



HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

The legally binding text is the original French version

OPINION

21 June 2006

Granocyte 13 (13.4 million IU/1 mL), powder and solvent in prefilled syringe for solution for injection

Box of 1 (CIP code: 349 756-7)

Granocyte 34 (33.6 million IU/1 mL), powder and solvent in prefilled syringe for solution for injection

Box of 1 (CIP code: 349 761-0)

Applicant: Chugai Pharma France

lenograstim

List I; initial 3-month prescription in hospital

Date of Marketing Authorisation: 06 December 1996

Included on the list of medicines approved for hospital use.

Included on the list of medicines reimbursed by National Insurance for the indication "Reduction of duration of severe neutropenia and associated complications in patients undergoing established chemotherapy, known to be associated with a significant incidence of febrile neutropenia".

Reason for request: inclusion on the list of medicines reimbursed by National Insurance (no longer exclusively for hospital use) for the following indications:

- reduction of duration of neutropenia in patients (with nonmyeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and at increased risk of severe, prolonged neutropenia.
- mobilisation of peripheral blood progenitor cells (PBPCs).

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lenograstim

1.2. Background

Lenograstim is a leukocyte growth factor.

Granocyte can be kept at room temperature up to + 30°C.

1.3. Indications

Reduction of duration of neutropenia in patients (with nonmyeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and at increased risk of severe, prolonged neutropenia.

Reduction of duration of severe neutropenia and associated complications in patients undergoing established chemotherapy, known to be associated with a significant incidence of febrile neutropenia.

Mobilisation of Peripheral Blood Progenitor Cells (PBPC).

1.4. Dosage

The recommended dose of Granocyte is 150 µg(19.2 x 10⁶ IU)/m²/day, equivalent in efficacy to a dose of 5 µg(0.64 x 10⁶ IU)/kg/day:

- in neutropenia induced by chemotherapy for bone marrow transplantation,
- after established cytotoxic chemotherapy,
- in PBPC mobilisation after chemotherapy.

For PBPC mobilisation with Granocyte alone, the recommended dose is 10 µg(1.28 x 10⁶ IU)/kg/day.

• Adults

– *After bone marrow transplantation*

Granocyte should be administered daily at the recommended dose of 150 µg(19.2 x 10⁶ IU)/m²/day as a 30-minute intravenous infusion diluted in isotonic saline solution, or as a subcutaneous injection, starting the day after transplantation (see [SPC] "Instructions for use and handling").

Daily administration should continue until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, up to a maximum of 28 days of treatment if necessary.

It is anticipated that by day 14 following bone marrow transplantation, 50% of patients will reach a normal neutrophil count or a count compatible with treatment discontinuation.

– *For PBPC mobilisation after chemotherapy*

Granocyte should be administered daily at the recommended dose of 150 µg(19.2 x 10⁶ IU)/m²/day as a subcutaneous injection, starting the day following completion of chemotherapy and continuing until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation.

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

– **For PBPC mobilisation with Granocyte alone**

Granocyte should be administered daily at the recommended dose of 10 µg(1.28×10^6 IU)/kg/day as a subcutaneous injection for 4–6 days.

Leukapheresis should be performed between days 5 and 7.

In patients not pretreated with intensive chemotherapy, one leukapheresis is usually sufficient to obtain the acceptable minimum yield ($\geq 2.0 \times 10^6$ CD34⁺ cells per kg).

In healthy donors, with a 10 µg/kg daily dose administered subcutaneously for 5-6 days, a CD34⁺ cell yield $\geq 3 \times 10^6$ /kg bodyweight is possible with a single leukapheresis in 83% of subjects and with 2 leukaphereses in 97%.

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

Granocyte therapy should be started and supervised by a specialist in medical oncology and/or haematology.

• **Elderly patients**

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

• **Children**

The safety and efficacy of Granocyte have been established in patients older than 2 years, in bone marrow transplantation.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2005

L	:	antineoplastic and immunomodulating agents
03	:	immunomodulating agents
A	:	cytokines and immunomodulating agents
A	:	growth factors
10	:	lenograstim

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines

Neupogen (filgrastim) (included on the list of medicines approved for hospital use and reimbursed by National Insurance)

2.3. Medicines with a similar therapeutic aim

See section 2.2.

3. ANALYSIS OF AVAILABLE DATA

3.1. Reduction of duration of neutropenia in patients (with nonmyeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation and at increased risk of severe, prolonged neutropenia.

Clinical data relating to this indication were drawn from a randomised double-blind placebo-controlled phase III pivotal trial (GHBA 269)¹ in 315 patients (including 49 children aged 2–15) who had received bone marrow transplantation after chemotherapy and/or total body irradiation. Granocyte was administered at a dosage of 5 µg/kg/day.

Primary endpoint:

Time to reach an absolute neutrophil count $\geq 0.2 \times 10^9/L$, $\geq 0.5 \times 10^9/L$ and $\geq 1.0 \times 10^9/L$ for 3 consecutive days.

Secondary endpoints

Incidence of clinically and/or microbiologically confirmed infections, duration of febrile neutropenia (oral temperature $\geq 38^\circ\text{C}$ and neutropenia $< 1 \times 10^9/L$), number of days admitted to hospital.

Results

In 298 patients for whom efficacy data could be established, there was a significant decrease in median time to neutrophil recovery (primary endpoint) in the Granocyte group:

$\geq 0.2 \times 10^9/L$ (11 vs. 15 days, $p < 0.001$), $\geq 0.5 \times 10^9/L$ (14 vs. 20 days, $p < 0.001$) and $\geq 1.0 \times 10^9/L$ (16 vs. 27 days, $p < 0.001$).

The median duration of febrile neutropenia improved by 2 days in the Granocyte group: 3 days vs. 5 days in the placebo group, $p = 0.014$.

The median duration of microbiologically confirmed infections was 8 days vs. 12 days ($p = 0.017$), and 10 days vs. 12 days ($p = 0.02$) for all types of infection (clinical and confirmed by laboratory test).

Admission to hospital was 25 days in the Granocyte group versus 29 days in the placebo group ($p = 0.023$).

In the subgroup of patients aged 2–15, time to reach neutrophil count $\geq 0.5 \times 10^9/L$ was a week shorter in the Granocyte group than in the placebo group (median 13 days vs. 20 days; $p < 0.001$).

Incidence of undesirable events was similar in the 2 groups.

3.2 Mobilisation of Peripheral Blood Progenitor Cells

Five trials were conducted comparing Granocyte with filgrastim (Neupogen), 3 in healthy volunteers (trial LRO 012, trial GCS 306 and the Fischer trial) and 2 trials in patients with a malignant condition (Watts and De Arriba trials).

¹ Gisselbrecht C, Prentice HG, Bacigalupo A *et al.* Placebo-controlled phase III trial of lenograstim in bone-marrow transplantation. *Lancet* 1994; 343: 696-700

- **Trials in healthy volunteers**

Trial LRO 012

Randomised phase I trial in 20 healthy volunteers given Granocyte or Neupogen 5 µg/kg/day for 6 days. This dose is half that recommended in the Marketing Authorisation for Neupogen for PBPC mobilisation in healthy donors (1 MU(10 µg)/kg/day by the subcutaneous route for 4–5 days). This trial will not be discussed further.

Trial GCS 306

Randomised, single-blind crossover phase I trial in 30 healthy volunteers given Granocyte or Neupogen (according to randomisation order) 10 µg/kg/day for 5 days. After a 4-week treatment window each volunteer was given the other granulocyte-colony stimulating factor (G-CSF) (same dose and duration).

On day 6 after starting treatment, the Granocyte group had a higher mean CD34+ cell count than the Neupogen group (mean CD34+ cell peak: 103.6 cells/µL vs. 82.2; $p < 0.0001$). However, the CD3+, CD4+ and CD8+ cell counts did not differ between the two groups.

Apheresis was carried out in only 6 out of 30 volunteers enrolled.

Incidence of undesirable events was similar for the two G-CSFs (bone pain, headache, fatigue).

Fischer trial²

Randomised open-label trial comparing the efficacy of lenograstim and filgrastim in 570 donors, to mobilise haematopoietic progenitor cells for donation or allogenic transplantation.

Therapy studied:

- *filgrastim group*: 10 µg/kg/day, rounded up to the total contents of the calculated number of vials, for 5 or 6 days if the CD34+ cell yield on day 5 was insufficient;
- *lenograstim group*: 10 µg/kg/day, rounded up to the next vial, for 5 days, or 6 days if the CD34+ cell yield on day 5 was insufficient.

Apheresis was performed on day 5 (day 1 = first dose of G-CSF), with 4 blood volumes treated. If the circulating CD34+ cell count was $< 0.03 \text{ cells} \times 10^9/\text{L}$, 6 blood volumes were treated.

The number of CD34+ cells/donor bodyweight harvested at completion of apheresis on day 5 was significantly higher in donors given lenograstim than with filgrastim: 7.19×10^6 vs. 6.44×10^6 CD34+ cells/kg, $p < 0.03$).

Analysis by donor sex subgroup (included in the protocol) showed that lenograstim was superior to filgrastim in male donors: $7.73 \text{ CD34+ cells/kg donor bodyweight}$ in the male group treated with lenograstim vs. $6.88 \times 10^6 \text{ cells/kg donor bodyweight}$ with filgrastim ($p < 0.017$). However, there was no significant difference in female donors: $6.2 \times 10^6 \text{ CD34+ cells/kg donor bodyweight}$ in the lenograstim group vs. $6.0 \times 10^6 \text{ CD34+ cells/kg donor bodyweight}$ in the filgrastim group.

² Fischer, JC *et al*, Superior mobilisation of haematopoietic progenitor cells with glycosylated G-CSF in male but not female unrelated stem cell donors. *British Journal of Haematology*. 2005; 130: 740-746

- **Trials in patients with malignant conditions**

Watts³ trial

A non-randomised open-label trial comparing the quality parameters of autologous transplants harvested after a course of cyclophosphamide followed by either filgrastim or lenograstim in 101 patients previously treated for lymphoma, in relapse or with resistance.

The aim was to define parameters that predict for rapid engraftment after peripheral blood stem cell (PBSC) transplantation. Mobilisation was effected with Granocyte 263 µg/day or Neupogen 10 µg/kg/day.

There was no difference between lenograstim and filgrastim in terms of the quality of the harvested graft:

CD34+ = $2.2 \times 10^6/\text{kg}$ vs. $2.1 \times 10^6/\text{kg}$ ($p = 0.7$);

CMN = $2.2 \times 10^8/\text{kg}$ vs. $1.6 \times 10^8/\text{kg}$ ($p = 0.7$);

GM-CFC = $2.7 \times 10^5/\text{kg}$ vs. $2.1 \times 10^5/\text{kg}$ ($p = 0.11$).

De Arriba⁴ trial

A randomised single-blind trial comparing the efficacy of Granocyte and Neupogen, at bioequivalent doses, for mobilising peripheral blood progenitor cells (PBPCs) in 30 patients with breast cancer.

Patients received:

- either Granocyte 0.82 ± 0.02 MU/kg/day (i.e. 6.4 ± 0.1 µg/kg/day),

- or Neupogen 0.84 ± 0.01 MU/kg/day (i.e. 8.4 ± 0.1 µg/kg/day).

At bioequivalent dose, there was no difference between the 2 G-CSFs in number of progenitor cells mobilised (CD34+ and subpopulations).

There was no difference between Granocyte and Neupogen in haematopoietic stem cell mobilisation in terms of total population of CD34+ cells, concentration of CD34+/38- cells, or CD34+/DR harvested, at the first or second leukapheresis, or for the total material yielded.

3.1. Conclusion

For the indication "Reduction of duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation",

Assessment of the benefit of Granocyte was based on a placebo-controlled pivotal trial in 315 patients having had prior myeloablative chemotherapy followed by bone marrow transplantation. Granocyte reduced the duration of neutropenia by around a week ($\geq 0.5 \times 10^9/\text{L}$ (14 vs. 20 days, $p < 0.001$).

Incidence of undesirable effects was similar in the 2 groups.

For the indication "Mobilisation of peripheral blood progenitor cells":

The data comparing Granocyte with Neupogen submitted in the dossier showed a slight advantage for Granocyte in terms of CD34+ cell yield in two trials in volunteers (trial GCS 306 and Fischer trial). However, this advantage was not seen in trials conducted in patients who were to undergo autologous transplantation (Watts 1997 trial and De Arriba trial).

From the data available, the safety profiles of Granocyte and Neupogen appear to be similar, especially for incidence of bone pain.

3 Watts MJ, Sullivan AM, Jamieson E, Pearce R, Fielding A, Devereux S, Goldstone AH, Linch DC. Progenitor-cell mobilization after low-dose cyclophosphamide and granulocyte colony-stimulating factor: an analysis of progenitor-cell quantity and quality and factors predicting for these parameters in 101 pretreated patients with malignant lymphoma. J Clin Oncol 1997; 15: 535-46.

4 De Arriba, F, et al. Prospective randomized study comparing the efficacy of bioequivalent doses of glycosylated and nonglycosylated rG-CSF for mobilizing peripheral blood progenitor cells. British Journal of Haematology, 1997; 96: 418-420

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Mobilisation of peripheral blood progenitor cells

- Peripheral blood progenitor cell mobilisation prior to autologous or allogeneic transplantation is indicated in life-threatening conditions.
- Lenograstim (Granocyte) is curative therapy.
- The efficacy/safety ratio is substantial.
- Granocyte is first-line therapy.
- There is an alternative drug.
- Expected public health benefit :
 - Peripheral blood progenitor cell (PBPC) mobilisation prior to transplantation is a low burden on public health.
 - As with Neupogen, Granocyte is particularly expected to have an impact on the organisation of care for allogeneic transplantation, as it reduces hospitalisations for the donor and simplifies the transplantation technique. This simplification should make it easier to adopt a treatment strategy (PBPC transplantation) that benefits public health. Granocyte offers a similar response to a public health need as the other haematopoietic growth factor (Neupogen).
 - However, in view of the available data, the expected impact of these medicinal products on morbidity and mortality at population level can only be low.
 - Granocyte is therefore expected to benefit public health in this indication. This benefit is low for the same reasons as for the other haematopoietic growth factor (Neupogen) with this indication.

The actual benefit of Granocyte in this indication is substantial.

Reduction of duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation

- The conditions concerned in this indication are life-threatening.
- Lenograstim (Granocyte) is prophylactic therapy.
- The efficacy/safety ratio is substantial.
- Granocyte is first-line therapy.
- There is an alternative drug.
- Expected public health benefit.
 - The public health burden of neoplasms with neutropenia caused by chemotherapy for bone marrow transplantation is low because of the small number of patients concerned.
 - Since Granocyte is already available in hospitals, the public health requirement may be regarded as covered, and no additional impact on morbidity and mortality is expected as a result of its being made available in general practice.
 - It is not therefore expected that Granocyte will benefit public health in this indication.

The actual benefit of Granocyte in this indication is substantial.

4.2. Improvement in actual benefit

Mobilisation of peripheral blood progenitor cells in healthy donors prior to allogenic transplantation

Granocyte shares the IAB III rating as Neupogen.

Mobilisation of peripheral blood progenitor cells in patients prior to autologous transplantation and Reduction in duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation, and at increased risk of severe, prolonged neutropenia

The Committee considered that both growth factors, including Granocyte, still have an important role to play and occupy the same place in the treatment strategy.

4.3. Therapeutic use

Patients undergoing myeloablative chemotherapy followed by bone marrow transplantation

According to the Standards, Options and Recommendations (SOR) drawn up in May 1999 by the *Fédération Nationale des Centres de Lutte Contre le Cancer* [French national federation of cancer research centres] on the use of haematopoietic growth factors in oncology: “Using haematopoietic growth factors after autologous bone marrow transplantation makes it possible to reduce the duration of neutropenia (evidence level A), the incidence of infections (evidence level C), the length of antibiotic treatment (evidence level C) and the length of hospitalisation (evidence level C). Reduced duration of fever is reported in most trials with Granulocyte Colony Stimulating Factor (evidence level C)”.⁵

Mobilisation of peripheral blood progenitor cells prior to autologous or allogenic transplantation

Patients undergoing PBPC transplantation recover their haematological status more quickly than those undergoing bone marrow transplantation (BMT) (polymorphonuclear cells and especially platelets), probably because after stimulation, harvested peripheral blood contains more stem cells than harvested bone marrow. For both forms of transplant, the success rate is the same in terms of polymorphonuclear cells and platelets. Graft-versus-host (GVH) reaction rates for both strategies are practically identical for acute GVHD, but figures for chronic GVHD are higher in patients undergoing PBPC transplantation after 3 years of follow-up⁶. Survival rates are roughly the same.

Apheresis after stimulation with leukocyte growth factors (Granocyte or Neupogen) is a simpler procedure than bone marrow harvesting, as it can be done in an outpatient setting, at a separate time from reinfusion, does not require a general anaesthetic, and the platelet count recovers more rapidly, although the advantage for leukocyte recovery is less. Overall, a lower level of adjuvant care is required with PBPC than with BMT, for an identical result.

4.4. Target population

Target populations for Granocyte for 2004 were estimated on the basis of epidemiological data from the 2004 annual report on transplantation and grafts from the *Etablissement*

⁵ Fédération Nationale des Centres de Lutte Contre le Cancer. *Standards, Options, Recommandations pour l'utilisation des facteurs de croissance hématopoïétique en cancérologie*. May 1999. www.fnclcc.fr

⁶ Schmitz N, Beksac M, Bacigalupo A, et al. Filgrastim-mobilized peripheral blood progenitor cells versus bone marrow transplantation for treating leukemia: 3-year results from the EBMT randomized trial. *Haematologica* 2005;90:643-648

français des greffes (EFG), which became the *Agence de la Biomédecine*⁷ [French Biomedicine Agency] in May 2005.

Patients undergoing myeloablative chemotherapy followed by bone marrow transplantation.

The number of patients undergoing bone marrow transplantation is estimated from the number of bone marrow transplants carried out in 2004, i.e. 485 transplants.

The estimated target population for this indication is 485 patients per year.

Patients treated to mobilise peripheral blood progenitor cells for subsequent reinjection.

This population is divided into two subpopulations:

- patients undergoing autologous transplantation,
- healthy donors preparing for allogenic transplantation.

As leukocyte growth factors are used during peripheral blood progenitor cell mobilisation, , this population is estimated to be 3682 patients in 2004.

The estimated total target population for Granocyte in these two indications is therefore around 4200 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommended inclusion on the list of medicines reimbursed by National Insurance

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 100%

⁷ *Bilan des activités de prélèvement et de greffe en France en 2004. Etablissement Français des Greffes*
<http://www.efg.sante.fr>