ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection or infusion contains 60 million international units [MIU] (600 µg) of filgrastim.

Each pre-filled syringe contains 30 MIU (300 µg) of filgrastim in 0.5 mL solution for injection or infusion.

Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor) is produced in *Escherichia coli* K802 by recombinant DNA technology.

Excipient with known effect
Each mL of solution contains 50 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tevagrastim 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 filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Tevagrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

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 Tevagrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Tevagrastim 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

Special requirements

Filgrastim 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

The recommended dose of filgrastim is 0.5 MIU (5 µg)/kg/day. The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy. Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in glucose 50 mg/mL (5 %) solution for infusion given over 30 minutes (see section 6.6 for instructions on dilution).

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 randomised clinical trials, a subcutaneous dose of 23 MIU (230 µg)/m^2/day (4.0 to 8.4 µg/kg/day) was used.

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

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

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MIU (10 µg)/kg/day given as a 30 minute or 24 hour intravenous infusion or 1.0 MIU (10 µg)/kg/day given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of glucose 50 mg/mL (5 %) solution for infusion (see section 6.6 for instructions on dilution).

The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow infusion.

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

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MIU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period the dose of filgrastim should be re-escalated according to the above steps	

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

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MIU (10 µg)/kg/day as a 24 hour subcutaneous continuous infusion or a single daily subcutaneous injection for 5 to 7 consecutive days. For infusions, filgrastim should be diluted in 20 mL of glucose 50 mg/mL (5 %) solution for infusion (see section 6.6 for instructions on dilution). Timing of leukapheresis: 1 or

2 leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MIU (5 µg)/kg/day given daily by subcutaneous injection 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 leukaphereses are recommended.

For the mobilisation of PBPC in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MIU (10 µg)/kg/day subcutaneously for 4 to 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.

In patients with severe chronic neutropenia (SCN)

Congenital neutropenia
The recommended starting dose is 1.2 MIU (12 µg)/kg/day subcutaneously as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MIU (5 µg)/kg/day subcutaneously as a single dose or in divided doses.

Dose adjustment
Filgrastim 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 to 2 weeks to maintain the average neutrophil count between 1.5×10^9/L and 10×10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97 % of patients who responded had a complete response at doses of ≤ 2.4 MIU (24 µg)/kg/day. The long-term safety of filgrastim administration above 2.4 MIU (24 µg)/kg/day in patients with SCN has not been established.

In patients with HIV infection

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

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

For maintaining 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 MIU (300 µg)/day by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at $> 2.0 \times 10^9$/L. In clinical studies, dosing with 30 MIU (300 µg)/day on 1 to 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.

Special populations

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

Patients with renal or 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 programme 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 severe chronic neutropenia.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special warnings

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

Filgrastim should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics (see below).

Special precautions in patients with acute myeloid leukaemia

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

The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Therefore, 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.

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.

Other special precautions
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.

Rare pulmonary undesirable effects, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary 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 Adult Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given in these cases.

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

Special precautions in cancer patients

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5 % of patients receiving filgrastim at doses above 0.3 MIU/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. However, during the period of administration of filgrastim for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

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

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

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

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

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

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

Special precautions in patients undergoing peripheral blood progenitor cell mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an 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 BCNU together with filgrastim has been shown to be effective for progenitor mobilisation. When a peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

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

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

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

Special precautions in normal donors undergoing peripheral blood progenitor cell mobilisation

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

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

The safety and efficacy of filgrastim have not been assessed in normal donors < 16 years or > 60 years.

Transient thrombocytopenia (platelets < 100×10^9/L) following filgrastim administration and leukapheresis was observed in 35 % of subjects studied. Among these, two cases of platelets < 50×10^9/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 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets < 75 x 10^9/L.

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

Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

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

Transient cytogenic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of haematological malignancy is unknown. Long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone can not be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs. 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 pain or shoulder tip pain.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates, dyspnoea and hypoxia) have been reported very rarely in postmarketing experience. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with filgrastim should be considered and appropriate medical care given.

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

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

Special precautions in SCN patients

Blood cell counts
Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to intermittent cessation or decreasing the dose of filgrastim in patients who develop thrombocytopenia, i.e. platelets consistently < 100,000/mm^3.

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 severe chronic neutropenias to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

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

monosomy 7, on routine repeat evaluation. If patients with SCN develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully weighed; filgrastim should be discontinued if MDS or leukaemia occur. 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.

Splenic enlargement is a direct effect of treatment with filgrastim. Thirty-one percent (31 %) of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during filgrastim therapy and tended to plateau. Dose reductions were noted to slow or stop the progression of splenic enlargement and in 3 % of patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.

Haematuria/proteinuria occurred in a small number of patients. Regular urinanalysis should be performed to monitor this event.

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

Special precautions in patients with HIV infection

Blood cell counts
ANC should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice weekly for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MIU (300 µg)/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 medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

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

Special precautions in sickle cell disease

Sickle cells crises, in some cases fatal, have been reported with the use of filgrastim in subjects with sickle cell disease. Physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease and only after careful evaluation of the potential risks and benefits.

Excipients

Tevagrastim contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of filgrastim in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Filgrastim should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether filgrastim is excreted in human breast milk. The excretion of filgrastim in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with filgrastim should be made taking into account the benefit of breast-feeding to the child and the benefit of filgrastim therapy to the woman.

4.7 Effects on ability to drive and use machines

Filgrastim has minor or moderate influence on the ability to drive and use machines. If the patient is experiencing fatigue, caution is advised when driving a car or operating machines.

4.8 Undesirable effects

Summary of the safety profile

During clinical studies 541 cancer patients and 188 healthy volunteers were exposed to Tevagrastim. The safety profile of Tevagrastim observed in these clinical studies was consistent with that reported with the reference product used in these studies.

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilisation following administration of G-CSFs; see section 4.4 and subsection "Description of selected adverse reactions" of section 4.8.

The following undesirable effects and their frequencies have been observed under treatment with filgrastim based on published information.

The assessment of undesirable effects is based on the following frequency data:

Very common:	≥ 1/10
Common:	≥ 1/100 to < 1/10
Uncommon:	≥ 1/1,000 to < 1/100
Rare:	≥ 1/10,000 to < 1/1,000
Very rare:	< 1/10,000
Not known:	cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

In cancer patients

In clinical trials, the most frequent undesirable effects attributable to filgrastim at the recommended dose were mild or moderate musculoskeletal pain, occurring in 10 %, and severe musculoskeletal pain in 3 % of patients. Musculoskeletal pain is usually controlled with standard analgesics. Less frequent undesirable effects include urinary abnormalities predominantly mild or moderate dysuria.

In randomised, placebo-controlled clinical trials, filgrastim did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. Undesirable effects reported with equal frequency in patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalised weakness, sore throat, constipation and unspecified pain.

Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase (LDH), alkaline phosphatase, serum uric acid and gamma-glutamyltransferase (GGT) occurred with filgrastim in approximately 50 %, 35 %, 25 %, and 10 % of patients respectively, at recommended doses.

Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.

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

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with filgrastim has not been established.

Very rare events of cutaneous vasculitis have been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown.

The occurrence of Sweet's syndrome (acute febrile dermatosis) has been reported occasionally. However, since a significant percentage of these patients were suffering from leukaemia, a condition known to be associated with Sweet's syndrome, a causal relationship with filgrastim has not been established.

Exacerbation of rheumatoid arthritis has been observed in individual cases.

Pseudogout has been reported in patients with cancer treated with filgrastim.

Rare pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal (see section 4.4).

Allergic Reactions: Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension, occurring on initial or subsequent treatment, have been reported in patients receiving filgrastim. Overall, reports were more common after IV 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.

Isolated cases of sickle cells crises have been reported in patients with sickle cell disease (see section 4.4).

System organ class	**Frequency**	**Undesirable effect**
Metabolism and nutrition disorders	Very common	Elevated alkaline phosphatase, elevated LDH, elevated uric acid
Nervous system disorders	Common	Headache
Vascular disorders	Rare	Vascular disorder
	Uncommon	Capillary leak syndrome*
Respiratory, thoracic and mediastinal disorders	Common	Cough, sore throat
	Very rare	Pulmonary infiltrates
Gastrointestinal disorders	Very common	Nausea/Vomiting
	Common	Constipation, anorexia, diarrhoea, mucositis
Hepatobiliary disorders	Very common	Elevated GGT
Skin and subcutaneous tissue disorders	Common	Alopecia, skin rash
	Very rare	Sweet's syndrome, cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very common	Chest pain, musculoskeletal pain
	Very rare	Rheumatoid arthritis exacerbation
Renal and urinary disorders	Very rare	Urinary abnormalities
General disorders and administration site conditions	Common	Fatigue, generalised weakness
	Uncommon	Unspecified pain
	Very rare	Allergic reaction
*See subsection “Description of selected adverse reactions” of section 4.8		

In peripheral blood progenitor cell mobilisation in normal donors

The most commonly reported undesirable effect was mild to moderate transient musculo-skeletal pain. Leukocytosis (WBC > 50 x 10^9/L) was observed in 41 % of donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35 % of donors.

Transient, minor increases in alkaline phosphatase, LDH, SGOT (serum glutamic oxaloacetic transaminase) and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs (see section 4.4).

In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltration, dyspnoea and hypoxia) have been reported in postmarketing experience (see section 4.4).

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very common	Leukocytosis, thrombocytopenia
	Uncommon	Spleen disorder
Metabolism and nutrition disorders	Common	Elevated alkaline phosphatase, elevated LDH
	Uncommon	SGOT increased, hyperuricaemia
Nervous system disorders	Very common	Headache
Vascular disorders	Uncommon	Capillary leak syndrome*
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Uncommon	Rheumatoid arthritis exacerbation
General disorders and administration site conditions	Uncommon	Severe allergic reaction
*See subsection "Description of selected adverse reactions" of section 4.8		

In SCN patients

Undesirable effects related to filgrastim therapy in SCN patients have been reported and for some their frequencies tend to decrease with time.

The most frequent undesirable effects attributable to filgrastim were bone pain, and general musculoskeletal pain.

Other undesirable effects seen include splenic enlargement, which may be progressive in a minority of cases and thrombocytopenia. Headache and diarrhoea have been reported shortly after starting filgrastim therapy, typically in less than 10 % of patients. Anaemia and epistaxis have also been reported.

Transient increases with no clinical symptoms were observed in serum uric acid, lactic dehydrogenase and alkaline phosphatase. Transient, moderate decreases in non-fasting blood glucose have also been seen.

Undesirable effects possibly related to filgrastim therapy and typically occurring in < 2 % of SCN patients were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis and rash.

During long term use, cutaneous vasculitis has been reported in 2 % of SCN patients. There have been very few instances of proteinuria/haematuria.

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very common	Anaemia, splenomegaly
	Common	Thrombocytopenia
	Uncommon	Spleen disorder
Metabolism and nutrition disorders	Very common	Decreased glucose, elevated alkaline phosphatase, elevated LDH, hyperuricaemia
Nervous system disorders	Common	Headache
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Common	Diarrhoea
Hepatobiliary disorders	Common	Hepatomegaly
Skin and subcutaneous tissue disorders	Common	Alopecia, cutaneous vasculitis, injection site pain, rash
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Osteoporosis
Renal and urinary disorders	Uncommon	Haematuria, proteinuria

In patients with HIV

In clinical studies, the only undesirable effects that were consistently considered to be related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. The incidence of these events was similar to that reported in cancer patients.

Splenic enlargement was reported to be related to filgrastim therapy in < 3 % of patients. In all cases this was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Common	Spleen disorder
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain

Description of selected adverse reactions

Cases of capillary leak syndrome have been reported in the postmarketing setting with G-CSF use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

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

No case of overdose has been reported.

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

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

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Tevagrastim 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 prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50 % within 1 to 2 days, and to normal levels within 1 to 7 days.

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

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

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

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

Relative risk (95 % CI) of GvHD and TRM following treatment with G-CSF after bone marrow 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 bone marrow transplant during this period; some studies used GM-CSF (granulocyte-macrophage–colony stimulating factor) [b]Analysis includes patients receiving bone marrow transplant during this period					

Prior to allogeneic PBPC transplantation, use of filgrastim for the mobilisation of PBPC in normal donors allows a collection of 4 x 10^6 $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses. Normal donors are given a dose of a 10 μg/kg/day, administered subcutaneously for 4 to 5 consecutive days.

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 medicinal product. 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.

The efficacy and safety of Tevagrastim has been assessed in randomised, controlled phase III studies in breast cancer, lung cancer and Non-Hodgkin-Lymphoma. There were no relevant differences between Tevagrastim and the reference product with regard to duration of severe neutropenia and incidence of febrile neutropenia.

5.2 Pharmacokinetic properties

Randomised, single-blind, single dose, crossover studies in 196 healthy volunteers showed that the pharmacokinetic profile of Tevagrastim was comparable to that of the reference product after subcutaneous and intravenous administration.

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. There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 to 16 hours. The volume of distribution in blood is approximately 150 mL/kg.

In cancer patients, the pharmacokinetic profile of Tevagrastim and the reference product was comparable after single and repeated subcutaneous administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and local tolerance.

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

No effect was observed on the fertility of male and female rats or gestation in rats. There is no evidence from studies in rats and rabbits that filgrastim is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Tevagrastim should not be diluted with sodium chloride solution.

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

Diluted filgrastim may be adsorbed to glass and plastic materials except diluted, as mentioned in section 6.6.

6.3 Shelf life

30 months.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with injection needle (stainless steel), with or without a needle safety guard.

Packs containing 1, 5 or 10 pre-filled syringes with 0.5 mL solution or multipacks containing 10 (2 packs of 5) pre-filled syringes with 0.5 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, Tevagrastim may be diluted in glucose 50 mg/mL (5 %) solution for infusion.

Dilution to a final concentration less than 0.2 MIU (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 MIU (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 MIU (300 μg) should be given with 0.2 mL of 200 mg/mL (20 %) human albumin solution added.

When diluted in glucose 50 mg/mL (5 %) solution for infusion, Tevagrastim is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Tevagrastim does not contain any preservative. In view of the possible risk of microbial contamination, Tevagrastim syringes are for single use only.

Accidental exposure to freezing temperatures does not adversely affect the stability of Tevagrastim.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/001
EU/1/08/445/002

EU/1/08/445/003
EU/1/08/445/004
EU/1/08/445/009
EU/1/08/445/010
EU/1/08/445/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2008.
Date of latest renewal: 19 July 2013.

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

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection or infusion contains 60 million international units [MIU] (600 µg) of filgrastim.

Each pre-filled syringe contains 48 MIU (480 µg) of filgrastim in 0.8 mL solution for injection or infusion.

Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor) is produced in *Escherichia coli* K802 by recombinant DNA technology.

Excipient with known effect
Each mL of solution contains 50 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tevagrastim 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 filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Tevagrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

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 Tevagrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Tevagrastim 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

Special requirements

Filgrastim 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

The recommended dose of filgrastim is 0.5 MIU (5 µg)/kg/day. The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy. Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in glucose 50 mg/mL (5 %) solution for infusion given over 30 minutes (see section 6.6 for instructions on dilution).

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 randomised clinical trials, a subcutaneous dose of 23 MIU (230 µg)/m^2/day (4.0 to 8.4 µg/kg/day) was used.

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

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

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MIU (10 µg)/kg/day given as a 30 minute or 24 hour intravenous infusion or 1.0 MIU (10 µg)/kg/day given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of glucose 50 mg/mL (5 %) solution for infusion (see section 6.6 for instructions on dilution).

The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow infusion.

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

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MIU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period the dose of filgrastim should be re-escalated according to the above steps	

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

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MIU (10 µg)/kg/day as a 24 hour subcutaneous continuous infusion or a single daily subcutaneous injection for 5 to 7 consecutive days. For infusions, filgrastim should be diluted in 20 mL of glucose 50 mg/mL (5 %) solution for infusion (see section 6.6 for instructions on dilution). Timing of leukapheresis: 1 or

2 leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MIU (5 µg)/kg/day given daily by subcutaneous injection 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 leukaphereses are recommended.

For the mobilisation of PBPC in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MIU (10 µg)/kg/day subcutaneously for 4 to 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.

In patients with severe chronic neutropenia (SCN)

Congenital neutropenia
The recommended starting dose is 1.2 MIU (12 µg)/kg/day subcutaneously as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MIU (5 µg)/kg/day subcutaneously as a single dose or in divided doses.

Dose adjustment
Filgrastim 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 to 2 weeks to maintain the average neutrophil count between 1.5×10^9/L and 10×10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97 % of patients who responded had a complete response at doses of ≤ 2.4 MIU (24 µg)/kg/day. The long-term safety of filgrastim administration above 2.4 MIU (24 µg)/kg/day in patients with SCN has not been established.

In patients with HIV infection

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

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

For maintaining 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 MIU (300 µg)/day by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at $> 2.0 \times 10^9$/L. In clinical studies, dosing with 30 MIU (300 µg)/day on 1 to 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.

Special populations

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

Patients with renal or 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 programme 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 severe chronic neutropenia.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special warnings

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

Filgrastim should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics (see below).

Special precautions in patients with acute myeloid leukaemia

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

The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Therefore, 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.

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.

Other special precautions
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.

Rare pulmonary undesirable effects, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary 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 Adult Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given in these cases.

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

Special precautions in cancer patients

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5 % of patients receiving filgrastim at doses above 0.3 MIU/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. However, during the period of administration of filgrastim for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

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

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

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

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

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

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

Special precautions in patients undergoing peripheral blood progenitor cell mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an 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 BCNU together with filgrastim has been shown to be effective for progenitor mobilisation. When a peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

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

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

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

Special precautions in normal donors undergoing peripheral blood progenitor cell mobilisation

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

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

The safety and efficacy of filgrastim have not been assessed in normal donors < 16 years or > 60 years.

Transient thrombocytopenia (platelets < 100×10^9/L) following filgrastim administration and leukapheresis was observed in 35 % of subjects studied. Among these, two cases of platelets < 50×10^9/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.

Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to $> 70 \times 10^9$/L.

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

Transient cytogenic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of haematological malignancy is unknown. Long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone can not be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs. 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 pain or shoulder tip pain.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates, dyspnoea and hypoxia) have been reported very rarely in postmarketing experience. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with filgrastim should be considered and appropriate medical care given.

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

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

Special precautions in SCN patients

Blood cell counts
Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to intermittent cessation or decreasing the dose of filgrastim in patients who develop thrombocytopenia, i.e. platelets consistently $< 100{,}000/mm^3$.

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 severe chronic neutropenias to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

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

monosomy 7, on routine repeat evaluation. If patients with SCN develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully weighed; filgrastim should be discontinued if MDS or leukaemia occur. 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.

Splenic enlargement is a direct effect of treatment with filgrastim. Thirty-one percent (31 %) of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during filgrastim therapy and tended to plateau. Dose reductions were noted to slow or stop the progression of splenic enlargement and in 3 % of patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.

Haematuria/proteinuria occurred in a small number of patients. Regular urinanalysis should be performed to monitor this event.

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

Special precautions in patients with HIV infection

Blood cell counts
ANC should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice weekly for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MIU (300 µg)/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 medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

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

Special precautions in sickle cell disease

Sickle cells crises, in some cases fatal, have been reported with the use of filgrastim in subjects with sickle cell disease. Physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease and only after careful evaluation of the potential risks and benefits.

Excipients

Tevagrastim contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of filgrastim in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Filgrastim should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether filgrastim is excreted in human breast milk. The excretion of filgrastim in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with filgrastim should be made taking into account the benefit of breast-feeding to the child and the benefit of filgrastim therapy to the woman.

4.7 Effects on ability to drive and use machines

Filgrastim has minor or moderate influence on the ability to drive and use machines. If the patient is experiencing fatigue, caution is advised when driving a car or operating machines.

4.8 Undesirable effects

Summary of the safety profile

During clinical studies 541 cancer patients and 188 healthy volunteers were exposed to Tevagrastim. The safety profile of Tevagrastim observed in these clinical studies was consistent with that reported with the reference product used in these studies.

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilisation following administration of G-CSFs; see section 4.4 and subsection "Description of selected adverse reactions" of section 4.8.

The following undesirable effects and their frequencies have been observed under treatment with filgrastim based on published information.

The assessment of undesirable effects is based on the following frequency data:

Very common:	≥ 1/10
Common:	≥ 1/100 to < 1/10
Uncommon:	≥ 1/1,000 to < 1/100
Rare:	≥ 1/10,000 to < 1/1,000
Very rare:	< 1/10,000
Not known:	cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

In cancer patients

In clinical trials, the most frequent undesirable effects attributable to filgrastim at the recommended dose were mild or moderate musculoskeletal pain, occurring in 10 %, and severe musculoskeletal pain in 3 % of patients. Musculoskeletal pain is usually controlled with standard analgesics. Less frequent undesirable effects include urinary abnormalities predominantly mild or moderate dysuria.

In randomised, placebo-controlled clinical trials, filgrastim did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. Undesirable effects reported with equal frequency in patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalised weakness, sore throat, constipation and unspecified pain.

Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase (LDH), alkaline phosphatase, serum uric acid and gamma-glutamyltransferase (GGT) occurred with filgrastim in approximately 50 %, 35 %, 25 %, and 10 % of patients respectively, at recommended doses.

Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.

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

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with filgrastim has not been established.

Very rare events of cutaneous vasculitis have been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown.

The occurrence of Sweet's syndrome (acute febrile dermatosis) has been reported occasionally. However, since a significant percentage of these patients were suffering from leukaemia, a condition known to be associated with Sweet's syndrome, a causal relationship with filgrastim has not been established.

Exacerbation of rheumatoid arthritis has been observed in individual cases.

Pseudogout has been reported in patients with cancer treated with filgrastim.

Rare pulmonary undesirable effects including interstitial pneumonia, pulmonary oedema and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS) which may be fatal (see section 4.4).

Allergic Reactions: Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension, occurring on initial or subsequent treatment, have been reported in patients receiving filgrastim. Overall, reports were more common after IV 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.

Isolated cases of sickle cells crises have been reported in patients with sickle cell disease (see section 4.4).

System organ class	Frequency	Undesirable effect
Metabolism and nutrition disorders	Very common	Elevated alkaline phosphatase, elevated LDH, elevated uric acid
Nervous system disorders	Common	Headache
Vascular disorders	Rare	Vascular disorder
	Uncommon	Capillary leak syndrome*
Respiratory, thoracic and mediastinal disorders	Common	Cough, sore throat
	Very rare	Pulmonary infiltrates
Gastrointestinal disorders	Very common	Nausea/Vomiting
	Common	Constipation, anorexia, diarrhoea, mucositis
Hepatobiliary disorders	Very common	Elevated GGT
Skin and subcutaneous tissue disorders	Common	Alopecia, skin rash
	Very rare	Sweet's syndrome, cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very common	Chest pain, musculoskeletal pain
	Very rare	Rheumatoid arthritis exacerbation
Renal and urinary disorders	Very rare	Urinary abnormalities
General disorders and administration site conditions	Common	Fatigue, generalised weakness
	Uncommon	Unspecified pain
	Very rare	Allergic reaction
*See subsection “Description of selected adverse reactions” of section 4.8		

In peripheral blood progenitor cell mobilisation in normal donors

The most commonly reported undesirable effect was mild to moderate transient musculo-skeletal pain. Leukocytosis (WBC > 50 x 10^9/L) was observed in 41 % of donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35 % of donors.

Transient, minor increases in alkaline phosphatase, LDH, SGOT (serum glutamic oxaloacetic transaminase) and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs (see section 4.4).

In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltration, dyspnoea and hypoxia) have been reported in postmarketing experience (see section 4.4).

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very common	Leukocytosis, thrombocytopenia
	Uncommon	Spleen disorder
Metabolism and nutrition disorders	Common	Elevated alkaline phosphatase, elevated LDH
	Uncommon	SGOT increased, hyperuricaemia
Nervous system disorders	Very common	Headache
Vascular disorders	Uncommon	Capillary leak syndrome*
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Uncommon	Rheumatoid arthritis exacerbation
General disorders and administration site conditions	Uncommon	Severe allergic reaction
*See subsection "Description of selected adverse reactions" of section 4.8		

In SCN patients

Undesirable effects related to filgrastim therapy in SCN patients have been reported and for some their frequencies tend to decrease with time.

The most frequent undesirable effects attributable to filgrastim were bone pain, and general musculoskeletal pain.

Other undesirable effects seen include splenic enlargement, which may be progressive in a minority of cases and thrombocytopenia. Headache and diarrhoea have been reported shortly after starting filgrastim therapy, typically in less than 10 % of patients. Anaemia and epistaxis have also been reported.

Transient increases with no clinical symptoms were observed in serum uric acid, lactic dehydrogenase and alkaline phosphatase. Transient, moderate decreases in non-fasting blood glucose have also been seen.

Undesirable effects possibly related to filgrastim therapy and typically occurring in < 2 % of SCN patients were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis and rash.

During long term use, cutaneous vasculitis has been reported in 2 % of SCN patients. There have been very few instances of proteinuria/haematuria.

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very common	Anaemia, splenomegaly
	Common	Thrombocytopenia
	Uncommon	Spleen disorder
Metabolism and nutrition disorders	Very common	Decreased glucose, elevated alkaline phosphatase, elevated LDH, hyperuricaemia
Nervous system disorders	Common	Headache
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Common	Diarrhoea
Hepatobiliary disorders	Common	Hepatomegaly
Skin and subcutaneous tissue disorders	Common	Alopecia, cutaneous vasculitis, injection site pain, rash
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Osteoporosis
Renal and urinary disorders	Uncommon	Haematuria, proteinuria

In patients with HIV

In clinical studies, the only undesirable effects that were consistently considered to be related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. The incidence of these events was similar to that reported in cancer patients.

Splenic enlargement was reported to be related to filgrastim therapy in < 3 % of patients. In all cases this was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Common	Spleen disorder
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain

Description of selected adverse reactions

Cases of capillary leak syndrome have been reported in the postmarketing setting with G-CSF use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

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

No case of overdose has been reported.

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

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

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Tevagrastim 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 prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50 % within 1 to 2 days, and to normal levels within 1 to 7 days.

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

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

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

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

Relative risk (95 % CI) of GvHD and TRM following treatment with G-CSF after bone marrow 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 bone marrow transplant during this period; some studies used GM-CSF (granulocyte-macrophage–colony stimulating factor) [b]Analysis includes patients receiving bone marrow transplant during this period					

Prior to allogeneic PBPC transplantation, use of filgrastim for the mobilisation of PBPC in normal donors allows a collection of 4 x 10^6 $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses. Normal donors are given a dose of a 10 μg/kg/day, administered subcutaneously for 4 to 5 consecutive days.

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 medicinal product. 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.

The efficacy and safety of Tevagrastim has been assessed in randomised, controlled phase III studies in breast cancer, lung cancer and Non-Hodgkin-Lymphoma. There were no relevant differences between Tevagrastim and the reference product with regard to duration of severe neutropenia and incidence of febrile neutropenia.

5.2 Pharmacokinetic properties

Randomised, single-blind, single dose, crossover studies in 196 healthy volunteers showed that the pharmacokinetic profile of Tevagrastim was comparable to that of the reference product after subcutaneous and intravenous administration.

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. There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 to 16 hours. The volume of distribution in blood is approximately 150 mL/kg.

In cancer patients, the pharmacokinetic profile of Tevagrastim and the reference product was comparable after single and repeated subcutaneous administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and local tolerance.

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

No effect was observed on the fertility of male and female rats or gestation in rats. There is no evidence from studies in rats and rabbits that filgrastim is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Tevagrastim should not be diluted with sodium chloride solution.

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

Diluted filgrastim may be adsorbed to glass and plastic materials except diluted, as mentioned in section 6.6.

6.3 Shelf life

30 months.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with injection needle (stainless steel), with or without a needle safety guard.

Packs containing 1, 5 or 10 pre-filled syringes with 0.8 mL solution or multipacks containing 10 (2 packs of 5) pre-filled syringes with 0.8 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, Tevagrastim may be diluted in glucose 50 mg/mL (5 %) solution for infusion.

Dilution to a final concentration less than 0.2 MIU (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 MIU (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 MIU (300 μg) should be given with 0.2 mL of 200 mg/mL (20 %) human albumin solution added.

When diluted in glucose 50 mg/mL (5 %) solution for infusion, Tevagrastim is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Tevagrastim does not contain any preservative. In view of the possible risk of microbial contamination, Tevagrastim syringes are for single use only.

Accidental exposure to freezing temperatures does not adversely affect the stability of Tevagrastim.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/005
EU/1/08/445/006

EU/1/08/445/007
EU/1/08/445/008
EU/1/08/445/012
EU/1/08/445/013
EU/1/08/445/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2008.
Date of latest renewal: 19 July 2013.

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

SICOR Biotech UAB
Molėtų pl. 5
08409 Vilnius
Lithuania

Name and address of the manufacturer responsible for batch release

Teva Pharma B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 and any agreed 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled Syringe

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

1 pre-filled syringe with 0.5 mL
5 pre-filled syringes with 0.5 mL
10 pre-filled syringes with 0.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/001 1 pre-filled syringe
EU/1/08/445/002 5 pre-filled syringes
EU/1/08/445/004 10 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 30 MIU/0.5 mL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled Syringe

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

1 pre-filled syringe with 0.8 mL
5 pre-filled syringes with 0.8 mL
10 pre-filled syringes with 0.8 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/005 1 pre-filled syringe
EU/1/08/445/006 5 pre-filled syringes
EU/1/08/445/008 10 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 48 MIU/0.8 mL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

1 pre-filled syringe with 0.5 mL with a needle safety guard
5 pre-filled syringes with 0.5 mL with a needle safety guard
10 pre-filled syringes with 0.5 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/009 1 pre-filled syringe with a needle safety guard
EU/1/08/445/010 5 pre-filled syringe with a needle safety guard
EU/1/08/445/01110 pre-filled syringe with a needle safety guard

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 30 MIU/0.5 mL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

1 pre-filled syringe with 0.8 mL with a needle safety guard
5 pre-filled syringes with 0.8 mL with a needle safety guard
10 pre-filled syringes with 0.8 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/012 1 pre-filled syringe with a needle safety guard
EU/1/08/445/013 5 pre-filled syringe with a needle safety guard
EU/1/08/445/014 10 pre-filled syringe with a needle safety guard

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 48 MIU/0.8 mL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Wrapper Label on Multipacks - With Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

Multipack: 10 (2 packs of 5) pre-filled syringes containing 0.5 mL.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/003 2 x 5 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Wrapper Label on Multipacks - With Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

Multipack: 10 (2 packs of 5) pre-filled syringes containing 0.8 mL.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/007 2 x 5 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Multipack Carton - Without Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

5 pre-filled syringes containing 0.5 mL. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/003 2 x 5 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 30 MIU/0.5 mL

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Multipack Carton - Without Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

Filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL (60 MIU/mL, 600 microgram/mL).

3. LIST OF EXCIPIENTS

Excipients: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion

5 pre-filled syringes containing 0.8 mL. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use and intravenous use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE 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

After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

TEVA GmbH
Graf-Arco-Straße 3
89079 Ulm
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/445/007 2 x 5 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tevagrastim 48 MIU/0.8 mL

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

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

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion

Filgrastim

SC
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

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

Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

Filgrastim

SC
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion
Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

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 Tevagrastim is and what it is used for

What Tevagrastim is
Tevagrastim contains the active substance filgrastim. Filgrastim is a protein produced by biotechnology in bacteria called *Escherichia coli*. It belongs to a group of proteins called cytokines and is very similar to a natural protein (granulocyte-colony stimulating factor [G-CSF]) produced by your own body. Filgrastim stimulates the bone marrow (the tissue where new blood cells are made) to produce more blood cells, especially certain types of white cells. White cells are important as they help your body fight infection.

What Tevagrastim is used for
Your doctor has prescribed Tevagrastim for you to help your body make more white blood cells. Your doctor will tell you why you are being treated with Tevagrastim. Tevagrastim is useful in several different conditions, which are:
- chemotherapy;
- bone marrow transplantation;
- severe chronic neutropenia (low white blood cell count);
- neutropenia in patients with HIV infection;
- peripheral blood stem cell mobilisation (for blood stem cell donation).

2. What you need to know before you use Tevagrastim

Do not use Tevagrastim
- 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 Tevagrastim
- if you experience a cough, fever and difficulty breathing. It could be a consequence of a pulmonary disorder (see section “4. Possible side effects”).
- if you have sickle cell disease (an inherited disease characterised by sickle-shaped red blood cells).
- if you get left upper abdominal pain or pain at the tip of your shoulder. It could be a consequence of a spleen disorder (see section “4. Possible side effects”).
- if you have specific blood disorders (e.g. Kostman's syndrome, myelodysplastic syndrome, different types of leukaemia).
- if you have osteoporosis. Your doctor might check your bone density regularly.
- if you are suffering from any other illness, especially if you think you have an infection.

Talk to your doctor or nurse that you are treated with Tevagrastim if you are undergoing bone-imaging.

You will need to have regular blood tests whilst being treated with Tevagrastim to count the number of neutrophils and other white blood cells in your blood. This will tell your doctor how well the treatment is working and will also indicate if treatment needs to be continued.

Other medicines and Tevagrastim
Tell your doctor or pharmacist if you are using have recently used or might use any other medicines.

Do not use Tevagrastim in the 24 hours before or the 24 hours after your chemotherapy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Tevagrastim has not been tested in pregnant women. Therefore, your doctor may decide that you should not use this medicine.

It is unknown whether filgrastim passes over to the breast milk. Therefore, your doctor may decide that you should not use this medicine if you are breast-feeding.

Driving and using machines
If you experience fatigue, do not drive or use any tools or machines.

Tevagrastim contains sorbitol and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially ‘sodium-free’.

3. How to use Tevagrastim

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

The recommended dose is...
The amount of Tevagrastim you need, will depend on the condition you are taking Tevagrastim for and on your bodyweight. Your doctor will tell you when to stop using Tevagrastim. It is quite normal to have a number of courses of Tevagrastim treatment.

Tevagrastim and chemotherapy
The usual dose is 0.5 million international units (MIU) per kilogram of bodyweight each day. For example, if you weigh 60 kg your daily dose will be 30 million international units (MIU). You will normally receive your first dose of Tevagrastim at least 24 hours after your chemotherapy. Your treatment will usually last for about 14 days. In some disease types however, longer treatment lasting up to about one month may be required.

Tevagrastim and bone marrow transplantation
The usual starting dose is 1 million international units (MIU) per kilogram of bodyweight each day. For example, if you weigh 60 kg your daily dose will be 60 million international units (MIU). You will normally receive your first dose of Tevagrastim at least 24 hours after your chemotherapy but within 24 hours of receiving your bone marrow transfusion. Your doctor will test your blood daily to see how well the treatment is working and to find the dose that is best for you. The treatment will be discontinued when white cells in your blood reach a certain number.

Tevagrastim and severe chronic neutropenia
The usual starting dose is between 0.5 million and 1.2 million international units (MIU) per kilogram bodyweight each day in a single or divided dose. Your doctor will then test your blood to see how well your treatment is working and to find the dose that is best for you. Long-term treatment with Tevagrastim is required for neutropenia.

Tevagrastim and neutropenia in patients with HIV infection
The usual starting dose is between 0.1 and 0.4 million international units (MIU) per kilogram bodyweight each day. Your doctor will test your blood at regular intervals to see how well the treatment is working. Once the number of white cells in your blood have returned to normal it may be possible to reduce the dose frequency to less than once per day. Your doctor will continue to test your blood regularly and will recommend the best dose for you. Long-term treatment with Tevagrastim may be required to maintain a normal number of white cells in your blood.

Tevagrastim and peripheral blood stem cell mobilisation
If you are donating stem cells for yourself, the usual dose is 0.5 million to 1 million international units (MIU) per kilogram bodyweight each day. Tevagrastim treatment will last for up to 2 weeks and in exceptional cases longer. Your doctor will monitor your blood to determine the best time to collect the stem cells.

If you are acting as a stem cell donor for another person, the usual dose is 1 million international units (MIU) per kilogram bodyweight each day. Tevagrastim treatment will last for 4 to 5 days.

Method of administration
This medicine is given by injection, either through an intravenous (IV) infusion (drip) or a subcutaneous (SC) injection (into the tissue just under the skin). If you are receiving this medicine by subcutaneous injection, your doctor may suggest that you learn how to give yourself the injections. Your doctor or nurse will give you instructions on how to do this. Do not attempt to self-administer without this training. Some of the information you require is given at the end of this package leaflet, but proper treatment of your disease requires close and constant co-operation with your doctor.

If you use more Tevagrastim than you should
If you use more Tevagrastim than you should, contact your doctor or pharmacist as soon as possible.

If you forget to use Tevagrastim
Do not use a double dose to make up for a forgotten injection.

If you stop using Tevagrastim
Before you stop using Tevagrastim, talk to your doctor.

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

4. Possible side effects

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

Important side effects

- Allergic reactions such as skin rash, raised itchy areas of skin and serious allergic reactions with weakness, drop in blood pressure, difficulty breathing and swelling of the face have been reported. If you think you are having this type of reaction, you must stop your Tevagrastim injection and get medical help immediately.

- Increased spleen size and cases of spleen ruptures have been reported. Some cases of splenic rupture were fatal. It is important to contact your doctor immediately if you experience ***pain in the upper left side of the abdomen or left shoulder pain*** since this may relate to a problem with your spleen.

- Cough, fever and difficult or painful breathing can be signs of serious pulmonary side effects, such as pneumonia and acute respiratory distress syndrome, which may be fatal. If you have a fever or any of these symptoms, it is important to contact your doctor immediately.

- It is important to contact your doctor immediately if 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 an uncommon (may affect up to 1 in 100 people) condition called "capillary leak syndrome", which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

- If you have Sickle Cell Disease, make sure that you tell your doctor before you start taking Tevagrastim. Sickle cell crisis has happened in some patients with Sickle Cell Disease who have been given filgrastim.

- As a very common (may affect more than 1 in 10 people) side effect, filgrastim may cause bone and muscle pain. Ask your doctor which medicine you can take to help with this.

You may experience the following additional side effects:

<u>In cancer patients</u>

Very common (may affect more than 1 in 10 people):
- elevated levels of some liver or blood enzymes; high blood levels of uric acid;
- feeling sick; vomiting;
- chest pain.

Common (may affect up to 1 in 10 people):
- headache;
- cough; sore throat;
- constipation; loss of appetite; diarrhoea; mucositis, which is painful inflammation and ulceration of the mucous membranes lining the digestive tract;
- hair loss; rash;
- fatigue; generalised weakness.

Uncommon (may affect up to 1 in 100 people):
- unspecified pain.

Rare (may affect up to 1 in 1,000 people):
- vascular disorders, which can cause pain, redness and swelling in the limbs.

Very rare (may affect up to 1 in 10,000 people):
- painful, raised, plum-coloured sores on the limbs and sometimes the face and neck with fever (Sweet's syndrome); inflammation of blood vessels, often with skin rash;
- worsening of rheumatic conditions;
- pains or difficulties in passing urine.

Not known (frequency cannot be estimated from the available data):
- rejection of transplanted bone marrow;
- transient low blood pressure;
- pain and swelling of the joints, similar to gout.

In normal stem cell donors

Very common (may affect more than 1 in 10 people):
- rise in white blood cells; reduction in blood platelets, which increases risk of bleeding or bruising;
- headache.

Common (may affect up to 1 in 10 people):
- elevated levels of some blood enzymes.

Uncommon (may affect up to 1 in 100 people):
- elevated levels of some liver enzymes; high blood levels of uric acid;
- worsening of rheumatic conditions.

Not known (frequency cannot be estimated from the available data):
- cough; fever and difficulty breathing or coughing up blood.

In severe chronic neutropenia patients

Very common (may affect more than 1 in 10 people):
- reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness;
- low blood levels of glucose; elevated levels of some blood enzymes; high blood levels of uric acid;
- nosebleed.

Common (may affect up to 1 in 10 people):
- reduction in blood platelets, which increases risk of bleeding or bruising;
- headache;
- diarrhoea;
- enlargement of the liver;
- hair loss; inflammation of blood vessels, often with skin rash; pain at the site of injection; rash;
- loss of calcium from the bones; joint pain.

Uncommon (may affect up to 1 in 100 people):
- blood in the urine; protein in the urine.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Tevagrastim

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 that month.

Store in a refrigerator (2 °C – 8 °C).

Do not use this medicine if you notice it is cloudy or there are particles in it.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tevagrastim contains
- The active substance is filgrastim. Each mL of solution for injection or infusion contains 60 million international units [MIU] (600 microgram) of filgrastim.
  Tevagrastim 30 MIU/0.5 mL: Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL solution.
  Tevagrastim 48 MIU/0.8 mL: Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL solution.
- The other ingredients are: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections.

What Tevagrastim looks like and contents of the pack
Tevagrastim is a solution for injection or infusion in a pre-filled syringe. Tevagrastim is a clear and colourless solution. Each pre-filled syringe contains either 0.5 mL or 0.8 mL of solution.

Tevagrastim is supplied in packs of 1, 5 or 10 pre-filled syringes or multipacks of 10 (2 packs of 5) pre-filled syringes with injection needle and with or without a needle safety guard. Not all pack sizes may be marketed.

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Manufacturer
Teva Pharma B.V.
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2031 GA Haarlem
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This leaflet was last revised in .

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

7. Information for injecting yourself

This section contains information on how to give yourself an injection of Tevagrastim. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. If you are not sure about giving yourself the injection or you have any questions, please ask your doctor or nurse for help.

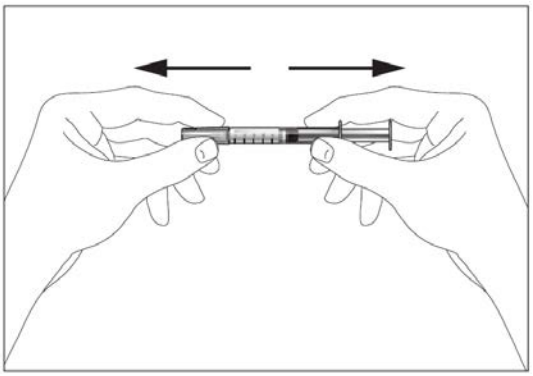
It is important that you dispose of used syringes in a puncture-proof container.

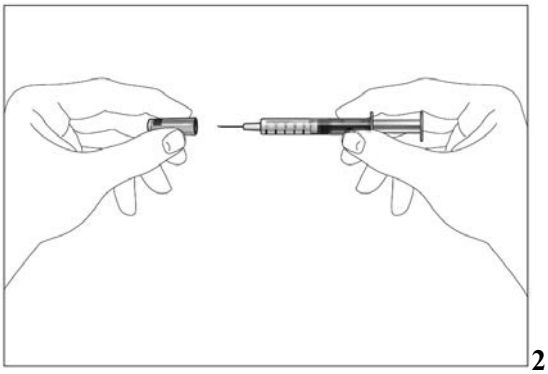
How do I inject Tevagrastim myself?
You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection. You will need to have your injections at about the same time every day.

Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Tevagrastim;
- alcohol wipes or similar;
- a puncture-proof container (plastic container provided by the hospital or pharmacy) so you can dispose of used syringes safely.

What should I do before I give myself a subcutaneous injection of Tevagrastim?
1. Try to self-inject at approximately the same time every day.
2. Take your Tevagrastim pre-filled syringe out of the refrigerator.
3. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
4. Check the appearance of Tevagrastim. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
5. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. Do not warm Tevagrastim in any other way (for example, do ***not*** warm it in a microwave or in hot water).
6. Do ***not*** remove the cover from the syringe until you are ready to inject.
7. ***Wash your hands thoroughly.***
8. Find a comfortable, well-lit place and put everything you need where you can reach them (the Tevagrastim pre-filled syringe, alcohol wipes and the puncture-proof container).

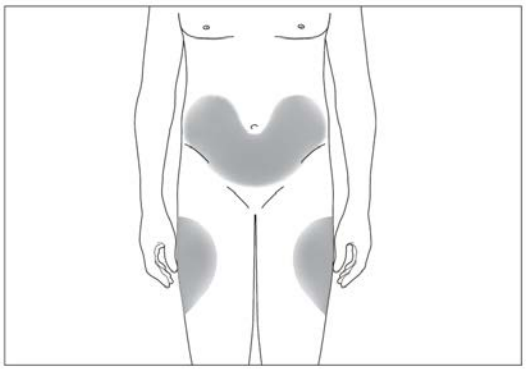
How do I prepare my Tevagrastim injection?
Before you inject Tevagrastim you must do the following:
1. Hold the syringe and gently take the cover from the needle without twisting. Pull straight as shown in pictures 1 and 2. Do not touch the needle or push the plunger.


1


2

2. You may notice a small air bubble in the pre-filled syringe. If there are air bubbles present, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. With the syringe pointing upwards, expel all air from the syringe by pushing the plunger upwards.
3. The syringe has a scale on the syringe barrel. Push the plunger up to the number (mL) on the syringe that matches the dose of Tevagrastim that your doctor prescribed.
4. Check again to make sure the correct dose of Tevagrastim is in the syringe.
5. You can now use the pre-filled syringe.

Where should I give my injection?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).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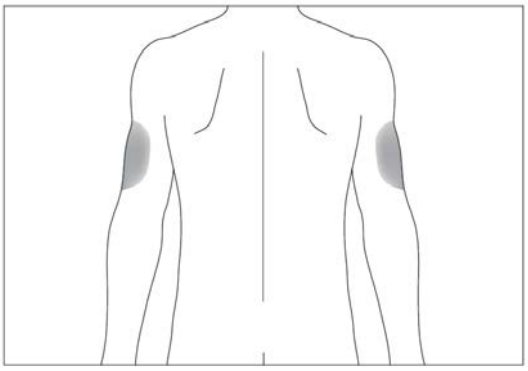
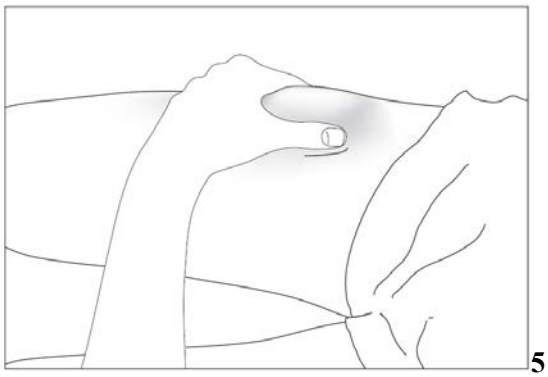

4

If someone else is injecting you, they can also use the back of your arms (see picture 4).

It is better to change the injection site every day to avoid the risk of soreness at any one site.

How do I give my injection?
1. Disinfect the injection site by using an alcohol wipe and pinch the skin between your thumb and forefinger, without squeezing it (see picture 5).
2. Put the needle fully into the skin as shown by your nurse or doctor (see picture 6).
3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and re-insert it in another place.
4. Inject the liquid slowly and evenly, always keeping your skin pinched.
5. Inject only the dose your doctor has told you.
6. After injecting the liquid, remove the needle and let go of your skin.
7. Only use each syringe for one injection. Do not use any Tevagrastim that is left in the syringe.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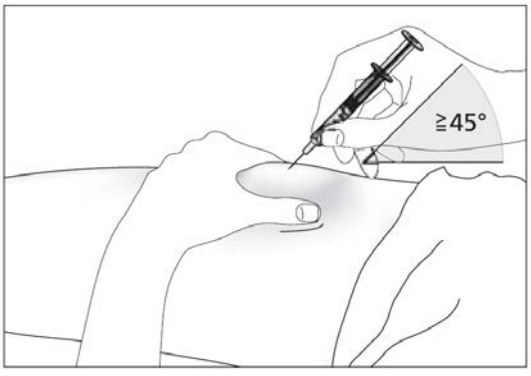

6

Remember
If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes
- Do not put the cover back on used needles.
- Put used syringes into the puncture-proof container and keep this container out of the sight and reach of children.
- Dispose of the full puncture-proof container as instructed by your doctor, nurse or pharmacist.
- Never put the syringes that you have used into your normal household rubbish bin.

8. The following information is intended for healthcare professionals only

Tevagrastim does not contain any preservative. In view of the possible risk of microbial contamination, Tevagrastim syringes are for single use only.

Accidental exposure to freezing temperatures does not adversely affect the stability of Tevagrastim.

Tevagrastim should not be diluted with sodium chloride solution. This medicinal product must not be mixed with other medicinal products except those mentioned below. Diluted filgrastim may be adsorbed to glass and plastic materials except diluted, as mentioned below.

If required, Tevagrastim may be diluted in glucose 50 mg/mL (5 %) solution for infusion. Dilution to a final concentration less than 0.2 MIU (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 MIU (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 MIU (300 µg) should be given with 0.2 mL of 200 mg/mL (20 %) human albumin solution added. When diluted in glucose 50 mg/mL (5 %) solution for infusion, Tevagrastim is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

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

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

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

Package leaflet: Information for the user

Tevagrastim 30 MIU/0.5 mL solution for injection or infusion
Tevagrastim 48 MIU/0.8 mL solution for injection or infusion

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 Tevagrastim is and what it is used for

What Tevagrastim is
Tevagrastim contains the active substance filgrastim. Filgrastim is a protein produced by biotechnology in bacteria called *Escherichia coli*. It belongs to a group of proteins called cytokines and is very similar to a natural protein (granulocyte-colony stimulating factor [G-CSF]) produced by your own body. Filgrastim stimulates the bone marrow (the tissue where new blood cells are made) to produce more blood cells, especially certain types of white cells. White cells are important as they help your body fight infection.

What Tevagrastim is used for
Your doctor has prescribed Tevagrastim for you to help your body make more white blood cells. Your doctor will tell you why you are being treated with Tevagrastim. Tevagrastim is useful in several different conditions, which are:
- chemotherapy;
- bone marrow transplantation;
- severe chronic neutropenia (low white blood cell count);
- neutropenia in patients with HIV infection;
- peripheral blood stem cell mobilisation (for blood stem cell donation).

2. What you need to know before you use Tevagrastim

Do not use Tevagrastim
- 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 Tevagrastim
- if you experience a cough, fever and difficulty breathing. It could be a consequence of a pulmonary disorder (see section “4. Possible side effects”).
- if you have sickle cell disease (an inherited disease characterised by sickle-shaped red blood cells).
- if you get left upper abdominal pain or pain at the tip of your shoulder. It could be a consequence of a spleen disorder (see section “4. Possible side effects”).
- if you have specific blood disorders (e.g. Kostman's syndrome, myelodysplastic syndrome. different types of leukaemia).
- if you have osteoporosis. Your doctor might check your bone density regularly.
- if you are suffering from any other illness, especially if you think you have an infection.

Talk to your doctor or nurse that you are treated with Tevagrastim if you are undergoing bone-imaging.

You will need to have regular blood tests whilst being treated with Tevagrastim to count the number of neutrophils and other white blood cells in your blood. This will tell your doctor how well the treatment is working and will also indicate if treatment needs to be continued.

Other medicines and Tevagrastim
Tell your doctor or pharmacist if you are using have recently used or might use any other medicines.

Do not use Tevagrastim in the 24 hours before or the 24 hours after your chemotherapy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Tevagrastim has not been tested in pregnant women. Therefore, your doctor may decide that you should not use this medicine.

It is unknown whether filgrastim passes over to the breast milk. Therefore, your doctor may decide that you should not use this medicine if you are breast-feeding.

Driving and using machines
If you experience fatigue, do not drive or use any tools or machines.

Tevagrastim contains sorbitol and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially ‘sodium-free’.

3. How to use Tevagrastim

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

The recommended dose is...
The amount of Tevagrastim you need, will depend on the condition you are taking Tevagrastim for and on your bodyweight. Your doctor will tell you when to stop using Tevagrastim. It is quite normal to have a number of courses of Tevagrastim treatment.

Tevagrastim and chemotherapy
The usual dose is 0.5 million international units (MIU) per kilogram of bodyweight each day. For example, if you weigh 60 kg your daily dose will be 30 million international units (MIU). You will normally receive your first dose of Tevagrastim at least 24 hours after your chemotherapy. Your treatment will usually last for about 14 days. In some disease types however, longer treatment lasting up to about one month may be required.

Tevagrastim and bone marrow transplantation
The usual starting dose is 1 million international units (MIU) per kilogram of bodyweight each day. For example, if you weigh 60 kg your daily dose will be 60 million international units (MIU). You will normally receive your first dose of Tevagrastim at least 24 hours after your chemotherapy but within 24 hours of receiving your bone marrow transfusion. Your doctor will test your blood daily to see how well the treatment is working and to find the dose that is best for you. The treatment will be discontinued when white cells in your blood reach a certain number.

Tevagrastim and severe chronic neutropenia
The usual starting dose is between 0.5 million and 1.2 million international units (MIU) per kilogram bodyweight each day in a single or divided dose. Your doctor will then test your blood to see how well your treatment is working and to find the dose that is best for you. Long-term treatment with Tevagrastim is required for neutropenia.

Tevagrastim and neutropenia in patients with HIV infection
The usual starting dose is between 0.1 and 0.4 million international units (MIU) per kilogram bodyweight each day. Your doctor will test your blood at regular intervals to see how well the treatment is working. Once the number of white cells in your blood have returned to normal it may be possible to reduce the dose frequency to less than once per day. Your doctor will continue to test your blood regularly and will recommend the best dose for you. Long-term treatment with Tevagrastim may be required to maintain a normal number of white cells in your blood.

Tevagrastim and peripheral blood stem cell mobilisation
If you are donating stem cells for yourself, the usual dose is 0.5 million to 1 million international units (MIU) per kilogram bodyweight each day. Tevagrastim treatment will last for up to 2 weeks and in exceptional cases longer. Your doctor will monitor your blood to determine the best time to collect the stem cells.

If you are acting as a stem cell donor for another person, the usual dose is 1 million international units (MIU) per kilogram bodyweight each day. Tevagrastim treatment will last for 4 to 5 days.

Method of administration
This medicine is given by injection, either through an intravenous (IV) infusion (drip) or a subcutaneous (SC) injection (into the tissue just under the skin). If you are receiving this medicine by subcutaneous injection, your doctor may suggest that you learn how to give yourself the injections. Your doctor or nurse will give you instructions on how to do this. Do not attempt to self-administer without this training. Some of the information you require is given at the end of this package leaflet, but proper treatment of your disease requires close and constant co-operation with your doctor.

If you use more Tevagrastim than you should
If you use more Tevagrastim than you should, contact your doctor or pharmacist as soon as possible.

If you forget to use Tevagrastim
Do not use a double dose to make up for a forgotten injection.

If you stop using Tevagrastim
Before you stop using Tevagrastim, talk to your doctor.

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

4. Possible side effects

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

Important side effects

- Allergic reactions such as skin rash, raised itchy areas of skin and serious allergic reactions with weakness, drop in blood pressure, difficulty breathing and swelling of the face have been reported. If you think you are having this type of reaction, you must stop your Tevagrastim injection and get medical help immediately.

- Increased spleen size and cases of spleen ruptures have been reported. Some cases of splenic rupture were fatal. It is important to contact your doctor immediately if you experience ***pain in the upper left side of the abdomen or left shoulder pain*** since this may relate to a problem with your spleen.

- Cough, fever and difficult or painful breathing can be signs of serious pulmonary side effects, such as pneumonia and acute respiratory distress syndrome, which may be fatal. If you have a fever or any of these symptoms, it is important to contact your doctor immediately.

- It is important to contact your doctor immediately if 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 an uncommon (may affect up to 1 in 100 people) condition called "capillary leak syndrome", which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

- If you have Sickle Cell Disease, make sure that you tell your doctor before you start taking Tevagrastim. Sickle cell crisis has happened in some patients with Sickle Cell Disease who have been given filgrastim.

- As a very common (may affect more than 1 in 10 people) side effect, filgrastim may cause bone and muscle pain. Ask your doctor which medicine you can take to help with this.

You may experience the following additional side effects:

<u>In cancer patients</u>

Very common (may affect more than 1 in 10 people):
- elevated levels of some liver or blood enzymes; high blood levels of uric acid;
- feeling sick; vomiting;
- chest pain.

Common (may affect up to 1 in 10 people):
- headache;
- cough; sore throat;
- constipation; loss of appetite; diarrhoea; mucositis, which is painful inflammation and ulceration of the mucous membranes lining the digestive tract;
- hair loss; rash;
- fatigue; generalised weakness.

Uncommon (may affect up to 1 in 100 people):
- unspecified pain.

Rare (may affect up to 1 in 1,000 people):
- vascular disorders, which can cause pain, redness and swelling in the limbs.

Very rare (may affect up to 1 in 10,000 people):
- painful, raised, plum-coloured sores on the limbs and sometimes the face and neck with fever (Sweet's syndrome); inflammation of blood vessels, often with skin rash;
- worsening of rheumatic conditions;
- pains or difficulties in passing urine.

Not known (frequency cannot be estimated from the available data):
- rejection of transplanted bone marrow;
- transient low blood pressure;
- pain and swelling of the joints, similar to gout.

In normal stem cell donors

Very common (may affect more than 1 in 10 people):
- rise in white blood cells; reduction in blood platelets, which increases risk of bleeding or bruising;
- headache.

Common (may affect up to 1 in 10 people):
- elevated levels of some blood enzymes.

Uncommon (may affect up to 1 in 100 people):
- elevated levels of some liver enzymes; high blood levels of uric acid;
- worsening of rheumatic conditions.

Not known (frequency cannot be estimated from the available data):
- cough; fever and difficulty breathing or coughing up blood.

In severe chronic neutropenia patients

Very common (may affect more than 1 in 10 people):
- reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness;
- low blood levels of glucose; elevated levels of some blood enzymes; high blood levels of uric acid;
- nosebleed.

Common (may affect up to 1 in 10 people):
- reduction in blood platelets, which increases risk of bleeding or bruising;
- headache;
- diarrhoea;
- enlargement of the liver;
- hair loss; inflammation of blood vessels, often with skin rash; pain at the site of injection; rash;
- loss of calcium from the bones; joint pain.

Uncommon (may affect up to 1 in 100 people):
- blood in the urine; protein in the urine.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Tevagrastim

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 that month.

Store in a refrigerator (2 °C – 8 °C).

Do not use this medicine if you notice it is cloudy or there are particles in it.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tevagrastim contains
- The active substance is filgrastim. Each mL of solution for injection or infusion contains 60 million international units [MIU] (600 microgram) of filgrastim.
  Tevagrastim 30 MIU/0.5 mL: Each pre-filled syringe contains 30 million international units [MIU] (300 microgram) of filgrastim in 0.5 mL solution.
  Tevagrastim 48 MIU/0.8 mL: Each pre-filled syringe contains 48 million international units [MIU] (480 microgram) of filgrastim in 0.8 mL solution.
- The other ingredients are: Sodium hydroxide, glacial acetic acid, sorbitol, polysorbate 80, water for injections.

What Tevagrastim looks like and contents of the pack
Tevagrastim is a solution for injection or infusion in a pre-filled syringe. Tevagrastim is a clear and colourless solution. Each pre-filled syringe contains either 0.5 mL or 0.8 mL of solution.

Tevagrastim is supplied in packs of 1, 5 or 10 pre-filled syringes or multipacks of 10 (2 packs of 5) pre-filled syringes with injection needle and with or without a needle safety guard. Not all pack sizes may be marketed.

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

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This leaflet was last revised in .

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

7. Information for injecting yourself

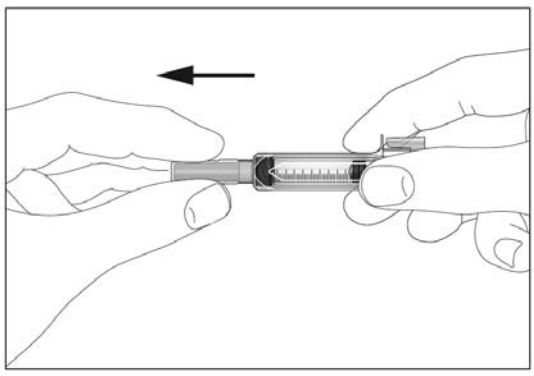
This section contains information on how to give yourself an injection of Tevagrastim. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. If you are not sure about giving yourself the injection or you have any questions, please ask your doctor or nurse for help.

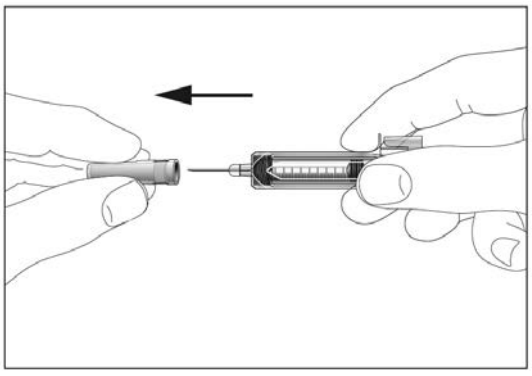
How do I inject Tevagrastim myself?
You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection. You will need to have your injections at about the same time every day.

Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Tevagrastim;
- alcohol wipes or similar.

What should I do before I give myself a subcutaneous injection of Tevagrastim?
1. Try to self-inject at approximately the same time every day.
2. Take your Tevagrastim pre-filled syringe out of the refrigerator.
3. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
4. Check the appearance of Tevagrastim. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
5. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. Do not warm Tevagrastim in any other way (for example, do ***not*** warm it in a microwave or in hot water).
6. Do ***not*** remove the cover from the syringe until you are ready to inject.
7. ***Wash your hands thoroughly.***
8. Find a comfortable, well-lit place and put everything you need where you can reach them (the Tevagrastim pre-filled syringe and alcohol wipes).

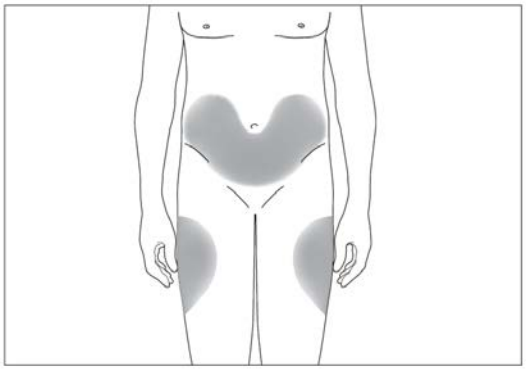
How do I prepare my Tevagrastim injection?
Before you inject Tevagrastim you must do the following:
1. Hold the syringe and gently take the cover from the needle without twisting. Pull straight as shown in pictures 1 and 2. Do not touch the needle or push the plunger.


1


2

2. You may notice a small air bubble in the pre-filled syringe. If there are air bubbles present, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. With the syringe pointing upwards, expel all air from the syringe by pushing the plunger upwards.
3. The syringe has a scale on the syringe barrel. Push the plunger up to the number (mL) on the syringe that matches the dose of Tevagrastim that your doctor prescribed.
4. Check again to make sure the correct dose of Tevagrastim is in the syringe.
5. You can now use the pre-filled syringe.

Where should I give my injection?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).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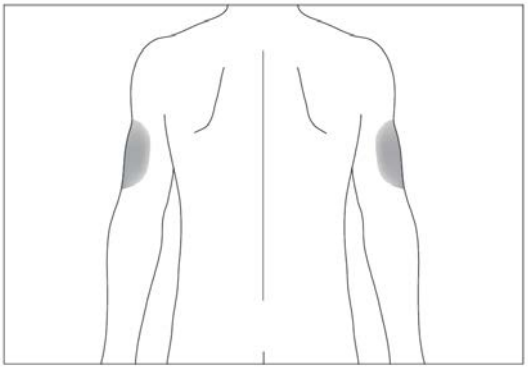
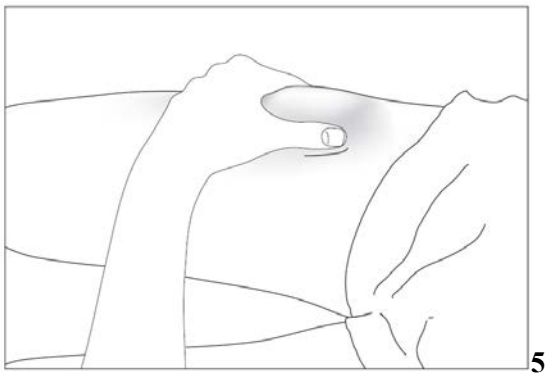

4

If someone else is injecting you, they can also use the back of your arms (see picture 4).

It is better to change the injection site every day to avoid the risk of soreness at any one site.

How do I give my injection?
1. Disinfect the injection site by using an alcohol wipe and pinch the skin between your thumb and forefinger, without squeezing it (see picture 5).
2. Put the needle fully into the skin as shown by your nurse or doctor (see picture 6).
3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and re-insert it in another place.
4. Always keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
5. Inject only the dose your doctor has told you.
6. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin.
7. Let go of the plunger. The needle safety guard will rapidly move to cover the needle (see picture 7).



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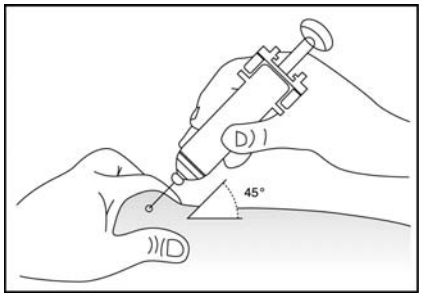

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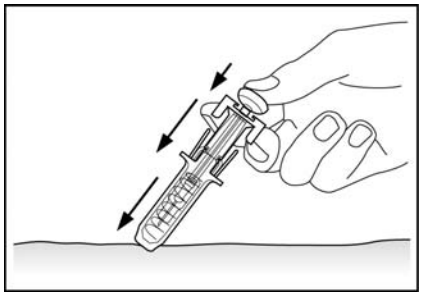

7

Remember
If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes
- The needle safety guard prevents needle stick injuries after use, so no special precautions for disposal are required. Dispose of the syringe as instructed by your doctor, nurse or pharmacist.

8. The following information is intended for healthcare professionals only

Tevagrastim does not contain any preservative. In view of the possible risk of microbial contamination, Tevagrastim syringes are for single use only.

Accidental exposure to freezing temperatures does not adversely affect the stability of Tevagrastim.

Tevagrastim should not be diluted with sodium chloride solution. This medicinal product must not be mixed with other medicinal products except those mentioned below. Diluted filgrastim may be adsorbed to glass and plastic materials except diluted, as mentioned below.

If required, Tevagrastim may be diluted in glucose 50 mg/mL (5 %) solution for infusion. Dilution to a final concentration less than 0.2 MIU (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 MIU (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 MIU (300 µg) should be given with 0.2 mL of 200 mg/mL (20 %) human albumin solution added. When diluted in glucose 50 mg/mL (5 %) solution for infusion, Tevagrastim is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

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

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Disposal

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