

Neupogen®

Filgrastim

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Hematopoietic growth factor (Cytokines)

ATC code: L03AA02

1.2 Type of Dosage Form

Single-use vials

Neupogen vial of 1.0 ml or 1.6 ml solution for injection

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.

Vials

1 vial of Neupogen of 1.0 ml injection solution contains 30 MU (= 300 µg) of filgrastim.

1 vial of Neupogen of 1.6 ml injection solution contains 48 MU (= 480 µg) of filgrastim.

Pre-filled syringes

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

1 pre-filled syringe of Neupogen of 0.5 ml contains 48 MU (= 480 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 leukemia 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 Pediatric Use).

Peripheral blood progenitor cell mobilization (PBPC)

Neupogen is indicated for the mobilization of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy and the mobilization 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) $\leq 0.5 \times 10^9/l$, 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 $\leq 1.0 \times 10^9/l$) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections, when other options to manage neutropenia are inappropriate.

Patients with Acute Myeloid Leukemia

Neupogen is indicated to reduce the duration of neutropenia and related clinical sequelae in patients undergoing induction or consolidation chemotherapy.

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 hematology and has the necessary diagnostic facilities.

The mobilization and apheresis procedures should be performed in collaboration with an oncology hematology center with acceptable experience in this field and where the monitoring of hematopoietic 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 leukemia, 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 leukemia 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 Pediatric 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 Pediatric Use):

Neutrophil count	Neupogen dose adjustment
> 1.0x10 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 mobilization

Mobilization 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 mobilization 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 mobilization 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.

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

For PBPC mobilization 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.

In the indication for mobilization of Peripheral Blood Progenitor Cells (PBPC) in normal donors prior to allogeneic peripheral blood progenitor cell transplantation the safety and efficacy of Neupogen have not been assessed in normal donors < 16 years or > 60 years.

For children, see section 2.5.3 Pediatric Use.

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 $1.5 \times 10^9/l$. 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 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 Pediatric 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 ($ANC > 2.0 \times 10^9/l$).

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 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 $> 2.0 \times 10^9/l$. In clinical studies, dosing with 30 MU (300 µg)/day on 1 to 7 days per week was required to maintain the $ANC > 2.0 \times 10^9/l$, with the median dose frequency being 3 days per week. Long term administration may be required to maintain the $ANC > 2.0 \times 10^9/l$.

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 pediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy (see section 2.5.3 Pediatric 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

Neupogen should not be administered to patients with known hypersensitivity to filgrastim or to any of the excipients.

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

Neupogen should not be administered to patients with severe congenital neutropenia (Kostmann's syndrome) with abnormal cytogenetics (see section 2.4 Warnings and Precautions).

2.4 Warnings and Precautions

2.4.1 General

a) Malignant cell growth

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

The safety and efficacy of Neupogen administration in patients with myelodysplastic syndrome, or chronic myelogenous leukemia 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 leukemia from acute myeloid leukemia.

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.

b) In patients receiving cytotoxic chemotherapy

Leukocytosis:

White blood cell counts of $100 \times 10^9/l$ or greater have been observed in less than 5% of patients receiving Neupogen at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported.

However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during Neupogen therapy. If leukocyte counts exceed $50 \times 10^9/l$ after the expected nadir, Neupogen should be discontinued immediately. However, during the period of administration of Neupogen for PBPC mobilization, Neupogen should be discontinued or its dosage should be reduced if the leukocyte counts rise to $> 70 \times 10^9/l$.

Risks associated with increased doses of chemotherapy:

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

Treatment with Neupogen alone does not preclude thrombocytopenia and anemia 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 anemia. Regular monitoring of platelet count and hematocrit 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-mobilized PBPC has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

c) In Peripheral Blood Progenitor Cell Mobilization

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

Mobilization: There are no prospectively randomized comparisons of the two recommended mobilization methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimum method. The choice of mobilization 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 mobilization 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 hematopoietic progenitor pool, and may adversely affect progenitor mobilization. Agents such as melphalan, carmustine (BCNU), and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilization may reduce progenitor yield. However, the administration of melphalan, carboplatin or BCNU together with Neupogen, has been shown to be effective for progenitor mobilization. When a peripheral blood progenitor cell transplantation is

envisaged it is advisable to plan the stem cell mobilization procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilized 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 hematologic reconstitution. Yields in excess of this appear to correlate with more rapid recovery, those below with slower recovery.

In normal donors undergoing peripheral blood progenitor cell mobilization prior to allogeneic peripheral blood progenitor cell transplantation

Mobilization 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 mobilization should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to hematological values and infectious disease (see sections 2.5.1 Pregnancy, 2.5.3 Nursing Mothers, 2.5.3 Pediatric Use and 2.5.4 Geriatric Use).

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 hemostasis.

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

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

A risk of promotion of a malignant clone can not be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors to ensure monitoring of long-term safety.

Special precautions in recipients of allogeneic peripheral blood progenitor cells mobilized 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 Graft versus Host Disease (GvHD) when compared with bone marrow transplantation.

d) In patients with severe chronic neutropenia (SCN)

Transformation to leukemia or myelodysplastic syndrome (MDS)

Special care should be taken in the diagnosis of severe chronic neutropenias to distinguish them from other hematopoietic disorders such as aplastic anemia, myelodysplasia, and myeloid leukemia. 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 or leukemia in clinical trial patients with severe chronic neutropenia treated with Neupogen. This observation has only been made in patients with congenital neutropenia (Kostmann's syndrome). MDS and leukemias 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 leukemia occur. It is currently unclear whether long-term treatment of patients with severe chronic neutropenia will predispose patients to cytogenetic abnormalities, MDS or leukemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients with Kostmann's syndrome at regular intervals (approximately every 12 months).

Blood cell counts

Platelet counts should be monitored closely, especially during the first few weeks of Neupogen therapy. Consideration should be given to intermittent cessation or decreasing the dose of Neupogen in patients who develop thrombocytopenia, i.e. platelets consistently $<100,000/\text{mm}^3$. Other blood cell changes occur, including anemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Others

Causes of transient neutropenia, such as viral infections, should be excluded. Splenic enlargement is a direct effect of treatment with Neupogen. 31 % of patients with SCN in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during Neupogen therapy and tended to plateau. Dose reductions were noted to slow or stop the progression of splenic enlargement, and in 3% of patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.

Hematuria/proteinuria occurred in a small number of patients. Regular urine analysis should be performed to monitor this event. The safety and efficacy in patients with autoimmune neutropenia have not been established (see section 2.5.3 Pediatric Use).

e) 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 anemia 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 anemia. 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.

f) Other special precautions

There have been isolated cases of splenic rupture in both healthy donors and patients with cancer following administration of filgrastim granulocyte-colony stimulating factors (G-CSFs). Some of these cases were fatal. Therefore, spleen size should be carefully monitored (eg clinical examination, ultrasound). A diagnosis of splenic rupture or enlarged spleen should be considered in donors or patients reporting left upper abdominal pain or shoulder tip pain.

Publications in the literature have reported that high leukocyte counts are disadvantageous prognostic factors in patients with sickle cell disease. Therefore, clinicians should exercise caution when administering Neupogen in patients with sickle

cell disease, should institute close monitoring of appropriate clinical parameters and laboratory status and be attentive of the possible association of Neupogen with splenic enlargement and vaso-occlusive crisis.

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

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

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 (such as those treated with extensive radiotherapy or chemotherapy or those with bone marrow infiltration by tumor), neutrophil response may be diminished.

The effect of Neupogen on Graft versus Host Disease (GvHD) has not been defined.

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

The onset of pulmonary signs, such as cough, fever and dyspnea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of adult respiratory distress syndrome (ARDS). Neupogen should be discontinued and appropriate treatment given.

2.4.2 Ability to Drive and Use Machines

No effects on ability to drive and use machines have been reported.

2.4.3 Laboratory Tests

See section 2.4.1 General (Warnings and Precautions).

2.4.4 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 hematopoietic 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.

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

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. In pregnancy, the possible risk of Neupogen use to the fetus must be weighed against the expected therapeutic benefit.

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 Pediatric 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) $\leq 0.5 \times 10^9/l$, 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 2.1 Special Dosage Instructions).

Pediatric use in the SCN and Cancer Settings

Sixty-five percent of 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 pediatric patients treated for severe chronic neutropenia.

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

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.

2.5.6 Hepatic Impairment

See section 2.2.1.

2.6 Undesirable Effects

2.6.1 Clinical Trials

In Cancer Patients

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

Symptoms suggestive of allergic-type reactions have been reported, approximately half associated with the initial dose. Overall, reports were more common after i.v. administration. In some cases, re-challenge resulted in a recurrence of symptoms.

Administration of Neupogen at the recommended dosage is frequently associated with musculoskeletal pain specifically in medullar bones. This is usually mild or moderate (10%), but occasionally severe (3%), and is generally controlled with standard analgesics. Less frequent adverse events include urinary abnormalities (predominantly mild or moderate dysuria). Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.

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

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

The occurrence of Sweet's syndrome (acute febrile dermatosis) has been reported occasionally. However, since a significant percentage of these patients were suffering

from leukemia, a condition known to be associated with Sweet's syndrome, a causal relationship with Neupogen has not been established.

Exacerbation of rheumatoid arthritis has been observed in individual cases.

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

Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase, alkaline phosphatase, serum uric acid and gamma-glutamyl transpeptidase may frequently occur.

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Gastrointestinal disorders Investigations	Nausea Vomiting Increased GGT Increased Alkaline Phosphatase Increased LDH Increased Uric Acid
Common (1 – 10%)	General disorders and administration site condition Nervous system disorders Gastrointestinal disorders Metabolic and nutrition disorders Musculoskeletal disorders	Fatigue Generalised weakness Mucosal inflammation Headache Constipation Diarrhea Anorexia Chest Pain Musculoskeletal Pain

Frequency	Body System	Undesirable Effect
	Respiratory disorders Skin and subcutaneous tissue disorders	Cough Pharyngolaryngeal pain Alopecia Skin Rash
Uncommon (< 1%)	General disorders and administration site condition	Unspecified Pain
Very Rare (< 0.01%)	Immune system disorders Musculoskeletal disorders Respiratory disorders Skin and subcutaneous disorders Renal and urinary disorders	Allergic Reaction Rheumatoid Arthritis exacerbation Pulmonary Infiltrates Sweet's Syndrome Cutaneous Vasculitis Urinary Abnormalities

In Patients with HIV

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

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

Frequency	Body System	Undesirable Effect
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Very Common (> 10%)	Musculoskeletal disorders	Musculoskeletal Pain
		Bone pain Myalgia
Common (1 – 10%)	Blood and lymphatic disorders	Splenic enlargement

In Normal Donors undergoing peripheral blood progenitor cell mobilization

The most commonly reported undesirable effect was mild to moderate transient musculoskeletal pain.

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

Exacerbation of arthritic symptoms has been observed very rarely.

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

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

Leukocytosis (WBC > 50 x 10⁹/l) was observed in 41% of donors and transient thrombocytopenia (platelets < 100 x 10⁹/l) following filgrastim and leukapheresis was observed in 35% of donors.

Common but generally asymptomatic cases of splenomegaly have been reported.

For allogeneic (also called normal or healthy) donors, pulmonary adverse events (hemoptysis, pulmonary infiltrates) have been reported very rarely (<0.01%).

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Nervous system disorders	Headache
	Blood and lymphatic system disorders	Leucocytosis Thrombocytopenia
	Musculoskeletal disorders	Musculoskeletal Pain
Common (1 – 10%)	Investigations	Increased Alkaline Phosphatase Increased LDH

Frequency	Body System	Undesirable Effect
	Blood and lymphatic system disorders	Splenomegaly
Uncommon (< 1%)	Immune system disorders Blood and lymphatic system disorders Investigations Metabolic and nutrition disorders	Severe Allergic Reaction Spleen Disorder SGOT Increased Hyperuricaemia
Very rare (<0.01%)	Respiratory disorders Musculoskeletal disorders	Hemoptysis Pulmonary infiltrates Rheumatoid Arthritis exacerbation

In Patients with SCN

The most frequent clinical adverse events attributed to Neupogen were bone pain and general musculoskeletal pain.

Undesirable effects related to Neupogen therapy in SCN patients have been reported and for some their frequency tends to decrease with time.

Other events seen include splenic enlargement, which may be progressive in a minority of cases, and thrombocytopenia. Headache and diarrhea have been reported shortly after starting Neupogen therapy, typically in less than 10% of patients. Anemia and epistaxis have also been reported.

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

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

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

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Blood and lymphatic	Anemia

Frequency	Body System	Undesirable Effect
	system disorders Investigations Metabolic and nutrition disorders Musculoskeletal disorders	Splenomegaly Decreased Glucose Increased Alkaline Phosphatase Increased LDH Hyperuricemia Musculoskeletal Pain
Common (1 – 10%)	Nervous system disorders Gastrointestinal disorders Hepatobiliary disorders Musculoskeletal disorders Skin and subcutaneous disorders Blood and lymphatic system disorders General disorders and administration site condition	Headache Diarrhea Hepatomegaly Osteoporosis Alopecia Rash Cutaneous Vasculitis Thrombocytopenia Injection Site Pain
Uncommon (< 1%)	Renal and urinary disorders Blood and lymphatic system disorders	Hematuria Proteinuria Spleen disorders

2.6.1.1 Laboratory Abnormalities

In Cancer Patients

See section 2.6.1 Clinical Trials.

In patients with SCN

See section 2.6.1 Clinical Trials.

In Normal Donors undergoing peripheral blood progenitor cell mobilization

See section 2.6.1 Clinical Trials.

2.6.2 Post Marketing

Allergic Reactions: Allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported in patients receiving filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship.

Allergic-type reactions to filgrastim have rarely been reported in post marketing experience.

Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Isolated cases of sickle cell crisis, in some cases fatal, have been reported in patients with sickle cell disease.

Very rare cases of splenic rupture in normal donors receiving G-CSFs and in patients have been reported (see section 2.4 Warnings and Precautions).

Rare cases ($\geq 0.01\%$ and $< 0.1\%$) of Sweet's syndrome (acute febrile dermatosis) have been reported.

2.6.2.1 Laboratory Abnormalities

Reversible, mild-to-moderate increases in uric acid, alkaline phosphatase, and lactate dehydrogenase, with no associated clinical effects, have been seen in patients receiving filgrastim after cytotoxic chemotherapy.

2.7 Overdose

The effects of Neupogen overdosage have not been established.

Doses up to 138 μ g/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 hospitalization and less antibiotics as compared to patients on cytotoxic chemotherapy alone.

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

Use of Neupogen, either alone, or after chemotherapy, mobilizes hematopoietic 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 hematopoietic recovery reducing the duration of risk for hemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic peripheral blood progenitor cells mobilized with Neupogen experienced significantly more rapid hematological 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 hematopoietic 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 mcg dose and 72% for a 750 mcg 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 hematopoietic 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

Pediatrics

The pharmacokinetics of filgrastim in pediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalized 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 metabolizing 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 mcg/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 - 8°C. 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 vials and syringes are for single use only.

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

Instructions for dilution

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.

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

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

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 vials and pre-filled syringes are for single-dose use only.

4.3 Packs

Vials containing 1.0 ml (30 million units) injection solution	5
Vials containing 1.6 ml (48 million units) injection solution	5
Pre-filled syringe of 0.5 ml (30 MU)	1, 5
Pre-filled syringe of 0.5 ml (48 MU)	1, 5

Medicine: keep out of reach of children

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