receiving an autologous or allogeneous bone marrow transplantation.
- Reduction in the duration of neutropenia and associated complications in patients during chemotherapy known to be associated with a significant incidence of febrile neutropenia.
- Mobilisation of Peripheral Blood Progenitor Cells (PBPCs).

Note: The safety of the use of GRANOCYTE with anticancer agents characterized by cumulative myelotoxicity or predominant toxicity towards the platelet lineage (nitrosourea, mitomycin) has not been established. In these situations, the use of GRANOCYTE might even increase the toxicities, particularly towards platelets.

Dosage and method of administration

Therapy should only be given in collaboration with an experienced oncology and/or haematology centre. The recommended dose of GRANOCYTE 34 is 150 micrograms (19.2 x 10^6 IU) per m^2 and per day, a dose equivalent in efficacy to that of 5 micrograms (0.64 x 10^6 IU) per kg and per day:

- in chemotherapy-induced neutropenia for bone Marrow Transplantation (BMT),
- following established cytotoxic chemotherapy,
- in the mobilization of PBPCs after chemotherapy.

GRANOCYTE 34 is used in patients with a body surface area of up to 1.8 m^2.
In the mobilization of PBPCs when GRANOCYTE is used alone, the recommended dose is 10 micrograms (1.28 x 10^6 IU) per kg and per day.

Adults:

After Bone Marrow Transplantation
GRANOCYTE 34 should be administered daily at the recommended dose of 150 micrograms (19.2 x 10^6 IU) per m^2 and per day by IV infusion lasting 30 minutes, diluted in isotonic saline serum or by subcutaneous injection starting the day following transplantation (see section "Instructions for use and handling"). Treatment should continue until the expected date of the nadir has passed and the neutrophil count has returned to a stable level compatible with treatment discontinuation, with a maximum of 28 days of treatment if necessary.
It is anticipated that by day 14 following bone marrow transplantation, 50% of patients will have recovered to a normal neutrophil count or to a count compatible with the discontinuation of the treatment.

After established cytotoxic chemotherapy
GRANOCYTE 34 should be administered daily at the recommended dose of 150 micrograms (19.2 x 10^6 IU) per m^2 and per day subcutaneous injection, starting the day following the end of chemotherapy (see section "instructions for use and handling"). Administration of GRANOCYTE 34 should continue until the expected date of the nadir has passed and the neutrophil count has returned to a stable level compatible with treatment discontinuation, with a maximum of 28 days of treatment if necessary.
A transient increase in neutrophil count can occur during the first two days of treatment, however the treatment must not be discontinuated, because with the continuation of treatment the nadir usually occurs earlier and recovery is quicker.
In PBPCs mobilization after chemotherapy, GRANOCYTE 34 should be administered daily at the recommended dose of 150 micrograms (19.2 x10^6 IU) per m^2 and per day by subcutaneous injection, starting the day after the end of chemotherapy until the expected date of the nadir has passed and the neutrophil count has returned to a stable level compatible with treatment discontinuation.
Leukapheresis should be performed when the post nadir leukocyte count is rising or after evaluation of $CD34^+$ cells count obtained by a validated method. In patients, who have not been intensively pretreated by chemotherapy, one leukapheresis is generally sufficient to obtain the minimum acceptable threshold of ≥ 2 x 10^6 $CD34^+$ cells collected per kg.
In order to mobilize PBPCs with GRANOCYTE 34 alone, it should be administered daily at the recommended dose of 10 micrograms (1.28 x 10^6 IU) per kg and per day by a subcutaneous injection for 4 to 6 days.
Leukapheresis should be performed between day 5 and 7.
In patients who have not been intensively pretreated by chemotherapy, one leukapheresis is generally sufficient to obtain the minimum acceptable threshold of ≥ 2 x 10^6 $CD34^+$ cells collected per kg.
In healthy donors, a 10 µg/kg daily dose administered subcutaneously for 5–6 days allows a $CD34^+$ cells collection ≥ 3 x 10^6/kg body weight with a single leukapheresis in 83% of subjects and with 2 leukapheresis in 97%.
Treatment must be administered only in cooperation with an establishment experienced in oncology and/or haematology.

Elderly:
Clinical trials with GRANOCYTE 34 included a small number of patients older than 70 but specific studies have not been performed in the elderly: therefore, specific dose recommendations cannot be made.

Children:

The safety and efficacy of GRANOCYTE 34 have been established in children older than 2 in bone marrow transplantation.

Contraindications

GRANOCYTE 34 is contraindicated in patients with known hypersensitivity to the product or to one of its constituents.

GRANOCYTE 34 should not be used to increase the dose intensity of myelotoxic chemotherapy beyond established doses and combinations since the drug could reduce myelotoxicity but has no effect on the general toxicity of chemotherapy.

GRANOCYTE should not be administered concurrently with cytotoxic chemotherapy.

GRANOCYTE should not be administered to patients:

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

Warnings and precautions for use

Malignant cell growth:

G-CSFs can promote growth of myeloid cells *in vitro* and similar effects may be observed in some non-myeloid cells *in vitro.*

The safety and efficacy of GRANOCYTE 34 in patients with myelodysplasia syndrome, secondary acute myeloid leukemia or chronic myelogenous leukemia have not been established. Therefore, GRANOCYTE 34 should not be used in these indications. Particular care should be taken to distinguish blast transformation of chronic myeloid leukemia from acute myeloid leukemia.

Clinical trials have not established whether GRANOCYTE 34 has an effect on the progression of myelodysplasic syndrome into acute myeloid leukemia.

Special caution is recommended when using GRANOCYTE in any pre-leukemic syndrome situation.

As some non-specific tumors may exceptionally express a G-CSF receptor, special caution is recommended as unexpected tumor regrowth may occur during rHuG-CSF therapy.

Hyperleukocytosis:

During clinical trials, a leukocyte count more than 50 x 10^9/l has never been observed in any of the 174 patients treated with 5 micrograms per kg per day (0.64 x 10^6 IU/kg/day) following BMT. A white blood cells count greater than 70 x 10^9/l has been observed in less than 5% of patients who received chemotherapy and were treated with GRANOCYTE 34 at 5 micrograms per kg per day (0.64 million IU/ kg/day). No adverse events directly attributable to this degree of hyperleukocytosis have been reported.

In view of the potential risks associated with severe hyperleukocytosis, a white blood cell count should be performed at regular intervals during GRANOCYTE 34 therapy.

If the leukocyte count exceeds 50 x 10^9/L after the expected date of the nadir, GRANOCYTE 34 should be discontinued immediately.

When GRANOCYTE 34 is used to mobilize PBPCs, suspension of treatment is recommended if leukocyte count exceeds 70 x 10^9/L.

Pulmonary adverse effects:

The onset of pulmonary signs, such as cough, fever and dyspnoea, in associated with radiological signs of pulmonary infiltrate and deterioration pulmonary function may be preliminary signs of adult respiratory distress syndroms (ARDS).

GRANOCYTE should be discontinued and appropriate treatment should be given.

In Bone marrow transplantation

The effect of GRANOCYTE 34 on the incidence and severity of acute and chronic graft-versus-host disease has not been accurately determined.

Risks associated with intensification of chemotherapy doses:
The safety and efficacy of GRANOCYTE 34 remains to be established in the context of intensified chemotherapy.
GRANOCYTE 34 should not be used to reduce the intervals between chemotherapy courses beyond the established limits, nor to increase the established doses of chemotherapy. In a phase II chemotherapy intensification trial with GRANOCYTE 34, non-myeloid toxicities have become limiting factors.

Capillary leak syndrome
Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. 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 "Undesirable effects").

Glomerulonephritis
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 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.

Special precaution in PBPC mobilization:

Choice of mobilization method
Clinical trials carried out in the same patient population have shown that PBPCs mobilization was higher when GRANOCYTE 34 is used after chemotherapy than when used alone (measurements being made in the same laboratory). However, the choice between these two methods of mobilization should take into consideration the overall therapeutic objectives in each individual patient.

Previous exposure to cytotoxic agents and/or radiotherapy
In patients who have undergone previous intensive chemotherapy and/or radiotherapy, it may be difficult to obtain the minimum acceptable threshold of 2 X 10^6 $CD34^+$ cells per kg, and then a sufficient hematological recovery.
Transplantation of PBPCs should be planned early in the treatment course of patients and particular care paid to the number of PBPCs mobilized before administration of high-dose chemotherapy. If yields prove insufficient, transplant program must be replaced by other forms of treatment.

Determination of PBPC yields
Particular care should be paid to the method of quantification of PBPCs as the results of flow cytometric analysis of $CD34^+$ cell vary among laboratories. The recommendation of a minimum threshold of $\geq 2 \times 10^6$ $CD34^+$ cells per kg to obtain a correct haematological recovery is based upon results published in the literature. However, the minimum threshold is not clearly defined. Yields higher than 2×10^6 $CD34^+$ cells per kg are associated with faster recovery, including platelets, while lower yields are associated with slower recovery.

In Healthy Donors
The PBPC mobilization which is a procedure without direct benefit for healthy donors should be considered imperatively in accordance with local regulations as a for a bone marrow donation when they are established.
The efficacy and safety of GRANOCYTE 34 has not been assessed in donors aged over 60 years.

Therefore the procedure cannot be recommended in these patients. Based on some local regulation and lack of studies, minors donors should not be considered.
PBPC mobilization should be considered for donors who fit usual clinical and laboratory eligibility criteria for bone marrow donation.
Marked leukocytosis (WBC ≥ 50 x 10^9/L) was observed in 24% of subjects studied.
Thrombocytopenia (platelets < 100 x 10^9/L) , aphaeresis-related, was observed in 42% of subjects studies and values < 50x10^9/L were occasionally noted following leukapheresis without related clinical adverse events and with normal value-back in every cases.
In any case mobilization of peripheral blood progenitor cells should not be performed in donors who are treated with anticoagulants or who have shown defects in haemotasis. If more than one leukapheresis is required, particular attention should be paid to donors with a platelets < 100 x 10^9/L prior to aphaeresis : in general aphaeresis should not be performed if platelets < 75 x 10^9/L.
Insertion of a central venous catheter should be avoided if possible with consideration given given to venous access in selection of donors. Data on long term follow-up of donors are available on a small number of subjects.
Transient cytogenetic changes have been observed in healthy donors following use of G-CSF. The implications of these changes are not known.
Up to 6 years, no emerging long-term adverse events have been reported after donation of PBPC. Nevertheless a risk of promotion of a malignant myeloid clone is possible. Therefore, it is recommended that systematic record and tracking of same of the stem cell gift be made by the aphaeresis centers.

In allogenic peripheral stem-cells recipients obtained after mobilization by GRANOCYTE
Allogenic stem-cell grafting may be associated with an increased risk for chronic Graft Versus Host Disease (GVH), and long-term data of graft functioning are sparse.

Other precautions
The safety and efficacy of GRANOCYTE 34 have not been established in patients with impaired renal or liver function.
In patients with decreased bone marrow reserves, for example due to prior intensive chemotherapy/ radiotherapy, neutrophil response is sometimes decreased and the safety of GRANOCYTE 34 has not been established.

Interactions with other medicines and other forms of interaction
Use of GRANOCYTE 34 is not recommended during the 24-hours period preceding or following chemotherapy, because of the sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy. Possible interactions with other growth factors of cytokines remain to be determined by clinical trials.

Pregnancy and lactation
The safety of GRANOCYTE 34 has not been established in pregnant women.
Animal studies in the rat and rabbit have failed to show any evidence of a teratogenic effect of GRANOCYTE 34. An increased spontaneous abortion rate was seen in the rabbit, but no malformations were found.
During pregnancy, the potential risk of GRANOCYTE 34 to the fetus must be weighed against the expected therapeutic benefit.
In the absence of data concerning penetration in the breast milk, treatment with GRANOCYTE 34 is not recommended during lactation.

Effects on the ability to drive or operate machines
None.

Undesirable effects

In Bone Marrow Transplantation

Particular attention must be paid to platelet recovery, since in controlled trials, the mean platelet count was lower in patients treated with GRANOCYTE 34 than in those who were given a placebo. However this did not lead to increased bleeding events and the median number of days between the transplantation and the last platelet transfusion was similar in both groups.
In controlled trials, the incidence of adverse events most frequently reported (15% in at least one of the treated groups) was identical in patients treated with GRANOCYTE 34 or placebo.
These adverse events were those usually observed in conditioning protocols and were apparently not attributable to GRANOCYTE 34. The events consisted of: stomatitis, fever, diarrhea, rash, abdominal pain, vomiting, alopecia, septic episod and infection.

In chemotherapy-induced neutropenia
The safety of GRANOCYTE 34 combined with cytotoxic agents with cumulative bone marrow toxicity or predominant toxicity vis-a-vis the platelet lineage (nitrosourea, mitomycin) has not been confirmed. The use of GRANOCYTE 34 might even lead to increased platelet toxicity in such circumstances.
In trials, the incidence of adverse events reported was the same in patients treated with GRANOCYTE 34 or placebo.
Effects most frequently reported were similar to those seen in patients treated with chemotherapy: alopecia, nausea, vomiting, fever and headache.
Bone pain and reactions at the injection site have been reported with a slightly higher incidence (about 10% and 5% respectively) in patients treated with GRANOCYTE 34.

PBPC mobilization in the peripheral blood
When GRANOCYTE is administered to healthy subjects, the most commonly reported clinical adverse events were headache in 30%, bone pain in 23%, back pain in 17.5%, asthenia in 11%, abdominal pain in 6% and pain in 6% of subjects.
The risk of occurrence of pain is increased in subjects with high peak white blood cells values, especially when white blood cells $\geq 50 \times 10^9$/L.
Marked leukocytosis $\geq 50 \times 10^9$/L was reported in 24% of donors and thrombocytopenia (platelets $< 100 \times 10^9$/L) aphaeresis-related in 42%.
Transient increase of ASAT and/or ALAT was observed in 12% of subjects and transient increase of alkaline phosphatase in 16%.

Other undesirable effects
Pulmonary infiltrates have been reported, in some cases with an outcome respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal.
In very rare cases, allergic reactions including isolated cases of anaphylactic shock have been reported during the course of GRANOCYTE 34 treatment.
Very rare cases of cutaneous vasculitis have been reported in patients treated with GRANOCYTE 34.
Very rare cases of Sweet's syndrome (acute febrile dermatosis), erythema nodosum and pyoderma gangrenosum have been reported. They were mainly described in patients with haematological malignancies, a condition known to be associated with neutrophilic dermatosis, but also in nonmalignant related neutropenia.
Very rare cases of Lyell syndrome have also been reported.
Increase of ASAT, ALAT and/or alkaline phosphatase has been reported during lenograstim treatment. In most cases, liver function abnormalities improved after treatment discontinuation.

Vascular disorders
Uncommon: Capillary leak syndrome
Rare frequency : Aortitis

Renal and urinary disorders:
Not known : Glomerulonephritis

Based on CCDS update version 6, 7 and 8

Musculoskeletal, and connective tissue disorders
Very common : Musculoskeletal pain*
*Includes bone pain, back pain, arthralgia, myalgia and pain in extremity

Overdosage
In the animal, acute (up to 1000 micrograms per kg per day in the mouse) and subacute (up to 100 micrograms per kg per day in the monkey) toxicity studies have shown that the effects of overdosage were limited to reversible exacerbation of pharmacological effects.
The effects of GRANOCYTE 34 overdosage have not been established.
The discontinuation of GRANOCYTE is usually accompanied by a 50% fall 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 seen in one of the three patients having received the highest doses of GRANOCYTE 34, of 40 micrograms per kg per day (5.12 x 106 IU per kg per day) on the 5^{th} day of treatment.
In humans, doses of up to 40 micrograms per kg per day were not associated with toxic effects, with the exception of bone and muscle pains.

Pharmacological properties

Pharmacodynamic properties
CYTOKINE: granulocyte stimulation factor. LO3AA10.

GRANOCYTE 34 (rHuG-CSF) belongs to the cytokines group, biologically active protein which regulate cell differentiation and growth.
rHuG-CSF is a factor which stimulates the neutrophil progenitor cells, as shown by the CFU-S and CFU-GM cell count increases in peripheral blood.
GRANOCYTE 34 induces a notable increase in peripheral blood neutrophil count during the 24 hours following administration. This increase in neutrophils is dose-dependent between the range of 1 to 10 micrograms per kg per day. At the recommended dose, repeated administrations lead to an increase in neutrophil response. Neutrophils produced in response to GRANOCYTE 34 show normal chemotaxis and phagocytosis functions.
As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.
Use of GRANOCYTE 34 in patients who underwent Bone Marrow Transplantation or who are treated with cytotoxic chemotherapy leads to significants reductions in duration of neutropenia and its associated complications.
Administration of GRANOCYTE 34 either alone or after chemotherapy mobilizes haematopoietic progenitor cells (PBPCs) into the peripheral blood. These PBPCs can be harvested and infused after high dose chemotherapy, either in place of, or in combination to bone marrow transplantation. Reinfused PBPCs obtained by mobilization with GRANOCYTE 34 have proved to be able to reconstitute the haematopoiesis and accelerate the engratment.
Independence of patients from platelet transfusion is hence achieved more rapidly in comparison with an autologous bone marrow transplant.
A pooled analysis of data from 3 double-blind placebo-controlled studies conducted in 861 patients (n = 411 ≥ 55 years) demonstrated a favorable benefit/risk ratio of lenograstim administration in patients over 55 years of age undergoing conventional chemotherapy for *de novo* acute myeloid leukemia, in the exception of AML with good cytogenetics, i.e. t(8; 21), t(15; 17) and inv (16).
In the sub-group of patients over 55 years, the benefit of the administration GRANOCYTE 34 appeared in terms of acceleration of neutrophil recovery, increase in the percentage of patients without infectious episode, and reduction in infection duration, reduction in the duration of hospitalization, reduction in the duration of I.V. 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 than in the placebo arm.
- Those results concerning survival are not found again in subgroup of patients with not good cytogenetics.

Pharmacokinetic properties

Pharmacokinetic of GRANOCYTE 34 are dose and time dependent.

Following repeated administration, peak serum concentration at the end of IV infusion or after SC injection is proportional to the injected dose, without any evidence of a cumulative effect.

- At the recommended dose, the absolute bioavailability of GRANOCYTE 34 is 30%. Apparent volume of distribution (Vdss) is approximately 1L/kg and the mean residence time close to 7 hours following subcutaneous administrations.
- The apparent serum half-life after subcutaneous injection is approximately 3–4 hours at steady state (repeated administrations) and shorter (1–1.5 hours) after repeated IV infusion.
- Plasma clearance of rHuG-CFS increased 3-fold (from 50 up to 150 mL/min) following repeated subcutaneous administrations.
- A very small proportion of GRANOCYTE 34 is eliminated in unchanged form in urine (less than 1% of the dose) since it must be metabolized to endogenous peptides. The peak is close to 100 pg/mL/ kg at the recommended dose by repeated subcutaneous injections. A positive correlation exists between dose and serum concentration and between neutrophil response and the total amount of GRANOCYTE 34 found in the serum.

Pharmaceutical particulars

Incompatibilities

Dilution of GRANOCYTE 34 (33.6×10^6 IU/vial) to a final concentration of less than 0.32×10^4 IU/ml (2.5 µg/ml) is not recommended.

Expiry date

Respect the date indicated on the outer packaging.

Shelf life:

30 months

Special precautions for storage

Do not store above 30°C. Do not freeze. The reconstituted solution of GRANOCYTE 34 must be administered within 24 hours after its preparation. Unused reconstituted or diluted solution should be discarded.

Nature and contents of containers

263 µg of lyophilisate in vial (glass) + 1 ml of solvent in pre-filled syringe (glass) + 2 needles (one 19 G for reconstitution and 26 G for administration).

One pack of 1 vial of lyophilized powder + 1 pre-filled syringe of solvent.

Reg. No.: DKI0185600344A1

Instruction for use and handling

GRANOCYTE 34 vials are for single-dose use only.

The active substance and its solvent are overfilled by 5%. Hence the extractable volume of solvent is 1.05 ml used to reconstitute the lyophilisate with the aim of finally obtaining 1 ml of reconstituted solution of GRANOCYTE.

Description :

Based on CCDS update version 6, 7 and 8

Under aseptic conditions add the extractable content of a syringe pre-filled with 1.05 ml of solvent (water for injections) to the GRANOCYTE 34 vial (see here under diagrams).
For intravenous infusion, GRANOCYTE 34 must be diluted in 0.9% NaCl solution or in 5% dextrose solution. Dilution of GRANOCYTE 34 to a final concentration of less than 0.32 x 106 IU/ml (2.5 µg/ml) is not recommended.
In any event, one vial of reconstituted GRANOCYTE 34 should be diluted in no more than 100 ml.
GRANOCYTE 34 is compatible with standard infusion devices (polyvinyl chloride bags and glass bottles) where diluted in 0.9% NaCl solution or in glass bottles where diluted in 5% dextrose solution.

Manufacturing Authorization Holder
Chugai Pharma France,
Tour Franklin - La Defense 8 100-101,
quartier Boieldieu 92042 Paris La Defense
Cedex, France.

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Manufactured by:
Sanofi Winthrop Industrie, Cedex, France
Registered by:
PT Aventis Pharma, Jakarta – Indonesia

Based on CCDS update version 6, 7 and 8

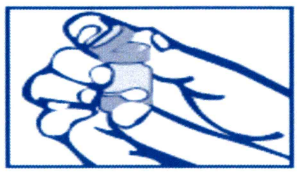

Diagram 1
Remove the plastic cap from the vial

Diagram 2
Clean the rubber stopper.

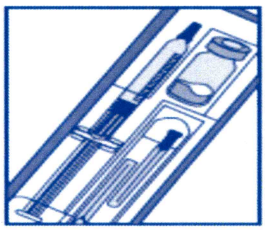

Diagram 3
Remove one pre-filled syringe from the blister and 2 needles [(one with the beige cone (19 G) and one with the brown cone (26 G)]

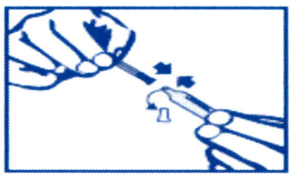

Diagram 4
Remove the tip-cap of the syringe and attach the beige cone needle to the syringe.

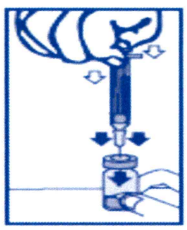

Diagram 5
Keeping the vial on a flat surface, push the needle through the rubber stopper and push the plunger rod to inject the solvent into the vial.

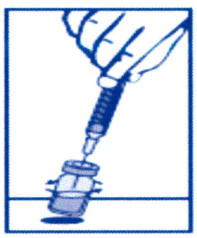

Diagram 6
Shake gently until it is completely dissolved (about 5 seconds). Do not shake vigorously.

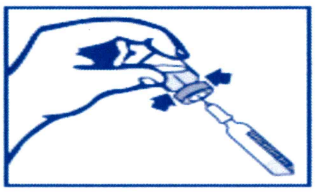

Diagram 7
Keeping the needle and the syringe attached to the vial, turn the vial upside down. Make sure the needle tip is in the solution.

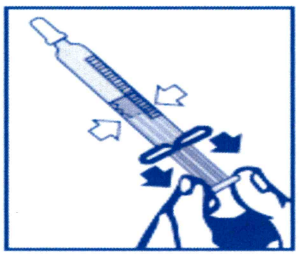

Diagram 8
Pull back slowly the plunger rod and withdraw the prescribed dose. Withdraw the required volume from the vial.

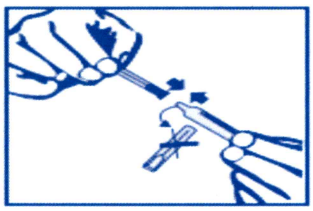

Diagram 9
Remove the beige cone needle from the syringe and replace it with the brown cone needle.

Diagram 10
Remove any air bubbles by gently tapping on the body of the syringe and push slowly the plunger rod to eliminate the air.

Diagram 11
If necessary, adjust the volume to be administered, GRANOCYTE is now ready for injection. Administer immediately by subcutaneous injection.