

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Nivestim 12 MU/ 0.2 ml solution for injection/infusion  
Nivestim 30 MU/ 0.5 ml solution for injection/infusion  
Nivestim 48 MU/ 0.5 ml solution for injection/infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Nivestim 12 MU/ 0.2 ml solution for injection/infusion.

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

Each pre-filled syringe contains 12 million units (MU) (120 micrograms) of filgrastim in 0.2 ml (0.6 mg/ml).

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

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).

### Nivestim 48 MU/ 0.5 ml solution for injection/infusion

Each ml of solution for injection or infusion contains 96 million units [MU] (960 micrograms) of filgrastim\*.

Each pre-filled syringe contains 48 million units (MU) (480 micrograms) of filgrastim in 0.5 ml (0.96 mg/ml).

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

### Excipient(s) 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/infusion (injection/ infusion).

Clear, colourless 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 (PBPCs).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of  $\leq 0.5 \times 10^9 /l$  and a history of severe or recurrent infections, long term

administration of 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  $1.0 \times 10^9/l$ ) 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

###### *Posology*

The recommended dose of filgrastim is 0.5 MU (5 micrograms)/kg/day. The first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 micrograms/m<sup>2</sup>/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 leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1 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.

###### *Method of administration*

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 patients treated with myeloablative therapy followed by bone marrow transplantation

###### *Posology*

The recommended starting dose of filgrastim is 1.0 MU (10 micrograms)/kg/day.

The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after 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 <sup>9</sup> /l for 3 consecutive days	Reduce to 0.5 MU (5 micrograms)/kg/day
Then, if ANC remains > 1.0 x 10 <sup>9</sup> /l for 3 more consecutive days	Discontinue Filgrastim
If the ANC decreases to < 1.0 x 10 <sup>9</sup> /l during the treatment period the dose of filgrastim should be re-escalated according to the above steps	

ANC = absolute neutrophil count

#### *Method of administration*

Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or 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).

#### For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

#### *Posology*

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 micrograms)/kg/day for 5 to 7 consecutive days. 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 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<sup>9</sup>/l to > 5.0 x 10<sup>9</sup>/l. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukaphereses are recommended.

#### *Method of administration*

Filgrastim for PBPC mobilisation when used alone:

Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions, filgrastim should be diluted in 20 ml of 50 mg/ml (5%) glucose solution for infusion (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy:

Filgrastim should be given by subcutaneous injection.

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

#### *Posology*

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 micrograms)/kg/day 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<sup>6</sup> CD34<sup>+</sup> cells/kg recipient bodyweight.

#### *Method of administration*

Filgrastim should be given by subcutaneous injection.

## In patients with severe chronic neutropenia (SCN)

### *Posology*

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

Idiopathic or cyclic neutropenia: the recommended starting dose is 0.5 MU (5 micrograms)/kg/day 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  $1.5 \times 10^9/l$ . When the response has been obtained the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between  $1.5 \times 10^9/l$  and  $10 \times 10^9/l$ . A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses  $\leq 24$  micrograms/kg/day. The long-term safety of filgrastim administration above 24 micrograms/kg/day in patients with SCN has not been established.

### *Method of administration*

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

## In patients with HIV infection

### *Posology*

For reversal of neutropenia:

The recommended starting dose of filgrastim is 0.1 MU (1 micrograms)/kg/day with titration up to a maximum of 0.4 MU (4 micrograms)/kg/day until a normal neutrophil count is reached and can be maintained ( $ANC > 2.0 \times 10^9/l$ ). In clinical studies, > 90% of patients responded at these doses, achieving 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 is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at  $> 2.0 \times 10^9/l$ . In clinical studies, dosing with 30 MU (300 micrograms)/day on 1 to 7 days per week was required to maintain the  $ANC > 2.0 \times 10^9/l$ , with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the  $ANC > 2.0 \times 10^9/l$ .

### *Method of administration*

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

### *Elderly*

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.

#### *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 program were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

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

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

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

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

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

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

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

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

#### Malignant cell growth

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

The safety and efficacy of 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.

Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of acute respiratory distress syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

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).

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

#### Special precautions in cancer patients

Cases of splenomegaly and splenic rupture have been reported uncommonly following administration of filgrastim. Some cases of splenic rupture were fatal. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

#### *Leukocytosis*

White blood cell (WBC) counts of  $100 \times 10^9/l$  or greater have been observed in less than 5% of patients receiving filgrastim at doses above 0.3 MU/kg/day (3 micrograms/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  $50 \times 10^9/l$  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  $> 70 \times 10^9/l$ .

#### *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).

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

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

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

### Special precautions in patients undergoing PBPC mobilisation

#### *Mobilisation*

There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of CD34<sup>+</sup> 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 ( $\geq 2.0 \times 10^6$  CD34<sup>+</sup> 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 PBPC 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<sup>+</sup> 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<sup>+</sup> cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

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

### Special precautions in normal donors undergoing PBPC mobilisation

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

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

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

Thrombocytopenia has been reported very commonly in patients receiving filgrastim. Platelet counts should therefore be monitored closely.

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

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

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

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 cytogenetic abnormalities have been observed in normal donors following G-CSF use. The significance of these changes is unknown. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

Common but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture have been reported in healthy donors (and patients) following administration of granulocyte-colony stimulating factors (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, dyspnoea has been reported commonly and other pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates and hypoxia) have been reported uncommonly. 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 PBPCs mobilised with filgrastim*

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

### Special precautions in SCN patients

#### *Blood cell counts*

Thrombocytopenia has been reported commonly in patients receiving filgrastim. 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 SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia, and myeloid leukaemia. Complete blood cell counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

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

Cases of splenomegaly have been reported very commonly and cases of splenic rupture have been reported commonly following administration of filgrastim. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Splenomegaly 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 was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

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

#### Special precautions in patients with HIV infection

Cases of splenomegaly have been reported commonly following administration of filgrastim. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should therefore be evaluated for an enlarged spleen or splenic rupture.

#### *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 2-3 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 micrograms)/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 medications. As a result of the potential to receive higher doses or a greater number of these medications

with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

#### *Infections and malignancies causing myelosuppression*

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

#### *Special precautions in sickle cell trait and sickle cell disease*

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

#### All patients

Nivestim contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not use this medicine.

Nivestim contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially sodium-free.

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

### **4.5 Interaction with other medicinal products and other forms of interaction**

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

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

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

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Filgrastim is not recommended during pregnancy.

#### Breastfeeding

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

#### Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3).

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

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

#### 4.8 Undesirable effects

##### a. Summary of the safety profile

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.

In clinical trials in cancer patients the most frequent undesirable effect was musculoskeletal pain which was mild or moderate in 10%, and severe in 3% of patients.

Graft versus Host Disease (GvHD) has also been reported (see section c below).

In PBPC mobilisation in normal donors, the most commonly reported undesirable effect was musculoskeletal pain. Leukocytosis was observed in donors and thrombocytopenia following filgrastim and leukapheresis was also observed in donors. Splenomegaly and splenic rupture were also reported. Some cases of splenic rupture were fatal.

In SCN patients, the most frequent undesirable effects attributable to filgrastim were bone pain, general musculoskeletal pain and splenomegaly. Myelodysplastic syndromes (MDS) or leukaemia have developed in patients with congenital neutropenia treated with filgrastim (see section 4.4).

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly ( $\geq 1/1000$  to  $< 1/100$ ) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilisation following administration of granulocyte colony-stimulating factors; see section 4.4 and subsection C of section 4.8.

In clinical studies in patients with HIV, the only undesirable effects that were consistently considered to be related to filgrastim administration were musculoskeletal pain, bone pain and myalgia.

##### b. Tabulated summary of adverse reactions

The data in the tables below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Data are presented separately for cancer patients, PBPC mobilisation in normal donors, SCN patients and patients with HIV, reflecting the different adverse reaction profiles in these populations.

##### *Cancer patients*

MedDRA system organ class	Adverse reactions				
	Very common ( $\geq 1/10$ )	Common ( $\geq 1/100$ to $< 1/10$ )	Uncommon ( $\geq 1/1000$ to $< 1/100$ )	Rare ( $\geq 1/10,000$ to $< 1/1000$ )	Very rare ( $< 1/10,000$ )
Blood and lymphatic system disorders			Splenic rupture <sup>a</sup> Splenomegaly <sup>a, e</sup> Sickle cell crisis <sup>a</sup>		
Immune system disorders		Drug hypersensitivity <sup>a</sup>	Graft versus Host Disease <sup>b</sup>		
Metabolism and nutrition disorders	Blood uric acid increased Blood lactate dehydrogenase		Pseudogout <sup>a</sup>		

	increased Decreased appetite <sup>a</sup>				
<b>Nervous system disorders</b>	Headache <sup>a</sup>				
<b>Vascular Disorders</b>		Hypotension	Veno-occlusive disease <sup>d</sup> Fluid volume disturbances Capillary leak syndrome <sup>a</sup>	Aortitis	
<b>Respiratory, thoracic and mediastinal disorders</b>	Oropharyngeal pain <sup>a</sup> Cough <sup>a</sup> Dyspnoea	Haemoptysis <sup>c</sup>	Acute respiratory distress syndrome <sup>a</sup> Respiratory failure <sup>a</sup> Pulmonary oedema <sup>a</sup> Interstitial lung disease <sup>a</sup> Lung infiltration <sup>a</sup> Pulmonary haemorrhage		
<b>Gastrointestinal disorders</b>	Diarrhoea <sup>a</sup> Vomiting <sup>a</sup> Constipation <sup>a</sup> Nausea <sup>a</sup>				
<b>Hepatobiliary disorders</b>	Gamma-glutamyl transferase increased Blood alkaline phosphatase increased				
<b>Skin and subcutaneous tissue disorders</b>	Rash <sup>a</sup> Alopecia <sup>a</sup>		Sweets syndrome Cutaneous vasculitis <sup>a</sup>		
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal pain <sup>c</sup>		Exacerbation of rheumatoid arthritis		
<b>Renal and urinary disorders</b>		Dysuria	Urine abnormality Glomerulonephritis		
<b>General disorders and administration site conditions</b>	Asthenia <sup>a</sup> Fatigue <sup>a</sup> Mucosal inflammation <sup>a</sup> Pain <sup>a</sup>	Chest pain <sup>a</sup>			

<sup>a</sup> See section c

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

<sup>c</sup> Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

<sup>d</sup> Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilization

<sup>e</sup> Cases were observed in the clinical trial setting

PBPC mobilisation in normal donors

MedDRA system organ class	Adverse reactions				
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)	Very rare (< 1/10,000)
Blood and lymphatic system disorders	Thrombocytopenia <sup>a</sup> Leukocytosis <sup>a</sup>	Splenomegaly <sup>a</sup>	Splenic rupture <sup>a</sup> Sickle cell crisis <sup>a</sup>		
Immune system disorders			Anaphylactic reaction Severe allergic reaction		
Metabolism and nutrition disorders		Blood lactate dehydrogenase increased	Hyperuricaemia (blood uric acid increased)		
Nervous system disorders	Headache				
Vascular Disorders			Capillary leak syndrome <sup>a</sup>	Aortitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Pulmonary haemorrhage Haemoptysis Lung infiltration Hypoxia		
Hepatobiliary disorders		Blood alkaline phosphatase increased	Aspartate aminotransferase increased		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain <sup>b</sup>		Rheumatoid arthritis aggravated		
Renal and urinary disorders			Glomerulonephritis		

<sup>a</sup> See section c

<sup>b</sup> includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

SCN patients

MedDRA system organ class	Adverse reactions				
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)	Very rare (< 1/10,000)
Blood and lymphatic system disorders	Splenomegaly <sup>a</sup> Anaemia	Splenic rupture <sup>a</sup> Thrombocytopenia <sup>a</sup>	Sickle cell crisis <sup>a</sup>		
Metabolism and nutrition disorders	Hyperuricaemia Blood glucose decreased				

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	Blood lactate dehydrogenase increased				
<b>Nervous system disorders</b>	Headache				
<b>Respiratory, thoracic and mediastinal disorders</b>	Epistaxis				
<b>Gastrointestinal disorders</b>	Diarrhoea				
<b>Hepatobiliary disorders</b>	Hepatomegaly Blood alkaline phosphatase increased				
<b>Skin and subcutaneous tissue disorders</b>	Rash	Cutaneous vasculitis Alopecia			
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal pain <sup>b</sup> Arthralgia	Osteoporosis			
<b>Renal and urinary disorders</b>		Haematuria Glomerulonephritis	Proteinuria		
<b>General disorders and administration site conditions</b>		Injection site reaction			

<sup>a</sup> See section c

<sup>b</sup> includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

#### Patients with HIV

MedDRA system organ class	Adverse reactions					
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)	Very rare (< 1/10,000)	Not known (cannot be estimated from the available data)
<b>Blood and lymphatic system disorders</b>		Splenomegaly <sup>a</sup>	Sickle cell crisis <sup>a</sup>			
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal pain <sup>b</sup>					
<b>Renal and urinary disorders</b>						Glomerulonephritis

<sup>a</sup> See section c

<sup>b</sup> includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

c. Description of selected adverse reactions

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

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).

*Cancer patients*

In randomised, placebo-controlled clinical trials, filgrastim did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. In those clinical trials, undesirable effects reported with equal frequency in patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia (decreased appetite), mucosal inflammation, headache, cough, rash, chest pain, asthenia, pharyngolaryngeal pain (oropharyngeal pain) and constipation.

In the post-marketing setting cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. The frequency is estimated as uncommon from clinical trial data.

Cases of Sweet's syndrome (acute febrile dermatosis) have been reported in the post-marketing setting. The frequency is estimated as uncommon from clinical trial data.

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

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

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post marketing experience. Overall, reports were more common after 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.

In the post-marketing setting, isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (see section 4.4). The frequency is estimated as uncommon from clinical trial data.

Pseudogout has been reported in patients with cancer treated with filgrastim. The frequency is estimated as uncommon from clinical trial data.

*PBPC mobilisation in normal donors*

Common but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture have been reported in healthy donors and patients following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltration, dyspnoea and hypoxia) have been reported (see section 4.4).

Exacerbation of arthritic symptoms has been uncommonly observed.

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

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### In SCN patients

Undesirable effects seen include splenomegaly, which may be progressive in a minority of cases, splenic rupture and thrombocytopenia (see section 4.4).

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.

### In patients with HIV

Splenomegaly 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 splenomegaly 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 (see section 4.4).

### d. Paediatric population

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

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

### e. Other special populations

#### *Geriatric use*

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

#### *Paediatric SCN patients*

Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim. The frequency is estimated as 'common' from clinical trial data.

#### Reporting of suspected adverse reactions

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

## **4.9 Overdose**

The effects of filgrastim overdosage have not been established.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

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 SCN patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

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

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

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

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective International study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective 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.

<b>Relative risk (95% CI) of GvHD and TRM Following treatment with G-CSF after bone marrow transplantation</b>					
<b>Publication</b>	<b>Period of Study</b>	<b>N</b>	<b>Acute Grade II - IV GvHD</b>	<b>Chronic GvHD</b>	<b>TRM</b>
Meta-Analysis (2003)	1986 - 2001 <sup>a</sup>	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 <sup>b</sup>	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 <sup>b</sup>	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)
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<sup>a</sup>Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

<sup>b</sup>Analysis includes patients receiving BM transplant during this period

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

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

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

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

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

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

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

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

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

### 6.2 Incompatibilities

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

#### Pre-filled syringe

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 to 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 refrigerated for future use. If exposure has been greater than 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 15 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

### Nivestim 12 MU/ 0.2 ml solution for injection/infusion

Pre-filled syringe (type I glass), with injection needle (stainless steel) with a needle guard, containing 0.2 ml solution for injection/ infusion.

### Nivestim 30 MU/ 0.5 ml solution for injection/infusion, Nivestim 48 MU/ 0.5 ml solution for injection/infusion

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, 8 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

Hospira UK Limited  
Horizon  
Honey Lane  
Hurley  
Maidenhead  
SL6 6RJ  
UK  
Tel: + 44 (0) 1628 515500  
Fax: + 44 (0) 1628 829827

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

EU/1/10/631/001  
EU/1/10/631/002  
EU/1/10/631/003  
EU/1/10/631/004  
EU/1/10/631/005  
EU/1/10/631/006  
EU/1/10/631/007  
EU/1/10/631/008  
EU/1/10/631/009EU/1/10/631/010  
EU/1/10/631/011  
EU/1/10/631/012

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

Date of first authorisation: 08 June 2010  
Date of latest renewal: 27 May 2015

**10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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

Name and address of the manufacturer of the biological active substance

Hospira Zagreb d.o.o.  
Prudnička cesta 60  
10291 Prigorje Brdovečko  
Croatia

Name and address of the manufacturers responsible for batch release

Hospira Enterprises B.V.  
Randstad 22-11  
1316 BN Almere  
The Netherlands

Hospira Zagreb d.o.o.  
Prudnička cesta 60  
10291 Prigorje Brdovečko  
Croatia

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

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

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

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, 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 shall be submitted annually until renewal.

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

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**  
**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Nivestim 12 MU/0.2 ml solution for injection/infusion  
Filgrastim

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 12 million units (MU) (120 micrograms) of filgrastim in 0.2 ml (0.6 mg/ml)

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection/ infusion.  
1 pre-filled syringe with 0.2 ml.  
5 pre-filled syringes with 0.2 ml  
8 pre-filled syringes with 0.2 ml  
10 pre-filled syringes with 0.2 ml.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For single use only.  
For intravenous or subcutaneous use.

**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**

Needle guard is attached to the pre-filled syringe in order to protect from needle stick injury. See package leaflet for direction for use of the needle safe device.

**8. EXPIRY DATE**

EXP:

After dilution use within 24 hours.

**9. SPECIAL STORAGE CONDITIONS**

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.

**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**

Hospira UK Limited  
Hurley  
SL6 6RJ  
UK

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

EU/1/10/631/001  
EU/1/10/631/002  
EU/1/10/631/003  
EU/1/10/631/010

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nivestim 12 MU/0.2 ml

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Nivestim 30 MU 0.5 ml solution for injection/infusion  
Filgrastim

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection/ infusion.  
1 pre-filled syringe with 0.5 ml  
5 pre-filled syringes with 0.5 ml  
8 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.  
For single use only.  
For intravenous or subcutaneous use.

**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**

Needle guard is attached to the pre-filled syringe in order to protect from needle stick injury. See package leaflet for direction for use of the needle safe device.

**8. EXPIRY DATE**

EXP:

After dilution use within 24 hours.

**9. SPECIAL STORAGE CONDITIONS**

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.

**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**

Hospira UK Limited  
Hurley  
SL6 6RJ  
UK

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

EU/1/10/631/004

EU/1/10/631/005

EU/1/10/631/006

EU/1/10/631/011

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nivestim 30 MU/0.5 ml

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Nivestim 48 MU/0.5 ml solution for injection/infusion  
Filgrastim

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 48 million units (480 micrograms) of filgrastim in 0.5 ml (0.96 mg/ml)

**3. LIST OF EXCIPIENTS**

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

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection/ infusion.  
1 pre-filled syringe with 0.5 ml  
5 pre-filled syringes with 0.5 ml  
8 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.  
For single use only.  
For intravenous or subcutaneous use.

**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**

Needle guard is attached to the pre-filled syringe in order to protect from needle stick injury. See package leaflet for direction for use of the needle safe device.

**8. EXPIRY DATE**

EXP:

After dilution use within 24 hours.

**9. SPECIAL STORAGE CONDITIONS**

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.

**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**

Hospira UK Limited  
Hurley  
SL6 6RJ  
UK

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

EU/1/10/631/007

EU/1/10/631/008

EU/1/10/631/009

EU/1/10/631/012

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Nivestim 48 MU/0.5 ml

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SYRINGE LABEL**

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

Nivestim 12 MU/0.2 ml injection/infusion  
Filgrastim  
SC/IV

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

0.2 ml

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SYRINGE LABEL**

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

Nivestim 30 MU/0.5 ml injection/infusion  
Filgrastim  
SC/IV

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

0.5 ml

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**SYRINGE LABEL**

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

Nivestim 48 MU/0.5 ml injection/infusion  
Filgrastim  
SC/IV

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

0.5 ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

**Nivestim 12 MU/0.2 ml solution for injection/infusion**  
**Nivestim 30 MU/0.5 ml solution for injection/infusion**  
**Nivestim 48 MU/0.5 ml solution for injection/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 Nivestim is and what it is used for
2. What you need to know before you use Nivestim
3. How to use Nivestim
4. Possible side effects
5. How to store Nivestim
6. Contents of the pack and other information

### **1. What Nivestim is and what it is used for**

#### **What Nivestim is**

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

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

Nivestim can be used:

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

### **2. What you need to know before you use Nivestim**

#### **Do not use Nivestim**

- 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 Nivestim.

Please tell your doctor before starting treatment if you have:

- sickle cell anaemia, as Nivestim may cause sickle cell crisis.
- osteoporosis (bone disease).

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

- get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of an enlarged spleen (splenomegaly), or possibly rupture of the spleen).
- notice unusual bleeding or bruising (these may be symptoms of a decrease in blood platelets (thrombocytopenia), with a reduced ability of your blood to clot).
- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction.
- experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.

Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

### **Loss of response to filgrastim**

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

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

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

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

### **Take special care with other products that stimulate white blood cells**

Nivestim is one of a group of products that stimulate the production of white blood cells. Your healthcare professional should always record the exact product you are using.

### **Other medicines and Nivestim**

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

### **Pregnancy and breast-feeding**

Nivestim has not been tested in pregnant or breast-feeding women.

It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or
- are planning to have a baby.

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

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

### **Driving and using machines**

Nivestim should not affect your ability to drive and use machines. However, it is advisable to wait and see how you feel after taking Nivestim and before driving or operating machinery.

### **Nivestim contains sodium and sorbitol**

Nivestim contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially sodium-free.

Nivestim contains sorbitol (E420). If you have been told by your doctor that you have a reaction to some sugars, contact your doctor before taking this medicinal product.

## **3. How to use Nivestim**

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

### **How is Nivestim given and how much should I take?**

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

Patients having a bone marrow transplant after chemotherapy:

You will normally receive your first dose of Nivestim at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

### **How long will I have to take Nivestim?**

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

### **Use in children**

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

### **If you use more Nivestim than you should**

If you think you have had more than you should, contact your doctor as soon as possible.

### **If you forget to use Nivestim**

If you have missed an injection, contact your doctor as soon as possible.

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

## **4. Possible side effects**

### **Please tell your doctor immediately during treatment:**

- if you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea). Hypersensitivity is common in patients with cancer;
- if you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS). ARDS is uncommon in patients with cancer;
- if you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder, as there may be a problem with your spleen (enlargement of the spleen (splenomegaly) or rupture of the spleen).
- if you are being treated for severe chronic neutropenia and you have blood in your urine

(haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).

- 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 experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.

A very frequent side effect of filgrastim use is pain in your muscles or bones (musculoskeletal pain), which can be helped by taking standard pain relief medicines (analgesics). In patients undergoing a stem cell or bone marrow transplant, Graft versus host disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints. Very commonly seen in normal stem cell donors is increase in white blood cells (leukocytosis) and decrease of platelets which reduces the ability of blood to clot (thrombocytopenia), these will be monitored by your doctor.

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

**Very common side effects** (may affect more than 1 in 10 people):

**in cancer patients**

- changes in blood chemistry
- increase of certain enzymes in the blood
- decreased appetite
- headache
- pain in your mouth and throat (oropharyngeal pain)
- cough
- diarrhoea
- vomiting
- constipation
- nausea
- skin rash
- unusual hair loss or thinning (alopecia)
- pain in your muscles or bones (musculoskeletal pain)
- generalised weakness (asthenia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- shortness of breath (dyspnoea)
- pain

**in normal stem cell donors**

- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- increase in white blood cells (leukocytosis)
- headache
- pain in your muscles or bones (musculoskeletal pain)

**in severe chronic neutropenia patients**

- enlargement of the spleen (splenomegaly)
- low red blood cell count (anaemia)
- changes in blood chemistry

- increase of certain enzymes in the blood
- headache
- nose bleeds (epistaxis)
- diarrhoea
- enlargement of the liver (hepatomegaly)
- skin rash
- pain in your muscles or bones (musculoskeletal pain)
- joint pain (arthralgia)

**in HIV patients**

- pain in your muscles or bones (musculoskeletal pain)

**Common side effects** (may affect up to 1 in 10 people)

**in cancer patients**

- allergic reaction (drug hypersensitivity)
- low blood pressure (hypotension)
- pain when passing urine (dysuria)
- chest pain
- coughing up blood (haemoptysis)

**in normal stem cell donors**

- increase of certain enzymes in the blood
- shortness of breath (dyspnoea)
- enlargement of the spleen (splenomegaly)

**in severe chronic neutropenia patients**

- rupture of the spleen
- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- changes in blood chemistry
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- unusual hair loss or thinning (alopecia)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- blood in the urine (haematuria)
- injection site pain
- damage to the tiny filters inside your kidneys (glomerulonephritis)

**in HIV patients**

- enlargement of the spleen (splenomegaly)

**Uncommon side effects** (may affect up to 1 in 100 people):

**in cancer patients**

- rupture of the spleen
- enlargement of the spleen (splenomegaly)
- severe pain in the bones, chest, gut or joints (sickle cell crisis)
- rejection of transplanted bone marrow (graft versus host disease)
- pain and swelling of the joints, similar to gout (pseudogout)
- severe lung inflammation causing difficulty in breathing (acute respiratory distress syndrome)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweet's syndrome)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)

- worsening of rheumatoid arthritis
- unusual change in the urine
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- bleeding from the lung (pulmonary haemorrhage)
- a change in how your body regulates fluids within your body and may result in puffiness
- damage to the tiny filters inside your kidneys (glomerulonephritis)

#### **in normal stem cell donors**

- rupture of the spleen
- severe pain in the bones, chest, gut or joints (sickle cell crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- severe allergic reaction
- changes in blood chemistry
- bleeding in the lung (pulmonary haemorrhage)
- coughing up blood (haemoptysis)
- abnormal x-rays of the lung (lung infiltration)
- lack of absorption of oxygen in the lung (hypoxia)
- increase of certain enzymes in the blood
- worsening of rheumatoid arthritis
- damage to the tiny filters inside your kidneys (glomerulonephritis)

#### **in severe chronic neutropenia patients**

- severe pain in the bones, chest, gut or joints (sickle cell crisis)
- excess protein in the urine (proteinuria)

#### **in HIV patients**

- severe pain in the bones, chest, gut or joints (sickle cell crisis)

**Rare side effects** (may affect up to 1 in 1,000 people):

#### **in cancer patients and in normal stem cell donors**

- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), see section 2.

**Not known side effects** (frequency cannot be estimated from the available data)

- damage to the tiny filters inside your kidneys (glomerulonephritis)

#### **Reporting of side effects**

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

## **5. How to store Nivestim**

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 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.

The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 15 days (but not above 25°C).

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

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

## 6. Contents of the pack and other information

### What Nivestim contains

- The active substance is filgrastim. Each ml contains 60 million units [MU] (600 micrograms) or 96 million units [MU] (960 micrograms) of filgrastim.
- Nivestim 12 MU/ 0.2 ml solution for injection/ infusion: each pre-filled syringe contains 12 million units (MU), 120 micrograms of filgrastim in 0.2 ml (corresponding to 0.6 mg/ml).
- Nivestim 30 MU/ 0.5 ml solution for injection/ infusion: each pre-filled syringe contains 30 million units (MU), 300 micrograms of filgrastim in 0.5 ml (corresponding to 0.6 mg/ml).
- Nivestim 48 MU/ 0.5 ml solution for injection/ infusion: each pre-filled syringe contains 48 million units (MU), 480 micrograms of filgrastim in 0.5 ml (corresponding to 0.96 mg/ml).
- The other ingredients are acetic acid (glacial), sodium hydroxide, sorbitol E420, polysorbate 80, and water for injections.

### What Nivestim looks like and contents of the pack

Nivestim is a clear colourless solution for injection/ infusion in a glass pre-filled syringe with an injection needle (stainless steel) with a needle guard. There are 1, 5, 8 or 10 syringes in each pack. Not all pack sizes may be marketed.

### Marketing Authorisation Holder

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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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Pfizer, podružnica za svetovanje s področja  
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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>

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### **Information on self administration by the patient**

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

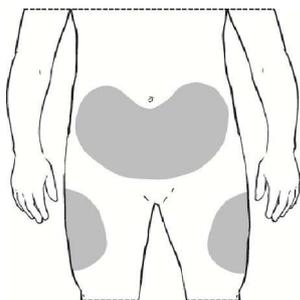
#### ***How do I administer my Nivestim?***

Nivestim is usually given once a day by injection, usually into the tissue just under the skin. This is known as a subcutaneous injection.

Learning to give your own injections will mean that you will not have to wait at home for a nurse to call, nor will you have to go to the hospital or clinic every day to receive your injections.

You will need to have your injections at about the same time every day. The most suitable places for injection are:

- the front of the thighs,
- the abdomen, except for the area around the navel.



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

#### ***Equipment required for administration***

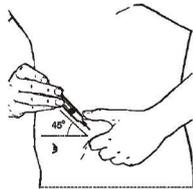
To give yourself a subcutaneous injection you will need the following items:

- A new pre-filled syringe of Nivestim.
- A sharps container (puncture proof container) for disposing of used syringes safely.
- Antiseptic wipes (if recommended by your doctor or nurse).

#### ***How do I give my subcutaneous Nivestim injection?***

1. Try to self-inject at approximately the same time every day.
2. Remove the Nivestim syringe from the fridge and allow it to reach room temperature (approximately 25 °C). This will take 15–30 minutes. Check the date on the pack to make sure that the medicine has not passed the expiry date. Make sure you have your sharps container nearby.
3. Find a comfortable well lit working place to give your injection and check the dose that you have been prescribed.
4. Wash your hands thoroughly with soap and water.
5. Remove the syringe from the blister pack and check that the solution is clear, colourless and practically free from visible particles. Do not use the Nivestim syringe if the liquid has particles floating in it or any of the liquid has leaked out of the syringe.

6. Hold the syringe with the needle pointing upwards. Remove the protective cap from the injection needle. The syringe is now ready for use. You may notice a small air bubble in the syringe. You do not have to remove the air bubble before injecting. Injecting the solution with an air bubble present is harmless.
7. Decide where to inject Nivestim - find a place on the front of your abdomen or the front of your thigh. Choose a different injection site each time. Do not choose an area which is tender, red, bruised or scarred. If your nurse or doctor recommends it, clean the area of skin with an antiseptic wipe.
8. Pinch a large area of skin, taking care not to touch the area you have cleaned.
9. With your other hand, insert the needle at an approximate 45° angle.



10. Pull the plunger back slightly to check if any blood appears in the syringe. If you do see blood inside the syringe, remove the needle and re-insert it in a different site. Slowly push down the plunger until all the contents of the syringe have been emptied.
11. After injecting the solution remove the needle from the skin.
12. Ensure the needle guard covers the needle according to the instructions for active needle guard or passive needle guard below.
13. Place the syringe into the sharps container. Do not try to replace the protective cap.

- Keep used syringes out of the reach and sight of children
- NEVER put used syringes into your normal household waste bin.

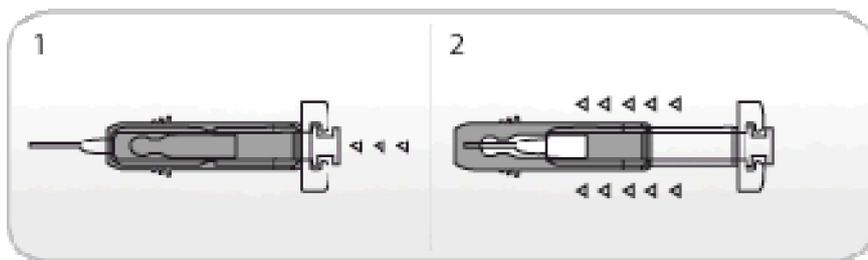
### Remember

Most people can learn to give themselves a subcutaneous injection, but if you are experiencing a lot of difficulty, please do not be afraid to ask for help and advice from your doctor or nurse.

### *Use of Active Ultrasafe Needle Guard for Nivestim 12 MU/ 0.2 ml solution for injection/ infusion*

The pre-filled syringe has an UltraSafe Needle Guard attached in order to protect from needle stick injury. When handling the pre-filled syringe, keep hands behind the needle.

1. Perform the injection using the technique described above.
2. When you have completed the injection, slide the needle guard forward until the needle is completely covered (device 'clicks' into place).

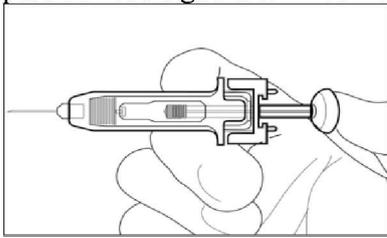


### *Use of Ultrasafe Passive Needle Guard for Nivestim 30 MU/ 0.5 ml solution for injection/ infusion and Nivestim 48 MU/ 0.5 ml solution for injection/ infusion*

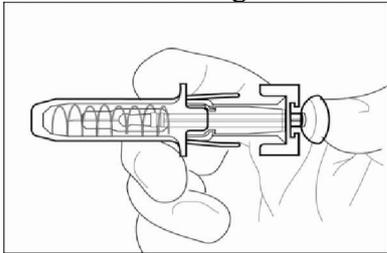
The pre-filled syringe has an UltraSafe Needle Guard attached in order to protect from needle stick injury. When handling the pre-filled syringe, keep hands behind the needle.

1. Perform the injection using the technique described above.

- Depress the plunger while grasping the finger flange until the entire dose has been given. The passive needle guard will NOT activate unless the ENTIRE dose has been given.



- Remove the needle from your skin, then let go of the plunger and allow the syringe to move up until the entire needle is guarded and locks into place.



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**THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:**

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

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 refrigerated for future use. If exposure has been greater than 24 hours or frozen more than once, then Nivestim should NOT be used.

Nivestim must 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, Nivestim may be diluted in glucose 50 mg/ml (5%) 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 200 mg/ml (20%) human albumin solution added. When diluted in glucose 50 mg/ml (5%) solution for infusion, Nivestim 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.