## 1. NAME OF THE MEDICINAL PRODUCT

Neupogen 30 MU (0.3 mg/ml) solution for injection
filgrastim

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 30 million units (MU)/300 micrograms (mcg) of filgrastim in 1 ml (0.3 mg/ml).

Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor) is produced by r-DNA technology in *E. coli* (K12).

Excipient with known effect

Each ml of solution contains 50 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Concentrate for solution for infusion.

Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Neupogen 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 Neupogen are similar in adults and children receiving cytotoxic chemotherapy.

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

Neupogen 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

Neupogen 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 Neupogen is 0.5 MU (5 mcg)/kg/day. The first dose of Neupogen should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 mcg/$m^2$/day (4.0 to 8.4 mcg/kg/day) was used.

Daily dosing with Neupogen 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 Neupogen therapy. However, for a sustained therapeutic response, Neupogen therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of Neupogen therapy, prior to the time of the expected neutrophil nadir, is not recommended.

*Method of administration*

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

In patients treated with myeloablative therapy followed by bone marrow transplantation

*Posology*

The recommended starting dose of Neupogen is 1.0 MU (10 mcg)/kg/day. The first dose of Neupogen 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 Neupogen should be titrated against the neutrophil response as follows:

| Neutrophil count | Neupogen dose adjustment |
|---|---|
| $> 1.0 \times 10^9$/l for 3 consecutive days | Reduce to 0.5 MU (5 mcg)/kg/day |
| Then, if ANC remains $> 1.0 \times 10^9$/l for 3 more consecutive days | Discontinue Neupogen |
| If the ANC decreases to $< 1.0 \times 10^9$/l during the treatment period the dose of Neupogen should be re-escalated according to the above steps | |

ANC = absolute neutrophil count

*Method of administration*

Neupogen may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Neupogen should be diluted in 20 ml of 5% glucose solution (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 Neupogen for PBPC mobilisation when used alone is 1.0 MU (10 mcg)/kg/day for 5 to 7 consecutive days. Timing of leukapheresis: one or two leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Neupogen dosing should be maintained until the last leukapheresis.

The recommended dose of Neupogen for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 mcg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from $< 0.5 \times 10^9$/l to $> 5.0 \times 10^9$/l. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

*Method of administration*

Neupogen for PBPC mobilisation when used alone:
Neupogen may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions Neupogen should be diluted in 20 ml of 5% glucose solution (see section 6.6).

Neupogen for PBPC mobilisation after myelosuppressive chemotherapy:
Neupogen 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, Neupogen should be administered at 1.0 MU (10 mcg)/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 $4 \times 10^6$ $CD34^+$ cells/kg recipient bodyweight.

*Method of administration*

Neupogen 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 mcg)/kg/day, as a single dose or in divided doses.

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

Dose adjustment: Neupogen 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 ≤ 24 mcg/kg/day. The long term safety of Neupogen administration above 24 mcg/kg/day in patients with SCN has not been established.

*Method of administration*

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

In patients with HIV infection

*Posology*

For reversal of neutropenia:
The recommended starting dose of Neupogen is 0.1 MU (1 mcg)/kg/day, with titration up to a maximum of 0.4 MU (4 mcg)/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 mcg)/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 mcg)/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 mcg)/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: Neupogen should be given by subcutaneous injection.

Older people

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

Patients with renal impairment

Studies of Neupogen 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 Neupogen are similar in both adults and children receiving cytotoxic chemotherapy.

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

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Special warnings and precautions across indications

*Hypersensitivity*

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

*Pulmonary adverse effects*

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

*Glomerulonephritis*

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

*Capillary leak syndrome*

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

*Splenomegaly and splenic rupture*

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

*Malignant cell growth*

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

*Myelodysplastic syndrome or chronic myeloid leukaemia*

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

*Acute myeloid leukaemia*

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

*Thrombocytopenia*

Thrombocytopenia has been reported in patients receiving Neupogen. Platelet counts should be monitored closely, especially during the first few weeks of Neupogen therapy. Consideration should be given to temporary discontinuation or dose reduction of Neupogen in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < $100 \times 10^9$/l).

*Leucocytosis*

White blood cell counts of $100 \times 10^9$/l or greater have been observed in less than 5% of cancer patients receiving Neupogen at doses above 0.3 MU/kg/day (3 mcg/kg/day). No undesirable effects directly attributable to this degree of leucocytosis have been reported. However, in view of the potential risks associated with severe leucocytosis, a white blood cell count should be performed at regular intervals during Neupogen therapy. If leucocyte counts exceed $50 \times 10^9$/l after the expected nadir, Neupogen should be discontinued immediately. When administered for PBPC mobilisation, Neupogen should be discontinued or its dosage should be reduced if the leucocyte counts rise to > $70 \times 10^9$/l.

*Immunogenicity*

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

*Arteritis*

Large and medium vessel arteritis, including 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, headache and neck pain. Laboratory findings included increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases, arteritis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

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

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

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

*Osteoporosis*

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

Special precautions in cancer patients

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

*Risks associated with increased doses of chemotherapy*

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

*Effect of chemotherapy on erythrocytes and thrombocytes*

Treatment with Neupogen 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 Neupogen mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

*Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients*

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

*Other special precautions*

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

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

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

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

Special precautions in patients undergoing PBPC mobilisation

*Mobilisation*

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

*Prior exposure to cytotoxic agents*

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

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool, and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU), and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation may reduce progenitor yield. However, the administration of melphalan, carboplatin or BCNU together with Neupogen, 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 Neupogen, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used and recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

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

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

Special precautions in normal donors undergoing 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 Neupogen have not been assessed in normal donors < 16 years or > 60 years.

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

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

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

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

*Special precautions in recipients of allogeneic PBPCs mobilised with Neupogen*

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

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

*Blood cell counts*

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

*Transformation to leukaemia or myelodysplastic syndrome*

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

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with Neupogen. 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 Neupogen therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

*Other special precautions*

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

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

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

Special precautions in patients with HIV infection

*Blood cell counts*

Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of Neupogen therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of Neupogen. It is recommended that the ANC is measured daily for the first 2-3 days of Neupogen 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 mcg)/day of Neupogen, 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 Neupogen.

*Risk associated with increased doses of myelosuppressive medications*

Treatment with Neupogen 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 Neupogen 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 Neupogen for treatment of neutropenia. The effects of Neupogen on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established.

All patients

Neupogen contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

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

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

Neupogen contains less than 1 mmol (23 mg) sodium per 0.3 mg/ml vial, that is to say 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 Neupogen 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 Neupogen 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 Neupogen 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 Neupogen. 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.

Neupogen is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Neupogen 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

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

## 4.8 Undesirable effects

a. Summary of the safety profile

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

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

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

| MedDRA system organ class | Adverse reactions | | | |
|---|---|---|---|---|
| | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Uncommon (≥ 1/1,000 to < 1/100)** | **Rare (≥ 1/10,000 to < 1/1,000)** |
| **Infections and infestations** | | Sepsis<br>Bronchitis<br>Upper respiratory tract infection<br>Urinary tract infection | | |
| **Blood and lymphatic system disorders** | Thrombocytopenia<br>Anaemia[e] | Splenomegaly[a]<br>Haemoglobin decreased[e] | Leucocytosis[a] | Splenic rupture[a]<br>Sickle cell anaemia with crisis<br>Extramedullary haematopoiesis |
| **Immune system disorders** | | | Hypersensitivity<br>Drug hypersensitivity[a]<br>Graft versus host disease[b] | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | | Decreased appetite[e]<br>Blood lactate dehydrogenase increased | Hyperuricaemia<br>Blood uric acid increased | Blood glucose decreased<br>Pseudogout[a] (Chondrocalcinosis Pyrophosphate)<br>Fluid volume disturbances |
| **Psychiatric disorders** | | Insomnia | | |
| **Nervous system disorders** | Headache[a] | Dizziness<br>Hypoaesthesia<br>Paraesthesia | | |
| **Vascular disorders** | | Hypertension<br>Hypotension | Veno-occlusive disease[d] | Capillary leak syndrome[a]<br>Aortitis<br>Arteritis |
| **Respiratory, thoracic and mediastinal disorders** | | Haemoptysis<br>Dyspnoea<br>Cough[a]<br>Oropharyngeal pain[a, e]<br>Epistaxis | Acute respiratory distress syndrome[a]<br>Respiratory failure[a]<br>Pulmonary oedema[a]<br>Pulmonary haemorrhage<br>Interstitial lung disease[a]<br>Lung infiltration[a]<br>Hypoxia | |
| **Gastrointestinal disorders** | Diarrhoea[a, e]<br>Vomiting[a, e]<br>Nausea[a] | Oral pain<br>Constipation[e] | | |
| **Hepatobiliary disorders** | | Hepatomegaly<br>Blood alkaline phosphatase increased | Aspartate aminotransferase increased<br>Gamma-glutamyl transferase increased | |
| **Skin and subcutaneous tissue disorders** | Alopecia[a] | Rash[a]<br>Erythema | Rash maculo-papular | Cutaneous vasculitis[a]<br>Sweets syndrome (acute febrile neutrophilic dermatosis) |

| MedDRA system organ class | Adverse reactions | | | |
|---|---|---|---|---|
| | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Uncommon (≥ 1/1,000 to < 1/100)** | **Rare (≥ 1/10,000 to < 1/1,000)** |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain[c] | Muscle spasms | Osteoporosis | Bone density decreased<br>Exacerbation of rheumatoid arthritis |
| **Renal and urinary disorders** | | Dysuria<br>Haematuria | Proteinuria | Glomerulonephritis<br>Urine abnormality |
| **General disorders and administration site conditions** | Fatigue[a]<br>Mucosal inflammation[a]<br>Pyrexia | Chest pain[a]<br>Pain[a]<br>Asthenia[a]<br>Malaise[e]<br>Oedema peripheral[e] | Injection site reaction | |
| **Injury, poisoning and procedural complications** | | Transfusion reaction[e] | | |

[a] See section c (Description of selected adverse reactions)

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

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

[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilisation

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

c. Description of selected adverse reactions

*Hypersensitivity*

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

*Pulmonary adverse events*

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

*Splenomegaly and splenic rupture*

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

*Capillary leak syndrome*

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

*Cutaneous vasculitis*

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

*Leucocytosis*

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

*Sweets syndrome*

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

*Pseudogout (chondrocalcinosis pyrophosphate*)

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

*GvHD*

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

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of Neupogen 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 Neupogen 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 Neupogen use in geriatric subjects for other approved Neupogen 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 Neupogen.

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:

HPRA Pharmacovigilance
Website: www.hpra.ie

### 4.9 Overdose

The effects of Neupogen overdosage have not been established. Discontinuation of Neupogen 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: Cytokines, ATC Code: L03AA02

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Neupogen 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 PBPC accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

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

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

**Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow transplantation**

| Publication | Period of study | N | Acute Grade II-IV GvHD | Chronic GvHD | TRM |
|---|---|---|---|---|---|
| Meta-Analysis (2003) | 1986-2001[a] | 1198 | 1.08 (0.87, 1.33) | 1.02 (0.82, 1.26) | 0.70 (0.38, 1.31) |
| European Retrospective Study (2004) | 1992-2002[b] | 1789 | 1.33 (1.08, 1.64) | 1.29 (1.02, 1.61) | 1.73 (1.30, 2.32) |
| International Retrospective Study (2006) | 1995-2000[b] | 2110 | 1.11 (0.86, 1.42) | 1.10 (0.86, 1.39) | 1.26 (0.95, 1.67) |

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

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

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

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

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

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

## 5.2 Pharmacokinetic properties

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 Neupogen 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 leucocytes, 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 mcg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Acetate*
Sorbitol (E420)
Polysorbate 80
Water for Injections
* Sodium acetate is formed by titrating glacial acetic acid with sodium hydroxide

### 6.2 Incompatibilities

Neupogen should not be diluted with saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

### 6.3 Shelf life

30 months.

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store at 2 to 8°C.

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

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

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

### 6.5 Nature and contents of container

Package containing one or five vial(s) of 1 ml Neupogen solution for injection.

The vials are made from type I glass with rubber stoppers.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

If required, Neupogen may be diluted in 5% glucose.

Dilution to a final concentration less than 0.2 MU (2 mcg) 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 mcg) 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 mcg) should be given with 0.2 ml of 20% human albumin solution Ph. Eur. added.

Neupogen contains no preservative. In view of the possible risk of microbial contamination, Neupogen vials are for single use only.

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

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

## 7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

PA 1026/1/1

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

Date of first authorisation: 15 March 1991
Date of latest renewal: 21 December 2018

## 10. DATE OF REVISION OF THE TEXT

23 July 2026