ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nivestim 30 MU/ 0.5 ml solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 60 million units [MU] (600 micrograms) of filgrastim*.

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

*recombinant methionyl granulocyte-colony stimulating factor [G-CSF] produced in *Escherichia Coli* (BL21) by recombinant DNA technology.

Excipient(s) with know 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/infusion (injection/ infusion).

Clear, colourlesss solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Filgrastim 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.

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

Filgrastim 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

Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in 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 MU (5 micrograms)/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 dilutions).

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 230 micrograms/m^2/day (4.0 to 8.4 micrograms/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.

<u>In patients treated with myeloablative therapy followed by bone marrow transplantation</u>
The recommended starting dose of filgrastim is 1.0 MU (10 micrograms)/kg/day given as a 30 minute or 24 hour intravenous infusion or 1.0 MU (10 micrograms)/kg/day given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 ml of 50 mg/ml (5%) glucose solution for infusion (see section 6.6).

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 MU/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	

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

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 micrograms)/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 50 mg/ml (5%) glucose solution for infusion (see section 6.6). Timing of leukapheresis: one or two 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 MU (5 micrograms)/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 x 10^9/l to > 5.0 x 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 peripheral blood progenitor cells (PBPCs) in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 10 micrograms/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 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

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

Idiopathic or cyclic neutropenia: the recommended starting dose is 0.5 MU (5 micrograms)/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 x 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 x 10^9/l and 10 x 10^9/l. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses ≤24 micrograms/kg/day. The long-term safety of filgrastim administration above 24 micrograms/kg/day in patients with severe chronic neutropenia has not been established.

In patients with HIV infection
For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU (1 micrograms)/kg/day given daily by subcutaneous injection with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x10^9/l). In clinical studies, > 90% of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU (10 micrograms)/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 MU (300 micrograms)/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 x 10^9/l. In clinical studies, dosing with 30 MU (300 micrograms)/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 posology 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 severe chronic neutropenia (SCN) and cancer settings
Sixty-five percent of the patients studied in the SCN trial program were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for 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 posology recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) 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 posology regimens.

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

Malignant cell growth
GCSF can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

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

Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

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 (> 0.01% and <0.1%) pulmonary adverse events 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.

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

Special precautions in cancer patients

Leukocytosis

White blood cell (WBC) 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 MU/kg/day (3 μg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10^9/l after the expected nadir, filgrastim should be discontinued immediately. 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 prescribing information 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)

Known cases of Hereditary Fructose Intolerance (HFI).

Filgrastim contains sorbitol as an excipient at a concentration of 50 mg/ml. It is unlikely that as a consequence of treatment with filgrastim alone that sufficient sorbitol will be infused to result in clinically relevant toxicity in affected individuals. However, in cases of HFI caution is advised

The effect of filgrastim on GvHD has not been defined.

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 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 appear to correlate with more rapid recovery, those below with slower recovery.

<u>Special precautions in normal donors undergoing peripheral blood progenitor cell mobilisation</u>

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

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

The safety and efficacy of filgrastim 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 < 100×10^9/l prior to leukapheresis; in general apheresis should not be performed if platelets < 75×10^9/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 posology should be reduced if the leukocyte counts rise to > 70×10^9/l.

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

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

Long-term safety follow-up of donors is ongoing. Nevertheless, 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 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, pulmonary infiltrates, dyspnoea and hypoxia) have been reported very rarely in post marketing experience with other filgrastim-containing medicinal products. 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 peripheral blood progenitor cells 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 Graft versus Host Disease (GvHD) when compared with bone marrow transplantation.

Special precautions in severe chronic neutropenia (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 x 10^9/l.

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 severe chronic neutropenia treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. If patients with severe chronic neutropenia develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully weighed; filgrastim should be discontinued if MDS or leukaemia occurs. It is currently unclear whether long-term treatment of patients with severe chronic neutropenia 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
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 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 medicine. 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
Nivestim contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product. It also contains less than 1 mmol sodium (23 mg) per dose, 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, lithium is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

The safety of filgrastim has not been established in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. 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. In pregnancy, the possible risk of filgrastim use to the foetus must be weighed against the expected therapeutic benefit.

It is not known whether filgrastim is excreted in human milk, therefore filgrastim is not recommended for use in breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

During clinical studies 183 cancer patients and 96 healthy volunteers were exposed to Nivestim.
The safety profile of filgrastim observed in these clinical studies was consistent with that reported with the reference product used in these studies.

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.

<u>In cancer patients</u>
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, alkaline phosphatase, serum uric acid, and gamma-glutamyl transpeptidase 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.

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

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.

Rare pulmonary adverse events 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 intravenous administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

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

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

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	Uncommon	Capillary leak syndrome
	Rare	Vascular disorder, Angiopathy
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	Common	Alopecia, skin rash

System organ class	Frequency	Undesirable effect
disorders	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

In peripheral blood progenitor cell mobilisation in normal donors
The most commonly reported undesirable effect was mild to moderate transient musculo-skeletal pain. Leukocytosis (White Blood Cell (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 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, pulmonary infiltrates, dyspnoea and hypoxia) have been reported very rarely in post marketing experience with other filgrastim-containing medicinal products (see section 4.4).

Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony-stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4). Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony-stimulating factors; see also 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	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

In severe chronic neutropenia (SCN) patients
Undesirable effects related to filgrastim therapy in SCN patients have been reported and for some their frequency 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	Blood glucose decreased, 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

4.9 Overdose

The effects of filgrastim overdose have not been established.

Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Nivestim 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. Nivestim containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within twenty-four hours, with minor increases in monocytes. In some severe chronic neutropenia patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

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

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into peripheral blood. These autologous peripheral blood progenitor cells (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 peripheral blood progenitor cells 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 - 2001a	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002b	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 - 2000b	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

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

[b]Analysis includes patients receiving BM transplant during this period

Prior to allogeneic PBPC transplantation, use of filgrastim for the mobilisation of PBPC in normal donors allows a collection of 4 x 106 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 severe chronic neutropenia (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 medicine. 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 Nivestim has been assessed in randomised, controlled phase III study in breast cancer. There were no relevant differences between Nivestim and the reference product with regard to duration of severe neutropenia and incidence of febrile neutropenia.

5.2 Pharmacokinetic properties

A randomised, open-label, single-dose, comparator-controlled, two-way crossover study in 46 healthy volunteers showed that the pharmacokinetic profile of Nivestim was comparable to that of the reference product after subcutaneous and intravenous administration. Another randomised, double-blind, multiple-dose, comparator-controlled, two-way crossover study in 50 healthy volunteers showed that the pharmacokinetic profile of Nivestim was comparable to that of the reference product after subcutaneous 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Nivestim must not be diluted with sodium chloride solutions.
Diluted filgrastim may be adsorbed to glass and plastic materials unless it is diluted in 50mg/ml (5%) glucose solution for infusion (see section 6.6).
This medicinal product must not be mixed with other medicinal products except those 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 and transport refrigerated (2°C - 8°C).
Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

Accidental exposure to freezing temperatures for up to 24 hours does not affect the stability of Nivestim. The frozen pre-filled syringes can be thawed and then refrigerate for future use. If exposure has been greater then 24 hours or frozen more than once then Nivestim should NOT be used.

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 7 days. At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

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 a needle guard, containing 0.5 ml solution for injection/ infusion
Pack sizes of 1, 5 or 10 pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Dilution to a final concentration less than 0.2 MU (2 micrograms) per ml is not recommended at any time.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

For patients treated with filgrastim diluted to concentrations below 1.5 MU (15 micrograms) per ml, human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.

Example: In a final injection volume of 20 ml, total doses of filgrastim less than 30 MU (300 micrograms) should be given with 0.2 ml of 20% human albumin solution added.

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

Nivestim contains no preservative. In view of the possible risk of microbial contamination, Nivestim syringes are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/631/004
EU/1/10/631/005
EU/1/10/631/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/06/2010

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/.