

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Grastofil 30 MU/0.5 mL solution for injection or infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 60 million units (MU) (equivalent to 600 micrograms [μg]) of filgrastim.

Each pre-filled syringe contains 30 MU (equivalent to 300 micrograms of filgrastim in 0.5 mL solution for injection or infusion).

Filgrastim is a recombinant methionyl human granulocyte-colony stimulating factor produced in *Escherichia coli* (BL21) by recombinant DNA technology.

Excipient with known effect

Each mL of solution contains 50 mg of sorbitol (E420)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion

Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Grastofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

The safety and efficacy of Grastofil are similar in adults and children receiving cytotoxic chemotherapy.

Grastofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9/\text{L}$, and a history of severe or recurrent infections, long term administration of Grastofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Grastofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to $1.0 \times 10^9/\text{L}$) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections

when other options to manage neutropenia are inappropriate.

4.2 Posology and method of administration

Grastofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Established cytotoxic chemotherapy

Posology

The recommended dose of Grastofil is 0.5 MU/kg/day (5 micrograms/kg/day). The first dose of Grastofil should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical studies, a subcutaneous dose of 230 micrograms/m²/day (4.0 to 8.4 micrograms/kg/day) was used.

Daily dosing with Grastofil should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemias, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of Grastofil therapy. However, for a sustained therapeutic response, Grastofil therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of Grastofil therapy, prior to the time of the expected neutrophil nadir, is not recommended.

Method of administration

Grastofil may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes (see section 6.6). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

In patients treated with myeloablative therapy followed by bone marrow transplantation

Posology

The recommended starting dose of Grastofil is 1.0 MU/kg/day (10 micrograms/kg/day). The first dose of Grastofil should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of Grastofil should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count (ANC)	Grastofil dose adjustment
ANC > 1.0 x 10 ⁹ /L for 3 consecutive days	Reduce to 0.5 MU/kg/day (5 micrograms/kg/day)
Then, if ANC remains > 1.0 x 10 ⁹ /L for 3 more consecutive days	Discontinue Grastofil
If the ANC decreases to < 1.0 x 10 ⁹ /L during the treatment period, the dose of Grastofil should be re-escalated according to the above steps	
ANC = absolute neutrophil count	

Method of administration

Grastofil may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Grastofil should be diluted in 20 mL of 5% glucose solution- (see section 6.6).

For the mobilisation of peripheral blood progenitor cells (PBPC) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

Posology

The recommended dose of Grastofil for PBPC mobilisation when used alone is 1.0 MU/kg/day (10 micrograms/kg/day) for 5-7 consecutive days. The timing of leukapheresis: one or two leukaphereses on days 5 and 6 which is often sufficient. In other circumstances, additional leukaphereses may be necessary. Grastofil dosing should be maintained until the last leukapheresis.

The recommended dose of Grastofil for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU/kg/day (5 micrograms/kg/day) from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from < 0.5 x 10⁹/L to > 5.0 x 10⁹/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukaphereses are recommended.

Method of administration

Grastofil for PBPC mobilisation when used alone:

Grastofil may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions Grastofil should be diluted in 20 mL of 5% glucose solution (see section 6.6).

Grastofil for PBPC mobilisation after myelosuppressive chemotherapy:

Grastofil should be given by subcutaneous injection.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

Posology

For PBPC mobilisation in normal donors, Grastofil should be administered at 1.0 MU/kg/day (10 micrograms/kg/day) for 4 - 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10⁶ CD34⁺ cells/kg recipient bodyweight.

Method of administration

Grastofil should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)

Posology

Congenital neutropenia: the recommended starting dose is 1.2 MU/kg/day (12 micrograms/kg/day) as a single dose or in divided doses.

Idiopathic or cyclic neutropenia: the recommended starting dose is 0.5 MU/kg/day (5 micrograms/kg/day) as a single dose or in divided doses.

Dose adjustment: Grastofil should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than $1.5 \times 10^9/L$. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently, the dose may be individually adjusted every 1-2 weeks to maintain the average neutrophil count between $1.5 \times 10^9/L$ and $10 \times 10^9/L$. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical studies, 97% of patients who responded had a complete response at doses of ≤ 2.4 MU/kg/day (24 micrograms/kg/day). The long-term safety of administration of Grastofil at doses above 2.4 MU/kg/day (24 micrograms/kg/day) in patients with SCN has not been established.

Method of administration

Congenital, idiopathic or cyclic neutropenia: Grastofil should be given by subcutaneous injection.

In patients with HIV infection

Posology

For reversal of neutropenia:

The recommended starting dose of Grastofil is 0.1 MU/kg/day (1 micrograms/kg/day) with titration up to a maximum of 0.4 MU/kg/day (4 micrograms/kg/day) until a normal neutrophil count is reached and can be maintained ($ANC > 2.0 \times 10^9/L$). In clinical studies, > 90% of patients responded at these doses, achieving a reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU/kg/day (10 micrograms/kg/day) were required to achieve reversal of neutropenia.

For maintenance of normal neutrophil counts:

When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU/day (300 micrograms/day) is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at $> 2.0 \times 10^9/L$. In clinical studies, dosing with 30 MU/day (300 micrograms/day) on 1 - 7 days per week was required to maintain the $ANC > 2.0 \times 10^9/L$, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the $ANC > 2.0 \times 10^9/L$.

Method of administration

Reversal of neutropenia or maintaining normal neutrophil counts: Grastofil should be given by subcutaneous injection.

Special populations

Elderly patients

Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific posology recommendations cannot be made.

Patients with renal/hepatic impairment

Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Paediatric patients in the SCN and cancer settings

Sixty-five percent of patients studied in a SCN trial program, were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy.

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special warnings and precautions across indications

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim. Permanently discontinue filgrastim in patients with clinically significant hypersensitivity. Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects

Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. 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 Acute Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte colony-stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and Splenic rupture

Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder tip pain. Dose reductions of filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

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*.

Myelodysplastic syndrome or Chronic myeloid leukemia

The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Acute myeloid leukaemia

In view of limited safety and efficacy data in patients with secondary AML, filgrastim should be administered with caution. The safety and efficacy of filgrastim administration in de novo AML patients aged < 55 years with good cytogenetics [t(8; 21), t(15; 17), and inv(16)] have not been established.

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to temporary discontinuation or dose reduction of filgrastim in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < 100 x 10⁹/l).

Leukocytosis

White blood cell counts of 100 x 10⁹/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10⁹/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10⁹/L.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis

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. See also section 4.8.

Special warning and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease

Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis

Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy

Special caution should be used when treating patients with high dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes

Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Other special precautions

The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by transplantation.

There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation

There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of CD34⁺ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimal method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield (2.0×10^6 CD34⁺ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

Assessment of progenitor cell yields

In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of CD34⁺ cell numbers vary depending on the precise methodology used and therefore, recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of CD34⁺ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yield of $\geq 2.0 \times 10^6$ CD34⁺ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this minimum yield appear to correlate with more rapid recovery; those below with slower recovery.

Special precautions in normal donors undergoing peripheral blood progenitor cell mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be

considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases.

The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years of age.

Transient thrombocytopenia (platelets $< 100 \times 10^9/L$) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9/L$ were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets $< 100 \times 10^9/L$ prior to leukapheresis; in general apheresis should not be performed if platelets are $< 75 \times 10^9/L$.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

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

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts

Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome

Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline was subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term

treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions

Causes of transient neutropenia such as viral infections should be excluded. Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor this event.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

Special precautions in patients with HIV infection

Blood cell counts

ANC should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice weekly for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 microgram)/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medications

Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression

Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow-infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

All patients

Grastofil contains sorbitol (E420) as an excipient at a concentration of 50 mg/mL. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 0.035 mg sodium (less than 1 mmol sodium (23 mg)) per dose, that is to say essentially 'sodium-free'.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, it is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3).. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim / metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3). The impact of filgrastim on human fertility is not known.

4.7 Effects on ability to drive and use machines

Filgrastim may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of filgrastim (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes

bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the tables below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Adverse reactions				
	Very common (≥ 1/10)	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)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection			
Blood and lymphatic system disorders	Thrombocytopenia Anaemia ^e	Splenomegaly ^a Haemoglobin decreased ^e	Leukocytosis ^a	Splenic rupture ^a Sickle cell anaemia with crisis	
Immune system disorders			Hypersensitivity Drug hypersensitivity ^a Graft versus Host Disease ^b	Anaphylactic reaction	
Metabolism and nutrition disorders		Decreased appetite ^a Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout ^a (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances	
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache ^a	Dizziness Hypoaesthesia Paraesthesia			
Vascular Disorders		Hypertension Hypotension	Veno-occlusive disease ^d	Capillary leak syndrome ^a Aortitis	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough ^a	Acute respiratory distress syndrome ^a Respiratory failure ^a Pulmonary		

MedDRA system organ class	Adverse reactions				
	Very common (≥ 1/10)	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)
		Oropharyngeal pain ^{a, e} Epistaxis	oedema ^a Pulmonary haemorrhage Interstitial lung disease ^a Lung infiltration ^a Hypoxia		
Gastrointestinal disorders	Diarrhoea ^{a, e} Vomiting ^{a, e} Nausea ^a	Oral Pain Constipation ^e			
Hepatobiliary disorders		Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased		
Skin and subcutaneous tissue disorders	Alopecia ^a	Rash ^a Erythema	Rash maculo-papular	Cutaneous vasculitis ^a Sweets syndrome (acute febrile neutrophilic dermatosis)	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ^c	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis	
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Glomerulonephritis Urine abnormality	
General disorders and administration site conditions	Fatigue ^a Mucosal inflammation ^a Pyrexia	Chest pain ^a Pain ^a Asthenia ^a Malaise ^e Oedema peripheral ^e	Injection site reaction		
Injury, poisoning and procedural complications		Transfusion reaction ^e			

^a See section c (Description of selected adverse reactions)

^b There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)

^c Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

^d Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilization

^e Adverse events with higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

Hypersensitivity

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after intravenous administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Pulmonary adverse events

In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4).

Splenomegaly and Splenic rupture

Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Capillary leak syndrome

Cases of capillary leak syndrome have been reported with granulocyte colony-stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Cutaneous vasculitis

Cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. During long-term use cutaneous vasculitis has been reported in 2% of SCN patients.

Leukocytosis

Leukocytosis ($WBC > 50 \times 10^9/L$) was observed in 41% of normal donors and transient thrombocytopenia (platelets $< 100 \times 10^9/L$) following filgrastim treatment and leukapheresis was observed in 35% of donors (see section 4.4).

Sweets syndrome

Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pseudogout (chondrocalcinosis pyrophosphate)

Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

GvHD

There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric Use

No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate filgrastim use in elderly subjects for other approved Grastofil indications.

Paediatric SCN patients

Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

The effects of Grastofil overdose have not been established. Discontinuation of filgrastim 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, colony stimulating factors, ATC code: L03AA02

Grastofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Pharmacodynamic effects

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Grastofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim

therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation					
Publication	Period of Study	N	Acute Grade II - IV GvHD	Chronic GvHD	TRM
Meta-Analysis (2003)	1986 - 2001 ^a	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 – 2002 ^b	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 – 2000 ^b	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

^a Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

^b Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 micrograms/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ CD34⁺ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in ANCs in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive treatments. There is no evidence that

patients with HIV infection treated with filgrastim show an increase in HIV replication.

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

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 mL/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 mL/min/kg. Continuous infusion with filgrastim over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leukocytes, myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and fetal weight were observed.

Based on reported data for another filgrastim product similar to Grastofil, comparable findings plus increased fetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-fetal toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.

In pregnant rats, no maternal or fetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥ 20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).

Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Grastofil must not be diluted with saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

6.3 Shelf life

36 months.

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Accidental one-time exposure to freezing temperatures does not adversely affect the stability of Grastofil. If exposure has been greater than 24 hours or frozen more than once then Grastofil should NOT be used.

Within its shelf-life and for the purpose of ambulatory use, the patient may remove Grastofil from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 15 days. At the end of this period, Grastofil should not be put back in the refrigerator and should be disposed of in accordance with local requirements.

Keep the syringe in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Package containing one or five pre-filled syringe(s) of 0.5 mL Grastofil solution for injection. The pre-filled syringes are made from Type I glass with a permanently attached stainless steel needle in the tip and have 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.5 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, Grastofil may be diluted in 5% glucose. Dilution to a final concentration less than 0.2 MU (2 µg) per mL is not recommended at any time.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Do not shake.

For patients treated with filgrastim diluted to concentrations below 1.5 MU (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL. Example: In a final injection volume of 20 mL, total doses of filgrastim less than 30 MU (300 µg) should be given with 0.2 mL of 200 mg/mL (20%) human albumin solution added.

Grastofil contains no preservative. In view of the possible risk of microbial contamination, Grastofil pre-filled syringes are for single use only.

When diluted in 5% glucose, Grastofil is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Archimedesweg 2
2333 CN Leiden
Netherlands
Tel: +31 (0)71 565 77 77
Fax: +31 (0)71 565 77 78

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/877/001
EU/1/13/877/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18 October 2013

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation

There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of CD34⁺ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimal method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield (2.0×10^6 CD34⁺ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

Assessment of progenitor cell yields

In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of CD34⁺ cell numbers vary depending on the precise methodology used and therefore, recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of CD34⁺ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yield of $\geq 2.0 \times 10^6$ CD34⁺ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this minimum yield appear to correlate with more rapid recovery; those below with slower recovery.

Special precautions in normal donors undergoing peripheral blood progenitor cell mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory

eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases.

The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years of age.

Transient thrombocytopenia (platelets $< 100 \times 10^9/L$) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9/L$ were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets $< 100 \times 10^9/L$ prior to leukapheresis; in general apheresis should not be performed if platelets are $< 75 \times 10^9/L$.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

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

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts

Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome

Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline was subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions

Causes of transient neutropenia such as viral infections should be excluded.

Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor this event.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

Special precautions in patients with HIV infection

Blood cell counts

ANC should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice weekly for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 microgram)/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medications

Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression

Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow-infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

All patients

Grastofil contains sorbitol (E420) as an excipient at a concentration of 50 mg/mL. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 0.035 mg sodium (less than 1 mmol sodium (23 mg)) per dose, that is to say essentially 'sodium-free'.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, it is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim / metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3). The impact of filgrastim on human fertility is not known.

4.7 Effects on ability to drive and use machines

Filgrastim may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of filgrastim (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients

musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the tables below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Adverse reactions				
	Very common (≥ 1/10)	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)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection			
Blood and lymphatic system disorders	Thrombocytopenia Anaemia ^e	Splenomegaly ^a Haemoglobin decreased ^c	Leukocytosis ^a	Splenic rupture ^a Sickle cell anaemia with crisis	
Immune system disorders			Hypersensitivity Drug hypersensitivity ^a Graft versus Host Disease ^b	Anaphylactic reaction	
Metabolism and nutrition disorders		Decreased appetite ^a Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout ^a (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances	
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache ^a	Dizziness Hypoaesthesia Paraesthesia			
Vascular Disorders		Hypertension Hypotension	Veno-occlusive disease ^d	Capillary leak syndrome ^a Aortitis	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough ^a Oropharyngeal	Acute respiratory distress syndrome ^a Respiratory failure ^a Pulmonary oedema ^a		

		pain ^{a, e} Epistaxis	Pulmonary haemorrhage Interstitial lung disease ^a Lung infiltration ^a Hypoxia		
Gastrointestinal disorders	Diarrhoea ^{a, e} Vomiting ^{a, e} Nausea ^a	Oral Pain Constipation ^e			
Hepatobiliary disorders		Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased		
Skin and subcutaneous tissue disorders	Alopecia ^a	Rash ^a Erythema	Rash maculo-papular	Cutaneous vasculitis ^a Sweets syndrome (acute febrile neutrophilic dermatosis)	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ^c	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis	
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Glomerulonephritis Urine abnormality	
General disorders and administration site conditions	Fatigue ^a Mucosal inflammation ^a Pyrexia	Chest pain ^a Pain ^a Asthenia ^a Malaise ^e Oedema peripheral ^e	Injection site reaction		
Injury, poisoning and procedural complications		Transfusion reaction ^e			

^a See section c (Description of selected adverse reactions)

^b There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)

^c Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

^d Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilization

^e Adverse events with higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

Hypersensitivity

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after intravenous administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Pulmonary adverse events

In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4).

Splenomegaly and Splenic rupture

Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Capillary leak syndrome

Cases of capillary leak syndrome have been reported with granulocyte colony-stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Cutaneous vasculitis

Cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. During long-term use cutaneous vasculitis has been reported in 2% of SCN patients.

Leukocytosis

Leukocytosis ($WBC > 50 \times 10^9/L$) was observed in 41% of normal donors and transient thrombocytopenia (platelets $< 100 \times 10^9/L$) following filgrastim treatment and leukapheresis was observed in 35% of donors (see section 4.4).

Sweets syndrome

Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pseudogout (chondrocalcinosis pyrophosphate)

Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

GvHD

There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain which is no different from the experience in the adult population. There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric Use

No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate filgrastim use in elderly subjects for other approved Grastofil indications.

Paediatric SCN patients

Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

The effects of Grastofil overdose have not been established. Discontinuation of filgrastim 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, colony stimulating factors, ATC code: L03AA02

Grastofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Pharmacodynamic effects

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Grastofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim

therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation					
Publication	Period of Study	N	Acute Grade II - IV GvHD	Chronic GvHD	TRM
Meta-Analysis (2003)	1986 – 2001 ^a	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 – 2002 ^b	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 – 2000 ^b	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

^a Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

^b Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 micrograms/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ CD34⁺ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in ANC in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive treatments. There is no evidence that patients with HIV infection treated with filgrastim show an increase in HIV replication.

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

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 mL/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 mL/min/kg. Continuous infusion with filgrastim over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leukocytes, myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and fetal weight were observed.

Based on reported data for another filgrastim product similar to Grastofil, comparable findings plus increased fetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-fetal toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.

In pregnant rats, no maternal or fetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥ 20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).

Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Grastofil must not be diluted with saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

6.3 Shelf life

36 months.

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Accidental one-time exposure to freezing temperatures does not adversely affect the stability of Grastofil. If exposure has been greater than 24 hours or frozen more than once then Grastofil should NOT be used.

Within its shelf-life and for the purpose of ambulatory use, the patient may remove Grastofil from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 15 days. At the end of this period, Grastofil should not be put back in the refrigerator and should be disposed of in accordance with local requirements.

Keep the syringe in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Package containing one or five pre-filled syringe(s) of 0.5 mL Grastofil solution for injection. The pre-filled syringes are made from Type I glass with a permanently attached stainless steel needle in the tip and have 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.5 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, Grastofil may be diluted in 5% glucose. Dilution to a final concentration less than 0.2 MU (2 µg) per mL is not recommended at any time.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Do not shake.

For patients treated with filgrastim diluted to concentrations below 1.5 MU (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL. Example: In a final injection volume of 20 mL, total doses of filgrastim less than 30 MU (300 µg) should be given with 0.2 mL of 200 mg/mL (20%) human albumin solution added.

Grastofil contains no preservative. In view of the possible risk of microbial contamination, Grastofil pre-filled syringes are for single use only.

When diluted in 5% glucose, Grastofil is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/877/003
EU/1/13/877/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18 October 2013

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>