Neupogen®
Filgrastim

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Haematopoietic growth factor (Cytokines)
ATC code: L03AA02

1.2 Type of Dosage Form

Single-use pre-filled syringes
Neupogen solution for injection in pre-filled syringe of 0.5 ml.

1.3 Route of Administration

Intravenous infusion or subcutaneous injection.

1.4 Qualitative and Quantitative Composition

Active ingredient: filgrastim (recombinant-methionyl human granulocyte-colony stimulating factor, r-metHuG-CSF, from *E. coli* K12).

Filgrastim is a highly purified non-glycosylated protein comprising 175 amino acids. Filgrastim is produced in a laboratory strain of *Escherichia coli* bacteria which has been genetically altered by the addition of a gene for the granulocyte-colony stimulating factor.

Pre-filled syringes
1 pre-filled syringe of Neupogen of 0.5 ml contains 30 MU (= 300 μg) of filgrastim.

Excipients: sodium acetate*, sorbitol, polysorbate 80, water for injection.
*Sodium acetate is formed by titrating glacial acetic acid with sodium hydroxide.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Established cytotoxic chemotherapy
Neupogen is indicated for 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 and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia (see section 2.5.3 Paediatric Use).

Peripheral blood progenitor cell mobilisation (PBPC)
Neupogen is indicated for the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy and the mobilisation of peripheral blood progenitor cells in normal donors (allogeneic PBPC).

Severe chronic neutropenia (SCN)
Long-term administration of Neupogen is indicated in patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) ≤ 0.5 x 10^9/l, and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

HIV infection
Neupogen is indicated for the treatment of persistent neutropenia (ANC ≤ 1.0 x 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.

2.2 Dosage and Administration

Neupogen therapy should only be given in collaboration with an oncology center 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 center with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Established cytotoxic chemotherapy
The recommended dose of Neupogen is 0.5 MU (5 μg)/kg/day. The first dose of Neupogen should not be administered less than 24 hours following cytotoxic chemotherapy. 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 4.2 Special Instructions for Use, Handling and Disposal). 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 circumstances.

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 tumors, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfill 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.

For use in children see section 2.5.3 Paediatric Use.

In patients treated with myeloablative therapy followed by bone marrow transplantation
The recommended starting dose of Neupogen is 1.0 MU (10 μg)/kg/day given as a 30 minute or 24 hour intravenous infusion or 1.0 MU (10 μg)/kg/day given by continuous 24 hours subcutaneous infusion.

Neupogen should be diluted in 20 ml of 5% glucose solution (see section 4.2 Special Instructions for Use, Handling and Disposal).

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

The efficacy and safety of Neupogen given for longer than 28 days in this setting have not been established.

Once the neutrophil nadir has been passed, the daily dose of Neupogen should be titrated against the neutrophil response as follows (see also section 2.5.3 Paediatric Use):

Neutrophil count	Neupogen dose adjustment
$> 1.0 \times 10^9$/l for 3 consecutive days	Reduce to 0.5 MU/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

Peripheral blood progenitor cell mobilisation

Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation with or without bone marrow transplantation

The recommended dose of Neupogen for PBPC mobilisation when used alone is 1.0 MU (10 μg)/kg/day as a 24 hour subcutaneous continuous infusion or a single daily subcutaneous injection for 5 to 7 consecutive days. For infusions Neupogen should be diluted in 20 ml of 5% glucose solution (see section 4.2 Special Instructions for Use, Handling and Disposal). Timing of leukapheresis: one or two leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses 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 μg)/kg/day given daily by subcutaneous injection from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from $< 0.5 \times 10^9$/l to $> 5.0 \times 10^9$/l. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukaphereses are recommended.

Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, Neupogen should be administered at 10 μg/kg/day subcutaneously for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4×10^6 $CD34^+$ cells/kg recipients bodyweight.

Severe chronic neutropenia (SCN)

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

Idiopathic or cyclic neutropenia: The recommended starting dose is 0.5 MU (5 μg)/kg/day subcutaneously 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 1.5×10^9/l. When the response has been obtained the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5×10^9/l and 10×10^9/l. A faster schedule of dose escalation may be considered in patients presenting with severe infections.

In clinical trials, 97 % of patients who responded had a complete response at doses ≤ 24 μg/kg/day.

The long-term safety of Neupogen administration above 24 μg/kg/day in patients with severe chronic neutropenia has not been established.

For children see section 2.5.3 Paediatric Use.

HIV infection

For Reversal of Neutropenia:
The recommended starting dose of Neupogen is 0.1 MU (1 μg)/kg/day given daily by subcutaneous injection with titration up to a maximum of 0.4 MU (4 μg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0×10^9/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 μg)/kg/day were required to achieve reversal of neutropenia.

For Maintaining Normal Neutrophil Counts:
When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 μg)/day by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0×10^9/l. In clinical studies, dosing with 30 MU (300 μg)/day on 1 to 7 days per week was required to maintain the ANC > 2.0×10^9/l, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0×10^9/l.

2.2.1 Special Dosage Instructions

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 (see section 2.5.4 Geriatric Use).

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy (see section 2.5.3 Paediatric Use).

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.

2.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 1.4.

2.4 Warnings and Precautions

2.4.1 General

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 2.6).

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 < 100×10^9/l).

Leucocytosis

White blood cell counts of 100×10^9/l or greater have been observed in less than 5% of cancer patients receiving Neupogen at doses above 0.3 MU/kg/day (3 µg/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 50×10^9/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 > 70×10^9/l.

Immunogenicity

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

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 2.6.

<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 of 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 section 2.6).

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

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

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

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. If patients with severe chronic neutropenia develop abnormal cytogenetics, the risks and benefits of continuing Neupogen should be carefully weighed; Neupogen should be discontinued if MDS or leukaemia occur. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions

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

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

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

Special precautions in patients with HIV infection

Blood cell counts

Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of 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 μg)/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

The needle cover of the pre-filled syringe may contain dry natural rubber (a derivative of latex), which may cause allergic reactions.

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 (30 MU) pre-filled syringe contains less than 1 mmol (23 mg) sodium per pre-filled syringe, 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.

2.4.2 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 2.6).

2.4.3 Interactions 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.

2.5 Use in Special Populations

2.5.1 Pregnancy

The safety of Neupogen has not been established in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated (see section 3.3.3 Teratogenicity). Studies in animals have shown reproductive toxicity.

Neupogen is not recommended during pregnancy.

2.5.2 Nursing Mothers

It is not known whether Neupogen is excreted in human milk. Neupogen is not recommended for use in nursing women.

2.5.3 Paediatric Use

Established cytotoxic chemotherapy

The safety and efficacy of Neupogen are similar in adults and children receiving cytotoxic chemotherapy.

In patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation

The safety and efficacy of Neupogen have not been assessed in normal donors < 16 years.

In patients with severe chronic neutropenia (SCN)

The safety and efficacy in neonates have not been established.

Long term administration of Neupogen is indicated in children with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) ≤ 0.5 x 10^9/l, and a history of

severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events (see section 2.2.1 Special Dosage Instructions).

Paediatric use in the SCN and cancer settings
Sixty-five percent of patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for severe chronic neutropenia.

2.5.4 Geriatric Use
In patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation
The safety and efficacy of Neupogen have not been assessed in normal donors > 60 years.

2.5.5 Renal Impairment
See section 2.2.1 Special Dosage Instructions

2.5.6 Hepatic Impairment
See section 2.2.1 Special Dosage Instructions

2.6 Undesirable Effects

2.6.1 Clinical Trials
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 Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leucocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache[a]	Dizziness Hypoaesthesia Paraesthesia		
Vascular disorders		Hypertension Hypotension	Veno-occlusive disease[d]	Capillary leak syndrome[a] Aortitis
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a, e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary oedema[a] Pulmonary haemorrhage Interstitial lung disease[a] Lung infiltration[a] Hypoxia	
Gastrointestinal disorders	Diarrhoea[a,e] Vomiting[a,e] Nausea[a]	Oral pain Constipation[e]		

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)**
Hepatobiliary disorders		Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculo-papular	Cutaneous vasculitis[a] Sweets syndrome (acute febrile neutrophilic dermatosis)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Glomerulonephritis Urine abnormality
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Pain[a] Asthenia[a] Malaise[e] Oedema peripheral[e]	Injection site reaction	
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section 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 2.4).

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 2.4).

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 2.4).

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 2.4).

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 section 2.4).

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 as per local regulations.

2.7 Overdose

The effects of Neupogen overdosage have not been established.

Doses up to 138 µg/kg/day were administered to patients in BMT studies without toxic effects.

Discontinuation of Neupogen therapy usually results in a 50% decrease in circulating neutrophils within one to two days, with a return to normal levels in one to seven days.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Human granulocyte-colony stimulating factor 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 24 hours, with minor increases in monocytes. In some severe chronic neutropenia patients Neupogen 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 by the human body in response to Neupogen show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of Neupogen therapy, circulating neutrophil counts decrease by 50% within one to two days, and to normal levels within one to seven days.

Treatment with Neupogen in patients undergoing cytotoxic chemotherapy or myeloablative therapy followed by bone marrow transplantation leads to a significant reduction in the incidence, severity and duration of neutropenia and febrile neutropenia, and consequently, fewer admissions to the hospital, shorter duration of hospitalisation and less antibiotics as compared to patients on cytotoxic chemotherapy alone.

Treatment with Neupogen significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia. The incidence of fever and documented infections was not reduced in this setting.

Use of Neupogen, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood. These autologous peripheral blood progenitor cells (PBPC) 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 peripheral blood progenitor cells 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.

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

Use of Neupogen 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 Neupogen show an increase in HIV replication.

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

3.2 Pharmacokinetic Properties

3.2.1 Absorption

After s.c. administration, filgrastim is rapidly absorbed, and peak serum concentrations are attained 2 to 8 hours after dosing. Elimination half-life after i.v. and s.c. dosing is usually between 2 and 4 hours. Clearance and half-life are dependent on dose and neutrophil count. When neutrophil-mediated clearance is saturated by high filgrastim concentrations or is diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appear linear. The absolute bioavailability of filgrastim after s.c. administration is estimated to be 62% for a 375 μg dose and 72% for a 750 μg dose. After discontinuation of dosing, filgrastim concentrations decrease to endogenous concentrations within 24 hours.

A decrease in filgrastim serum concentrations is evidenced upon multiple dosing in healthy subjects and in cancer subjects before chemotherapy. This increase in clearance of filgrastim is dose dependent, and the magnitude of increase appears closely related to the degree of neutrophilia in the recipients, which is consistent with increased neutrophil-mediated clearance by the expanded neutrophil pool. In subjects receiving filgrastim after chemotherapy, plateau serum concentrations are maintained until onset of haematopoietic recovery.

3.2.2 Distribution

There is a positive linear correlation between the dose and the serum concentration of Neupogen, 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.

3.2.3 Elimination

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.

Clearance of Neupogen has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The mean serum elimination half-life of Neupogen is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg.

3.2.4 Pharmacokinetics in Special Populations

Paediatrics

The pharmacokinetics of filgrastim in paediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalised doses, suggesting no age-related differences in the pharmacokinetics of filgrastim.

Geriatrics

Pharmacokinetic data in geriatric patients (> 65 years) are not available.

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. A trend towards higher systemic exposure to filgrastim is observed in patients with ESRD compared with healthy subjects and subjects with creatinine clearance of 30-60 ml/min.

3.3 Preclinical Safety

3.3.1 Carcinogenicity

The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system.

Certain malignant cells have been shown to express granulocyte-colony stimulating factor (G-CSF) receptors. The possibility that filgrastim can act as growth factor for any tumor type cannot be excluded.

3.3.2 Impairment of Fertility

Filgrastim had no observed effect on the fertility of male or female rats, or gestation, at doses up to 500 μg/kg.

3.3.3 Teratogenicity

There is no evidence from studies in rats and rabbits that Neupogen is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Neupogen should be stored in a refrigerator at 2 - 8ºC. Accidental exposure to freezing temperatures does not adversely affect the stability of Neupogen.

This medicine should not be used after the expiry date (EXP) shown on the pack.

For storage of diluted solutions see section 4.2 Special Instructions for Use, Handling and Disposal.

4.2 Special Instructions for Use, Handling and Disposal

Avoid vigorous shaking.

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

Filgrastim syringes are for single use only.

Instructions for dilution
If required, filgrastim may be diluted in 5% glucose. Dilution to a final concentration less than 5 μg/per ml is not recommended at any time.

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

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

Diluted Neupogen solutions should not be prepared more than 24 hours before administration and should also be stored refrigerated at 2 - 8ºC.

Incompatibilities
Neupogen should not be diluted with saline solutions. If required, Neupogen may be diluted in 5% glucose.

Diluted Neupogen may be adsorbed to glass and plastic materials. However, when diluted in 5% glucose solution, Neupogen is compatible with glass and a variety of plastic including PCV, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Neupogen pre-filled syringes are for single-dose use only.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

4.3 Packs

Pre-filled syringe of 0.5 ml (30 MU)

Medicine: keep out of reach of children

Neupogen Pre-filled Syringe of 0.5 ml (30 MU)

Manufactured by:
Amgen Manufacturing Limited
State Road 31, Km 24.6, Juncos,
Puerto Rico, 00777-4060, United States

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