ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 30 million units (MU)/300 micrograms of filgrastim in 0.5ml (0.6 mg/ml) solution for injection/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/infusion.

Clear, colourless solution.

4. CLINCAL 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 $\leq 0.5 \times 10^9$/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 1.0×10^9/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 trials, a subcutaneous dose of 230 micrograms/m^2/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 leukaemia, 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 following cytotoxic chemotherapy and at least 24 hours after bone marrow injection/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 injection/infusion or given by continuous 24 hour subcutaneous injection/infusion. Grastofil should be diluted in 20 mL of 5% glucose solution- (see section 6.6).

For the mobilisation of peripheral blood progenitor cells (PBPCs) 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 leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis 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 $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis 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 injection/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 4×10^6 $CD34^+$ 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 1.5×10^9/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 x 10^9/L and 10 x 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 x 10^9/L). In clinical studies, > 90% of patients responded at these doses, achieving 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 x 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 x 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 x 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 studies 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 use in the SCN and cancer settings
Sixty-five percent of the patients studied in the 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, children and adolescents receiving cytotoxic chemotherapy.

The dose 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

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.

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 reactions
Pulmonary adverse reactions, 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 10^9/l).

Leukocytosis

White blood cell counts of 100 x 10^9/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 10^9/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 10^9/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.

<u>Special warnings and precautions associated with co-morbidities</u>

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.

<u>Special precautions in cancer patients</u>

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 medicinal products may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy medicinal products

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.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

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 sections 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.

<u>Special precautions in patients undergoing PBPC mobilisation</u>

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 optimum 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 yields 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 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 disease.

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 $< 75 \times 10^9$/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.

Special precautions in recipients of allogeneic PBPCs 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 were 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 these events.

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
Absolute neutrophil count (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 medications. As a result of the potential to receive higher doses or a greater number of these medications 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

This medicinal product contains 50 mg sorbitol. Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

This medicinal product contains 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.

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, lithium 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).

4.7 Effects on ability to drive and use machines

Filgrastim has 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

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.

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)**
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		

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)**
		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 pain[a, e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary 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	Injection site reaction	

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)**
		peripheral[e]		
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section: Description of selected adverse reactions
[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section Description of selected adverse reactions)
[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

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 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 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 patients with cancer 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).

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.
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 geriatric 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 overdosage 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 the 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 randomised 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 absolute neutrophil counts 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 medication. 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 elimination 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 foetal weight were observed.

Based on reported data for another filgrastim product similar to Grastofil, comparable findings plus increased foetal 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-foetal 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 foetal 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

Glacial acetic acid
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

3 years.

Chemical and physical in-use stability of the diluted solution for injection/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.

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

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.

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

6.5 Nature and contents of container

Type I glass pre-filled syringe with permanently attached stainless steel needle in the tip and 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 (latex, see section 4.4). Each pre-filled syringe contains 0.5 mL solution.

Pack sizes: Cartons containing 1 or 5 pre-filled syringes.

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 solution for injection/infusion. 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

Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

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 authorisation: 18 October 2013
Date of latest renewal: 4 October 2018

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Grastofil 48 MU/0.5 ml solution for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 48 million units (MU)/480 micrograms of filgrastim in 0.5ml, (0.960 mg/ml) solution for injection/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/infusion

Clear, colourless solution.

4. CLINCAL 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 $\leq 0.5 \times 10^9$/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 1.0×10^9/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 trials, a subcutaneous dose of 230 micrograms/m^2/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 leukaemia, 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 administered 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 following cytotoxic chemotherapy and at least 24 hours after bone marrow injection/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 injection/infusion or given by continuous 24 hour subcutaneous injection/infusion. Grastofil should be diluted in 20 mL of 5% glucose solution- (see section 6.6).

For the mobilisation of peripheral blood progenitor cells (PBPCs 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 leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis 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 $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis 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 injection/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 4×10^6 $CD34^+$ 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 1.5×10^9/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 x 10^9/L and 10 x 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 Grastofilat 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 x 10^9/L). In clinical studies, > 90% of patients responded at these doses, achieving 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 x 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 x 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 x 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 studies 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 use in the SCN and cancer settings
Sixty-five percent of the patients studied in the 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, children and adolescents receiving cytotoxic chemotherapy.

The dose 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

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.

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 reactions
Pulmonary adverse reactions, 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 10^9/l).

Leukocytosis
White blood cell counts of 100 x 10^9/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 10^9/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 10^9/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 warnings 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 medicinaal products may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy medicinal products 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.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

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 sections 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.

<u>Special precautions in patients undergoing PBPC mobilisation</u>

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 optimum 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 yields 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 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 disease.

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 $< 75 \times 10^9$/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.

Special precautions in recipients of allogeneic PBPCs 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 were 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 these events.

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
Absolute neutrophil count (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 medications . As a result of the potential to receive higher doses or a greater number of these medications 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

This medicinal product contains 50 mg sorbitol. Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

This medicinal product contains 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.

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, lithium 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).

4.7 Effects on ability to drive and use machines

Filgrastim has 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

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.

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)**
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			Hypersentivity 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 pain[a, e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary 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: Description of selected adverse reactions
[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section Description of selected adverse reactions)
[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

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 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 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 patients with cancer 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).

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.

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 geriatric 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 overdosage 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 the 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 randomised 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 absolute neutrophil counts 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 medication. 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 elimination 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 foetal weight were observed.

Based on reported data for another filgrastim product similar to Grastofil, comparable findings plus increased foetal 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-foetal 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 foetal 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

Glacial acetic acid
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

3 years.

Chemical and physical in-use stability of the diluted solution for injection/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.
Keep the syringe in the outer carton in order to protect from light.

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.

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

6.5 Nature and contents of container

Type I glass pre-filled syringe with permanently attached stainless steel needle in the tip and 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 (latex, see section 4.4). Each pre-filled syringe contains 0.5 mL solution.

Pack sizes: Cartons containing 1 or 5 pre-filled syringes.

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 solution for injection/infusion. 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

Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

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 authorisation: 18 October 2013
Date of latest renewal: 4 October 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Intas Pharmaceuticals Limited
Plot no: 423 P/A
Sarkhej Bavla Highway
Moraiya; Taluka: Sanand,
Ahmedabad – 382213 Gujarat, India

Name and address of the manufacturer(s) responsible for batch release

Apotex Nederland B.V.
Archimedesweg 2
2333 CN Leiden
Netherlands

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 mL solution contains 30 MU (300 micrograms) of filgrastim (600 micrograms/mL).

3. LIST OF EXCIPIENTS

Glacial acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
1 pre-filled syringe (0.5 mL)
5 pre-filled syringes (0.5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Do not shake.
Subcutaneous and intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

A diluted solution of Grastofil for injection/infusion should be used within 24 hours when stored at 2 °C to 8 °C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/877/001 1 prefilled syringe
EU/1/13/877/002 5 prefilled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Grastofil 30 MU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Grastofil 30 MU/0.5 mL solution for injection/infusion in pre-filled syringe
filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Grastofil 48 MU/0.5 mL solution for injection/infusion in pre-filled syringe
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 mL solution contains 48 MU (480 micrograms) of filgrastim (960 micrograms/mL).

3. LIST OF EXCIPIENTS

Glacial acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
1 pre-filled syringe (0.5 mL)
5 pre-filled syringes (0.5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Do not shake.
Subcutaneous and intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

A diluted solution of Grastofil for injection/infusion should be used within 24 hours when stored at 2 °C to 8 °C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/877/003 1 prefilled syringe
EU/1/13/877/004 5 prefilled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Grastofil 48 MU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Grastofil 48 MU/0.5 mL solution for injection/infusion in pre-filled syringe
filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Grastofil is and what it is used for

Grastofil contains the active substance filgrastim. Grastofil is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of medicines called cytokines. Growth factors are proteins that are produced naturally in the body but they can also be made using biotechnology for use as a medicine. Grastofil works by encouraging the bone marrow to produce more white blood cells.

A reduction in the number of white blood cells (neutropenia) can occur for several reasons and makes your body less able to fight infection. Filgrastim stimulates the bone marrow to produce new white cells quickly.

Grastofil can be used:

- to increase the number of white blood cells after treatment with chemotherapy to help prevent infections;
- to increase the number of white blood cells after a bone marrow transplant to help prevent infections;
- to increase the number of white blood cells if you suffer from severe chronic neutropenia to help prevent infections;
- in patients with advanced HIV infection which will help reduce the risk of infections;
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to you after your treatment. These can be taken from you or from a donor. The stem cells will then go back into the bone marrow and produce blood cells.

2. What you need to know before you use Grastofil

Do not use Grastofil
- if you are allergic to filgrastim or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Grastofil.

Please tell your doctor before starting treatment **if you have:**
- osteoporosis (bone disease),
- sickle cell anaemia, as filgrastim may cause sickle cell crisis.

Please tell your doctor immediately during treatment with Grastofil, if you:

- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction (hypersensitivity).
- experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual (glomerulonephritis).
- get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of an enlarged spleen (splenomegaly), or possibly rupture of the spleen).
- notice unusual bleeding or bruising (these may be symptoms of a decrease in blood platelets (thrombocytopenia), with a reduced ability of your blood to clot).
- have symptoms of inflammation of aorta (the large blood vessel which transports blood from the heart to the body), this has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience those symptoms.

Loss of response to filgrastim
If you experience a loss of response or failure to maintain a response with filgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise filgrastim's activity.

Your doctor may want to monitor you closely, see section 4 of the package leaflet.

If you are a patient with severe chronic neutropenia, you may be at risk of developing cancer of the blood (leukaemia, myelodysplastic syndrome (MDS)). You should talk to your doctor about your risks of developing cancers of the blood and what testing should be done. If you develop or are likely to develop cancers of the blood, you should not use Grastofil, unless instructed by your doctor.

If you are a stem cell donor, you must be aged between 16 and 60 years.

Take special care with other medicines that stimulate white blood cells
Grastofil is one of a group of medicines that stimulate the production of white blood cells. Your healthcare professional should always record the exact medicine you are using.

Other medicines and Grastofil
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Grastofil has not been tested in pregnant or breast-feeding women.

Grastofil is not recommended during pregnancy.

It is important to tell your doctor if you:
- are pregnant; or breast-feeding;
- think you may be pregnant, or
- are planning to have a baby.

If you become pregnant during Grastofil treatment, please inform your doctor.

Unless your doctor directs you otherwise, you must stop breast-feeding if you use Grastofil.

Driving and using machines
Grastofil may have a minor influence on your ability to drive and use machines. This medicine may cause dizziness. It is advisable to wait and see how you feel after taking Grastofil and before driving or operating machinery.

Grastofil contains sorbitol
Grastofil contains 50 mg sorbitol in each ml.
Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

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

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

3. How to use Grastofil

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How is Grastofil given and how much should I take?

Grastofil is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an intravenous infusion). The usual dose varies depending on your illness and weight. Your doctor will tell you how much Grastofil you should take.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Grastofil at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

You, or people caring for you, can be taught how to give subcutaneous injections so that you can continue your treatment at home. However, you should not attempt this unless you have been properly trained first by your health care provider.

How long will I have to take Grastofil?

You will need to take Grastofil until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take Grastofil.

Use in children

Grastofil is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dosing in children receiving chemotherapy is the same as for adults.

Instructions for injecting Grastofil

This section contains information on how to give yourself an injection of Grastofil.

Important: do not try to give yourself an injection unless you have received training from your doctor or nurse.

Grastofil is injected into the tissue just under the skin. This is known as a subcutaneuous injection.

Equipment that you need

To give yourself a subcutaneous injection you will need:
- a new pre-filled syringe of Grastofil; and
- alcohol wipes or similar.

What should I do before I give myself a subcutaneous injection of Grastofil?

1. Remove the syringe from the refrigerator. Leave the syringe at room temperature (15ºC to 25 ºC) for approximately 30 minutes or hold the pre-filled syringe gently in your hand for a few minutes. This will make the injection more comfortable. Do not warm Grastofil in any other way (for example, do not warm it in a microwave or in hot water).
2. Do not shake the pre-filled syringe.
3. Do not remove the needle cover until you are ready to inject.
4. Wash your hands thoroughly.
5. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

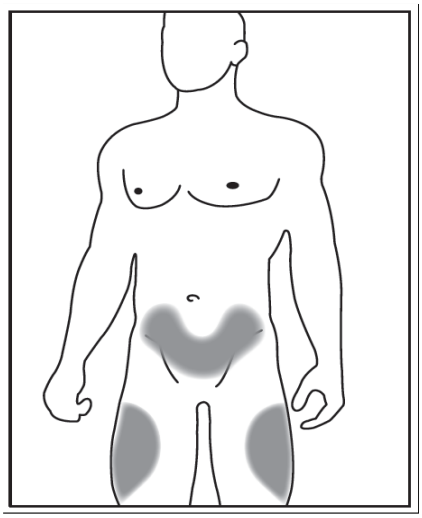
How do I prepare my Grastofil injection?

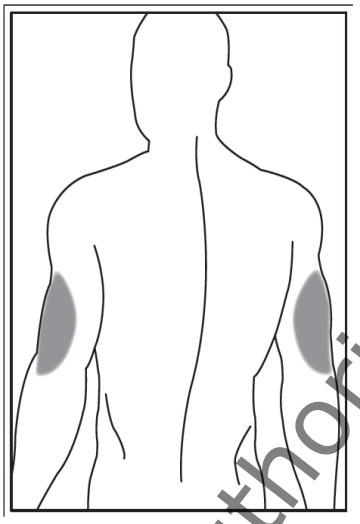
Before you inject Grastofil you must do the following:
1. To avoid bending the needle, gently pull the cover from the needle without twisting.
2. Do not touch the needle or push the plunger.
3. You may notice a small air bubble in the pre-filled syringe. You do not need to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
4. The Grastofil syringe has a scale on the syringe barrel. Hold the syringe with the needle pointing up. Push the plunger up slowly to the number (given in mL) that matches the dose of Grastofil which your doctor has prescribed.
5. You can now use the pre-filed syringe,

Where should I give my injection?

The best places to inject are the top of the thighs and the abdomen. If someone else is injecting you, they can also use the back of your arms.

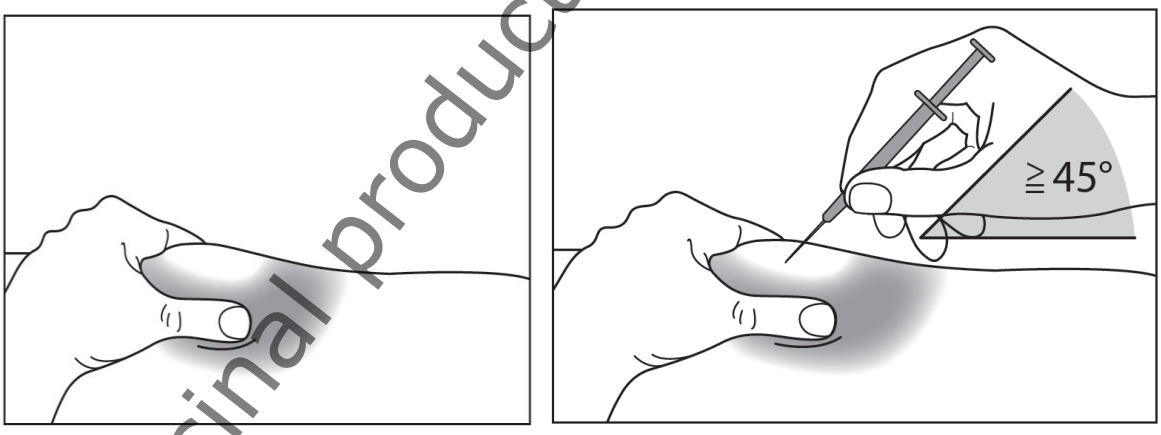
You may change the injection site if you notice the area is red or sore.





How do I give my injection?

1. Disinfect your skin by using an alcohol wipe and pinch (without squeezing) the skin between your thumb and forefinger.
2. Put the needle fully into the skin as shown by your nurse or doctor.
3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, pull the needle out and re-insert it in another place.
4. Push the plunger with a slow constant pressure, always keeping your skin pinched, until the syringe is empty.
5. Remove the needle and let go of your skin. Do not put the cover back on used needles, as you may accidentally prick yourself.
6. If you notice a spot of blood you may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
7. Only use each syringe for one injection. Do not use any Grastofil that may be left in the syringe.



Remember: if you have any problems, please ask your doctor or nurse for help and advice.

If you use more Grastofil than you should

Do not increase the dose your doctor has given you. If you think you have injected more than you should, contact your doctor as soon as possible.

If you forget to use Grastofil

If you have missed an injection, or injected too little, contact your doctor as soon as possible.

Do not take a double dose to make up for any missed doses.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately during treatment if:

- you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea).
- you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- you experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.
- you have any of the following or combination of the following side effects:
    - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

  These could be symptoms of a condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.
- you have a combination of any of the following symptoms:
    - fever, or shivering, or feeling very cold, high heart rate, confusion or disorientation, shortness of breath, extreme pain or discomfort and clammy or sweaty skin.

  These could be symptoms of a condition called “sepsis” (also called "blood poisoning"), a severe infection with whole-body inflammatory response which can be life threatening and needs urgent medical attention.
- you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder, as there may be a problem with your spleen (enlargement of the spleen (splenomegaly) or rupture of the spleen).
- you are being treated for severe chronic neutropenia and you have blood in your urine (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).

A common side effect of Grastofil use is pain in your muscles or bones (musculoskeletal pain), which can be helped by taking standard pain relief medicines (analgesics). In patients undergoing a stem cell or bone marrow transplant, Graft versus host disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints.

In normal stem cell donors an increase in white blood cells (leukocytosis) and a decrease of platelets may be seen, this reduces the ability of your blood to clot (thrombocytopenia), these will be monitored by your doctor.

Very common side effects (may affect more than 1 in 10 people):
- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)

- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever (pyrexia)

Common side effects (may affect up to 1 in 10 people):
- inflammation of the lung (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- decreased feeling of sensitivity, especially in the skin (hypoaesthesia)
- tingling or numbness of the hands or feet (paraesthesia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- cough
- coughing up blood (haemoptysis)
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin (erythema)
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain
- generalised weakness (asthenia)
- generally feeling unwell (malaise)
- swelling in the hands and feet (oedema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (may affect up to 1 in 100 people):
- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout (hyperuricaemia) (Blood uric acid increased)
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)
- bleeding from the lung (pulmonary haemorrhage)
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (rash macuo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction

Rare side effects (may affect up to 1 in 1,000 people):
- severe pain in the bones, chest, gut or joints (sickle cell anaemia with crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates fluids within your body and may result in puffiness (fluid volume disturbances)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body), see section 2.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Grastofil

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the pre-filled syringe after EXP. The expiry date refers to the last day of the month.

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

Keep the pre-filled syringe in the carton in order to protect from light.

Grastofil can be removed from the refrigerator and left at room temperature (not above 25℃) for a single period of up to 15 days that ends within the labelled expiry date. Once Grastofil has been out at room temperature it should not be put back into the refrigerator. Any Grastofil syringes that have been out of the refrigerator for longer than 15 days should not be used and should be disposed of in accordance with local requirements.

Do not use Grastofil if you notice it is cloudy, or there is discoloration or there are particles in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Grastofil contains

- The active substance is filgrastim. Each mL of solution contains 60 million units (MU) (equivalent to 600 micrograms [µg]) of filgrastim. Each pre-filled syringe contains 30 MU (300 µg) filgrastim in 0.5 mL solution.
- The other ingredients are glacial acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80 and water for injections. See section 2 “What you need to know before you use Grastofil”.

What Grastofil looks like and contents of the pack

Grastofil is a clear colourless solution for injection or infusion. It is supplied in a pre-filled syringe with an injection needle marked with 1/40 printed markings from 0.1 mL to 1 mL on the syringe barrel. Each pre-filled syringe contains 0.5 mL of solution.

Grastofil is available in packs containing 1 and 5 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

Manufacturer
Apotex Nederland B.V.
Archimedesweg 2
2333 CN Leiden
Netherlands

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT / BE / BG / CY / CZ / DE / DK / EE / ES / FI / FR / HR / HU / IE / IS / IT / LT / LV / LX / MT / NL / NO / PL / PT / RO / SE / SI / SK / UK(NI)
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Rafarm AEBE
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Τηλ: +30/2106776550

This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for medical or healthcare professionals only:

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

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.

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.
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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Grastofil 48 MU/0.5 mL solution for injection/infusion in pre-filled syringe
filgrastim

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- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
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- to increase the number of white blood cells if you suffer from severe chronic neutropenia to help prevent infections;
- in patients with advanced HIV infection which will help reduce the risk of infections;
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to you after your treatment. These can be taken from you or from a donor. The stem cells will then go back into the bone marrow and produce blood cells.

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Do not use Grastofil

- if you are allergic to filgrastim or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Grastofil:

Please tell your doctor before starting treatment **if you have:**

- osteoporosis (bone disease),
- sickle cell anaemia, as filgrastim can cause sickle cell crisis.

Please tell your doctor immediately during treatment with Grastofil, if you:

- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction (hypersensitivity).
- experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual (glomerulonephritis).
- get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of an enlarged spleen (splenomegaly), or possibly rupture of the spleen).
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Your doctor may want to monitor you closely, see section 4 of the package leaflet.

If you are a patient with severe chronic neutropenia, you may be at risk of developing cancer of the blood (leukaemia, myelodysplastic syndrome (MDS)). You should talk to your doctor about your risks of developing cancers of the blood and what testing should be done. If you develop or are likely to develop cancers of the blood, you should not use Grastofil, unless instructed by your doctor.

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It is important to tell your doctor if you
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- think you may be pregnant, or
- plan to have a baby.

If you become pregnant during Grastofil treatment, please inform your doctor.

Unless your doctor directs you otherwise, you must stop breast-feeding if you use Grastofil.

Driving and using machines

Grastofil may have a minor influence on your ability to drive and use machines. This medicine may cause dizziness. It is advisable to wait and see how you feel after taking Grastofil and before driving or operating machinery.

Grastofil contains sorbitol

Grastofil contains 50 mg sorbitol in each ml.
Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

Grastofil contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Grastofil pre-filled syringe contains dry natural rubber

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

3. How to use Grastofil

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How is Grastofil given and how much should I take?

Grastofil is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an intravenous infusion). The usual dose varies depending on your illness and weight. Your doctor will tell you how much Grastofil you should take.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Grastofil at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

You, or people caring for you, can be taught how to give subcutaneous injections so that you can continue your treatment at home. However, you should not attempt this unless you have been properly trained first by your health care provider.

How long will I have to take Grastofil?

You will need to take Grastofil until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take Grastofil.

Use in children

Grastofil is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dosing in children receiving chemotherapy is the same as for adults.

Instructions for injecting Grastofil

This section contains information on how to give yourself an injection of Grastofil.

Important: do not try to give yourself an injection unless you have received training from your doctor or nurse.

Grastofil is injected into the tissue just under the skin. This is known as a subcutaneuous injection.

Equipment that you need

To give yourself a subcutaneous injection you will need:
- a new pre-filled syringe of Grastofil; and
- alcohol wipes or similar.

What should I do before I give myself a subcutaneous injection of Grastofil?

1. Remove the syringe from the refrigerator. Leave the syringe at room temperature (15ºC to 25 ºC) for approximately 30 minutes or hold the pre-filled syringe gently in your hand for a few minutes. This will make the injection more comfortable. Do not warm Grastofil in any other way (for example, do not warm it in a microwave or in hot water).
2. Do not shake the pre-filled syringe.
3. Do not remove the needle cover until you are ready to inject.
4. Wash your hands thoroughly.
5. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

How do I prepare my Grastofil injection?

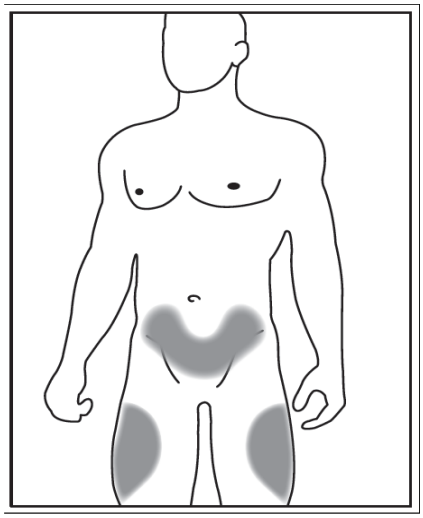
Before you inject Grastofil you must do the following:
1. To avoid bending the needle, gently pull the cover from the needle without twisting.
2. Do not touch the needle or push the plunger.

3. You may notice a small air bubble in the pre-filled syringe. You do not need to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
4. The Grastofil syringe has a scale on the syringe barrel. Hold the syringe with the needle pointing up. Push the plunger up slowly to the number (given in mL) that matches the dose of Grastofil which your doctor has prescribed.
5. You can now use the pre-filled syringe.

Where should I give my injection?

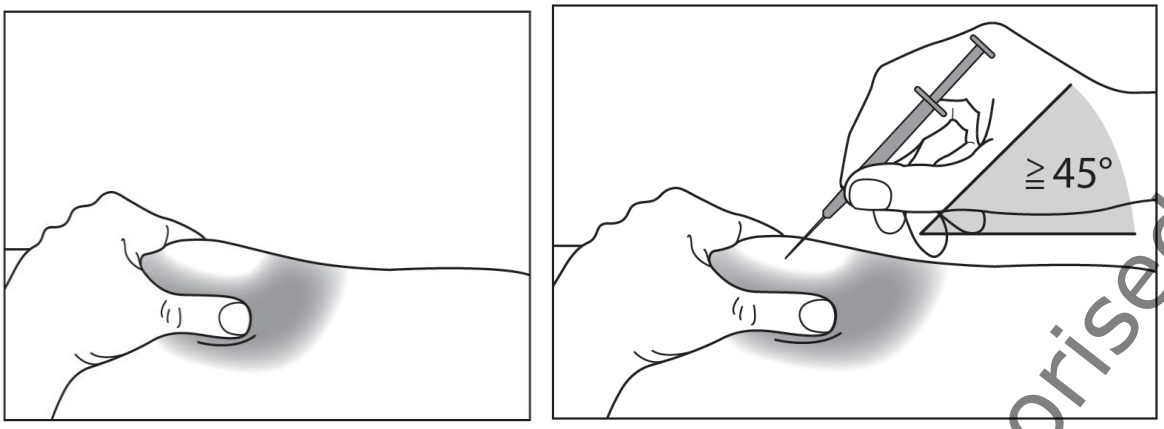
The best places to inject are the top of the thighs and the abdomen. If someone else is injecting you, they can also use the back of your arms.

You may change the injection site if you notice the area is red or sore.



How do I give my injection?

1. Disinfect your skin by using an alcohol wipe and pinch (without squeezing) the skin between your thumb and forefinger.
2. Put the needle fully into the skin as shown by your nurse or doctor.
3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, pull the needle out and re-insert it in another place.
4. Push the plunger with a slow constant pressure, always keeping your skin pinched, until the syringe is empty.
5. Remove the needle and let go of your skin. Do not put the cover back on used needles, as you may accidentally prick yourself.
6. If you notice a spot of blood you may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
7. Only use each syringe for one injection. Do not use any Grastofil that may be left in the syringe.



Remember: if you have any problems, please ask your doctor or nurse for help and advice.

If you use more Grastofil than you should

Do not increase the dose your doctor has given you. If you think you have injected more than you should, contact your doctoras soon as possible.

If you forget to use Grastofil

If you have missed an injection, or injected too little, contact your doctor as soon as possible.

Do not take a double dose to make up for any missed doses.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately during treatment if:

- you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea).
- you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- you experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.
- you have any of the following or combination of the following side effects:
    - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

  These could be symptoms of a condition called “Capillary Leak Syndrome” which causes the blood to leak from the small blood vessels into your body and needs urgent medical attention.
- you have a combination of any of the following symptoms:
    - fever, or shivering, or feeling very cold, high heart rate, confusion or disorientation, shortness of breath, extreme pain or discomfort and clammy or sweaty skin.

  These could be symptoms of a condition called “sepsis” (also called "blood poisoning"), a severe infection with whole-body inflammatory response which can be life threatening and needs urgent medical attention.

- you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder, as there may be a problem with your spleen (enlargement of the spleen (splenomegaly) or rupture of the spleen).
- you are being treated for severe chronic neutropenia and you have blood in your urine (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).

A common side effect of Grastofil use is pain in your muscles or bones (musculoskeletal pain), which can be helped by taking standard pain relief medicines (analgesics). In patients undergoing a stem cell or bone marrow transplant, Graft versus host disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints.

In normal stem cell donors an increase in white blood cells (leukocytosis) and a decrease of platelets may be seen this reduces the ability of your blood to clot (thrombocytopenia), these will be monitored by your doctor.

Very common side effects (may affect more than 1 in 10 people):
- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever (pyrexia)

Common side effects (may affect up to 1 in 10 people):
- inflammation of the lung (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- decreased feeling of sensitivity, especially in the skin (hypoaesthesia)
- tingling or numbness of the hands or feet (paraesthesia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- cough
- coughing up blood (haemoptysis)
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin (erythema)
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain

- generalised weakness (asthenia)
- generally feeling unwell (malaise)
- swelling in the hands and feet (oedema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (may affect up to 1 in 100 people):
- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout (hyperuricaemia) (Blood uric acid increased)
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)
- bleeding from the lung (pulmonary haemorrhage)
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (rash macuo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction

Rare side effects (may affect up to 1 in 1,000 people):
- severe pain in the bones, chest, gut or joints (sickle anaemia with cell crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates fluids within your body and may result in puffiness (fluidvolume disturbances)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body), see section 2.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Grastofil

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the pre-filled syringe after EXP. The expiry date refers to the last day of the month.

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

Keep the pre-filled syringe in the carton in order to protect from light.

Grastofil can be removed from the refrigerator and left at room temperature (not above 25℃) for a single period of up to 15 days that ends within the labelled expiry date. Once Grastofil has been out at room temperature it should not be put back into the refrigerator. Any Grastofil syringes that have been out of the refrigerator for longer than 15 days should not be used and should be disposed of in accordance with local requirements.
Do not use Grastofil if you notice it is cloudy, or there is discoloration or there are particles in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Grastofil contains

- The active substance is filgrastim. Each mL of solution contains 60 million units (MU) (equivalent to 600 micrograms [µg]) of filgrastim. Each pre-filled syringe contains 48 MU (480 µg) filgrastim in 0.5 mL solution.
- The other ingredients are glacial acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80 and water for injections. See section 2 “What you need to know before you use Grastofil”.

What Grastofil looks like and contents of the pack

Grastofil is a clear colourless solution for injection or infusion. It is supplied in a pre-filled syringe marked with 1/40 printed markings from 0.1 mL to 1 mL on the syringe barrel, with an injection needle. Each pre-filled syringe contains 0.5 mL of solution.

Grastofil is available in packs containing 1 and 5 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona
s/n, Edifici Est 6ª planta
08039 Barcelona
Spain

Manufacturer
Apotex Nederland B.V.
Archimedesweg 2
2333 CN Leiden
Netherlands

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT / BE / BG / CY / CZ / DE / DK / EE / ES / FI / FR / HR / HU / IE / IS / IT / LT / LV / LX / MT / NL / NO / PL / PT / RO / SE / SI / SK / UK(NI)
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This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for medical or healthcare professionals only:

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

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.

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.

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.