**SUMMARY OF PRODUCT CHARACTERISTICS**

# NAME OF THE MEDICINAL PRODUCT

<Trade name> <Strength>, powder and solvent for solution for injection/infusion.

<Trade name> <Strength>, powder and solvent for solution for injection/infusion in a pre-filled syringe.

<Trade name> <Strength>, powder and solvent for solution for injection/infusion.

<Trade name> <Strength>, powder and solvent for solution for injection/infusion in a pre-filled syringe.

# QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Excipients with known effect:

<Regarding the approval>

For the full list of excipients, see section 6.1.

# PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

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

<Regarding the approval>

# CLINICAL PARTICULARS

## **Therapeutic indications**

<GENERIC NAME> is indicated in adults, adolescents and children aged older than 2 years for:

The reduction of the duration of neutropenia in patients (with non myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation (BMT) and considered to be at increased risk of prolonged severe neutropenia.

The reduction of the duration of severe neutropenia and its associated complications in patients undergoing established cytotoxic therapy associated with a significant incidence of febrile neutropenia.

The mobilization of peripheral blood progenitor cells (PBPCs), for patients as well as healthy donors.

* 1. **Posology and method of administration**

## *Method of administration*

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

## *Posology*

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

The recommended dose of <Generic name> is 19.2 MIU (150 µg) per m2 per day, therapeutically equivalent to 0.64 MIU (5 µg) per kg per day for:

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

<Generic name> 13 million IU/mL can be used in patients with body surface area up to 0.7 m2.

<Generic name> 34 million IU/mL can be used in patients with body surface area up to 1.8 m2.

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

### Adults

* In Peripheral Stem Cells or Bone Marrow Transplantation

<Generic name> should be administered daily at the recommended dose of 19.2 MIU (150 µg) per m2 per day as a 30-minute intravenous infusion diluted in isotonic saline solution or as a subcutaneous injection. The first dose should not be administered within 24 hours of the bone marrow infusion. Dosing should continue until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, with, if necessary, a maximum of 28 consecutive days of treatment.

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

* In Established Cytotoxic Chemotherapy

<Generic name> should be administered daily at the recommended dose of 19.2 MIU (150 µg) per m2 per day as a subcutaneous injection. The first dose should not be administered less than 24 hours following cytotoxic chemotherapy (see 4.4 and 4.5). Daily administration of <Generic name> should continue until the expected nadir has passed and the neutrophil count returns to a stable level compatible with treatment discontinuation, with, if necessary, a maximum of 28 consecutive days of treatment.

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

* In Peripheral Blood Progenitor Cells (PBPCs) Mobilization

After chemotherapy, <Generic name> should be administered daily, at the recommended dose of 19.2 MIU (150 µg) per m2 per day as a subcutaneous injection starting within 1 to 5 days after completion of chemotherapy, according to the chemotherapy regimen administered for mobilization.

<Generic name> should be maintained until the last leukapheresis.

Leukapheresis should be performed when the post nadir leukocyte count is rising or after assessment of CD34+ cells in blood with a validated method. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient to obtain the acceptable minimum yield (≥ 2.0 x 106 CD34+ cells per kg).

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

In patients who have not had extensive chemotherapy one leukapheresis is often sufficient to obtain the acceptable minimum yield (≥ 2.0 x 106 CD34+ cells per kg).

In healthy donors, a 10µg/kg daily dose administered subcutaneously for 5-6 days allows a CD34+ cells collection ≥ 3 x 106 /kg body weight with a single leukapheresis in 83% of subjects and with 2 leukapheresis in 97%.

### Elderly

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

### Children

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

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

### Paediatric population

The safety and efficacy of <Generic name> in children aged less than 2 years have not been established.

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

<Generic name> 34 million IU/mL can be used in patients with body surface area up to 1.8 m².

#### Contraindications

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
* <GENERIC NAME>should not be used to increase the dose intensity of cytotoxic chemotherapy beyond established doses and dosage regimens since the drug could reduce myelotoxicity but not overall toxicity of cytotoxic drugs.
* It should not be administered concurrently with cytotoxic chemotherapy.
* Itshould not be administered to patients.
* with myeloid malignancy 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).

#### Special warnings and precautions for Use

Malignant Cell Growth

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

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

Clinical trials have not established whether <GENERIC NAME>influences the progression of myelodysplastic syndrome to acute myeloid leukemia. Caution should be exercised in using itin any premalignant myeloid condition. As some tumors with non-specific characteristics can exceptionally express a G-CSF receptor, caution should be exerted in the event of unexpected tumor regrowth concomitantly observed with rHuGCSF therapy.

In children with ALL

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

Leukocytosis

A leukocyte counts greater than 50 x 109/L has not been observed in any of the 174 clinical trials patients treated with 5 µg/kg/day (0.64 million units/kg/day) following bone marrow transplantation. White blood cell counts of 70 x 109/L or greater have been observed in less than 5% of patients who received cytotoxic chemotherapy and were treated by<GENERIC NAME>at 5 µg/kg/day (0.64 million units/kg/day). No adverse events directly attributable to this degree of leukocytosis have been reported. In view of the potential risks associated with severe leukocytosis, a white blood cell count should, however, be performed at regular intervals during <GENERIC NAME>therapy.

If leukocyte counts exceed 50 x 109/L after the expected nadir, <GENERIC NAME> should be discontinued immediately.

During PBPC mobilization, <GENERIC NAME> should be discontinued if the leukocyte counts rise to > 70 x 109/L.

Pulmonary adverse effects

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

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

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

<GENERIC NAME>should be immediately discontinued and appropriate treatment given.

In donors and patients, pulmonary adverse events (hemoptysis, pulmonary hemorrhage, lung infiltrates, dyspnea and hypoxia) have been reported in post marketing experience. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with <Generic name> should be considered and appropriate medical care given.

Venous and arterial thromboembolic events

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

In Peripheral Stem Cells or Bone Marrow Transplantation

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

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

In Established Cytotoxic Chemotherapy

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

The safety of the use of <GENERIC NAME> with antineoplastic agents characterized by cumulative or predominant platelet lineage myelotoxicity (nitrosurea, mitomycin) has not been established.

Administration of <GENERIC NAME>might enhance the toxicity of these agents, particularly to the platelets.

Risks Associated with Increased Doses of Chemotherapy

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

Special precautions in Peripheral Blood Progenitor Cells mobilization.

*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 <GENERIC NAME>was used after chemotherapy than when used alone. Nevertheless the choice between the two mobilisation methods should be considered in relation to the overall objectives of treatment for an individual patient.

*Prior exposure to radiotherapy and/or cytotoxic agents*

Patients, who have undergone extensive prior myelosuppressive therapy and/or radiotherapy, may not show sufficient PBPC mobilisation to achieve the acceptable minimum yield (≥ 2 x106 CD34+ /kg) and therefore adequate haematological reconstitution.

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

*Assessment of progenitor cell yields*

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

The minimum yield of CD34+ cells is not well defined. The recommendation of a minimum yield of ≥ 2.0 x 106 CD34+ cells/kg is based on published experience in order to achieve adequate hematological reconstitution. Yields higher than ≥ 2.0 x 106 CD34+ cells/kg are associated with more rapid recovery, including platelets, while lower yields result in slower recovery.

*In healthy donors*

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

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

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

Marked leukocytosis (WBC ≥ 50 x 109/L) was observed in 24% of subjects studied.

Apheresis-related thrombocytopenia (platelets < 100 x 109/L) was observed in 42% of subjects studied and values < 50 x 109/L were occasionally noted following leukapheresis without related clinical adverse events, all recovered. Therefore, leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. If more than one leukapheresis is required particular attention should be paid to donors with platelets < 100 x 109/L prior to apheresis; in general apheresis should not be performed if platelets < 75 x 109/L.

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

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

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

In recipients of allogeneic peripheral stem-cells mobilized with  <GENERIC NAME>. Allogeneic stem-cell grafting may be associated with an increased risk for chronic GVH (Graft Versus Host Disease), and long-term data of graft functioning are sparse.

Other Special Precautions

In patients with severe impairment of hepatic or renal function, the safetyand efficacy of <GENERIC NAME>have not been established.

In patients with substantially reduced myeloid progenitor cells (e.g. due to prior intensive radiotherapy/chemotherapy), neutrophil response issometimes diminished and the safety of <GENERIC NAME>has not been established.

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

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

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

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

<GENERIC NAME>contains phenylalanine, which may be harmful for people with phenylketonuria.

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

Traceability

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

#### Interaction with other medicinalproducts and other forms of interaction

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

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

* 1. **Fertility, pregnancy and lactation**

Pregnancy

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

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

<GENERIC NAME>should not be used during pregnancy unless clearly necessary.

## Breast-feeding

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

### **Effects on ability to drive and use machines**

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

### **Undesirable effects**

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

### In Peripheral Stem Cells or Bone Marrow Transplantation

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

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

In clinical trials, the most frequently reported adverse events (15%) were the same in patients treated with either <GENERIC NAME>or placebo. These adverse events were those usually encountered with conditioning regimens and those observed in cancer patients treated with chemotherapy. The most commonly reported adverse events were infection/inflammatory disorder of the buccal cavity, sepsis and infection, fever, diarrhoea, abdominal pain, vomiting, nausea, rash, alopecia, and headache.

In PBPC mobilisation in healthy donors

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

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

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

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

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

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

Frequency of adverse reactions issued from clinical trials and post-marketing surveillance data.

Very common (≥ 10%); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≥ 1/100); rare (≥ 1/10000 to ≥ 1/1000); very rare (≥ 1/10000); not known (cannot be estimated from the available data).

| **Medra System Organ Class** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
| --- | --- | --- | --- | --- | --- | --- |
| Investigations | Elevated LDH |  |  |  |  | C-reactive protein increased |
| Blood and lymphatic system disorders | Leucocytosis  Thrombocytopenia | Enlarged spleen size |  |  | Splenic rupture5 |  |
| Nervous system disorders | Headache  Asthenia |  |  |  |  |  |
| Vascular  Disorders |  |  | Capillary leak syndrome6 | Aortitis |  | Venous thromboembolism  Arterial thromboembolism |
| Respiratory, thoracic and mediastinal disorders |  |  | Haemoptysis8 | Pulmonary edema  Interstitial  pneumonia3  Pulmonary  infiltrates  Pulmonary fibrosis  Pulmonary  haemorrhage8 |  |  |
| Gastrointestinal disorders |  | Abdominal pain |  |  |  |  |
| Skin and subcutaneous tissue disorders |  |  |  |  | Cutaneous  vasculitis Sweet’s syndrome4 Erythema nodosum Pyoderma gangrenosum  Lyell’s syndrome |  |
| Musculoskeletal and connective tissue disorders | Musculoskeletal  Pain7 | Pain1 |  |  |  |  |
| Renal and urinary disorders |  |  |  |  |  | Glomerulo-nephritis |
| General disorders and administration site condition |  | Injection site reaction |  |  |  |  |
| Immune system  disorders |  |  |  |  | Allergic reaction  Anaphylactic shock |  |
| Hepatobiliary disorders | Elevated  ASAT/ALAT2  Elevated  Alkalinephos-phatase |  |  |  |  |  |

1. / The risk of occurrence of pain is increased in subjects with high peak WBC values, especially when WBC ≥ 50 x 109 /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 nonmalignant related neutropenia.
5. / Splenic ruptures have been reported in either healthy donors or patients receiving G-CSFs (see section 4.4)
6. / There have been post-marketing reports of life-threatening capillary leak syndrome (see section 4.4)
7. / includes bone pain, back pain, arthralgia, myalgia and pain in extremity
8. / Pulmonary adverse reactions have been reported like dyspnoea, hypoxia or haemoptysis, including very rarely Acute Respiratory Distress Syndrome (ARDS) (see section 4.4).

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC Thai.

### **Overdose**

The effects of <Generic name> overdose have not been established (see section 5.3). Discontinuation of <Generic name> 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 109/L was observed in one patient out of three receiving the highest <Generic name> dose of 40 µg/kg/day (5.12 MIU/kg/day) on the 5th day of treatment.

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

# PHARMACOLOGICAL PROPERTIES

# Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines

ATC code: L03AA10

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

Mechanism of action and Pharmacodynamic effects

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

<GENERIC NAME>induces a marked increase in peripheral blood neutrophil counts within 24 hours of administration.

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

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

## Clinical efficacy and safety

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

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

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

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

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

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

### **Pharmacokinetic properties**

Absorption and Distribution

The pharmacokinetics of <GENERIC NAME> are dose and time dependent.

During repeated dosing (IV and SC routes), peak serum concentration (immediately after IV infusion or after SC injection) is proportional to the injected dose. Repeated dosing with <GENERIC NAME> by the two administration routes showed no evidence of drug accumulation. At the recommended dose, the absolute bioavailability of <GENERIC NAME> is 30%. The apparent volume of distribution (Vd) is approximately 1 L/kg body weight and the mean residence time close to 7 h following subcutaneous dosing.

Elimination

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

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

#### Preclinical safety data

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

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

## **PHARMACEUTICAL PARTICULARS**

* 1. **List of excipients**

<Regarding the approval>

### **Incompatibilities**

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

* 1. **Shelf life**

<Regarding the approval>

* 1. **Special precautions for storage**

<Regarding the approval>

* 1. **Nature and contents of container**

<Regarding the approval>

* 1. **Special precautions for disposal and other handling**

<Regarding the approval>

1. **MARKETING AUTHORISATION HOLDER**

<Regarding the approval>

1. **MARKETING AUTHORISATION NUMBER(S)**

<Regarding the approval>

1. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<Regarding the approval>

# DATE OF REVISION OF THE TEXT[[1]](#footnote-1)

# <Regarding the approval>

1. Ref: GRANOCYTE, MHRA, 09/05/2022 [↑](#footnote-ref-1)