SCHEDULING STATUS
S4

PROPRIETARY NAME AND DOSAGE FORM

NEUPOGEN® Injection (in a vial)

NEUPOGEN® 30 MU
Injection (in a pre-filled syringe)

NEUPOGEN® 48 MU
Injection (in a pre-filled syringe)

COMPOSITION
Active ingredient: Filgrastim, non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF); 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.
Excipients for vials and pre-filled syringes: sorbitol, sodium acetate, polysorbate 80, water for injection.
Each vial contains 30 MU of filgrastim per 1 ml.
Each pre-filled syringe contains 30 MU or 48 MU of filgrastim per 0,5 ml, respectively

PHARMACOLOGICAL CLASSIFICATION
A30.4 Biologicals – other

PHARMACOLOGICAL ACTION
Pharmacodynamics
Mechanism of Action
Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. NEUPOGEN, which contains recombinant-metHuG-CSF, 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 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 1 to 2 days, and to normal levels within 1 to 7 days.
Use of NEUPOGEN in patients undergoing cytotoxic chemotherapy or myeloablative therapy followed by bone marrow transplantation leads to a statistically significant reduction in the incidence, severity and duration of neutropenia and febrile neutropenia.
Use of NEUPOGEN, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood.
Use of NEUPOGEN in patients, children or adults, with severe chronic neutropenia (severe congenital neutropenia, cyclic neutropenia, 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 filgrastim show an increase in HIV replication.

Pharmacokinetics
Absorption
After SC administration, filgrastim is rapidly absorbed, and peak serum concentrations are attained 2 to 8 hours after dosing. Elimination half-life after IV and SC 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 SC 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 haematopoietic recovery.

Distribution

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 to 16 hours. The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Clearance of filgrastim has been shown to follow first order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3,5 hours, with a clearance rate of approximately 0,6 ml/min/kg.

Continuous infusion with NEUPOGEN over a period of up to 28 days in patients recovering from autologous bone marrow transplantation, resulted in no evidence of accumulation and comparable elimination half-lives.

Pharmacokinetics in Special Populations

Paediatrics

The pharmacokinetics of filgrastim in paediatric 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 Impairment

Studies of filgrastim in patients with moderate impairment of renal 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. Higher systemic exposure to filgrastim is observed in patients with end-stage renal disease (ESRD) compared with healthy subjects and subjects with creatinine clearance of 30 - 60 ml/min.

Hepatic Impairment

Studies of filgrastim in patients with severe impairment of 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.

INDICATIONS Established cytotoxic chemotherapy

NEUPOGEN® is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia and its clinical sequelae in patients undergoing myeloablative therapy, followed by bone marrow transplantation.

Severe chronic neutropenia (SCN)

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) ≤ $0,5x10^9$/l, long term administration of NEUPOGEN is indicated to increase neutrophil count and to reduce the incidence and duration of infections.

Peripheral blood progenitor cell (PBPC) mobilisation

The mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate haematopoietic recovery by infusion of such cells after myelosuppressive or myeloablative therapy. The mobilisation of peripheral blood progenitor cells in normal donors (allogeneic) PBPC.

HIV infection

NEUPOGEN is indicated in patients with advanced HIV infection and neutropenia (absolute neutrophil count (ANC) < 1 x 10^9/l) to allow scheduled dosing of anti-retroviral medication.

CONTRA-INDICATIONS

NEUPOGEN should not be administered to patients with known sensitivity to the product or its constituents.

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.
Studies have not been performed with NEUPOGEN in patients with severe impairment of renal or hepatic function and therefore its use in this patient group cannot be recommended.

WARNINGS
Hypersensitivity, pulmonary toxicity, sickle cell crises. (See SIDE EFFECTS AND SPECIAL PRECAUTIONS).
Sickle cell crises, in some cases fatal, have been reported with the use of NEUPOGEN in subjects with sickle cell disease. Medical practitioners should exercise caution when considering the use of NEUPOGEN in patients with sickle cell disease, and only after careful evaluation of the potential risks and benefits.

INTERACTIONS
The safety and efficacy of NEUPOGEN given on the same day as myelosuppressive cytotoxic chemotherapy has not been 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. 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. This interaction has not been formally investigated.
Increased haematopoietic 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.

PREGNANCY AND LACTATION
The safety of NEUPOGEN in pregnant or lactating women has not been established.
There are reports in the literature that transplacental passage of filgrastim in pregnant women has been demonstrated. Studies in animals have shown reproductive toxicity. In pregnancy, the possible risk of NEUPOGEN use to the foetus must be weighed against the expected therapeutic benefit. NEUPOGEN should not be used in pregnancy.
It is not known whether NEUPOGEN is excreted in human milk. Women on NEUPOGEN should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE
Therapy should only be given in collaboration with an oncology centre which has experience in G-CSF treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Established cytotoxic chemotherapy
The recommended dose of NEUPOGEN is 0,5 MU (5 µg)/kg/day. The first dose of NEUPOGEN should not be administered within 24 hours of cytotoxic chemotherapy or bone marrow infusion. NEUPOGEN may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5 % glucose solution, given over 30 minutes (refer to instructions on dilution). 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 nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, 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 (AML), 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 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.

Patients treated with myeloablative therapy, followed by bone marrow transplantation (BMT):
The recommended starting dose of NEUPOGEN, following BMT, is 1,0 MU (10 µg)/kg/day, given as an *IV* infusion of 4 or 24 hours, or as a continuous 24-hour subcutaneous infusion. NEUPOGEN should be diluted in 20 ml of 5 % glucose solution. For patients receiving BMT, the first dose of NEUPOGEN should be administered at least 24 hours after 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 passed, the daily dose of NEUPOGEN should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count (ANC)	NEUPOGEN dose adjustment
When ANC > 1,0 x 10^9/l for 3 consecutive days:	Reduce to 0,5 MU (5 µg)/kg/day
Then, if ANC remains > 1,0 x 10^9/l for a further 3 consecutive days:	Discontinue NEUPOGEN
If the ANC decreases to <1,0 x 10^9/l during the treatment period, the dose of NEUPOGEN should be re-escalated according to the above steps.	

Patients with severe chronic neutropenia (SCN)
Congenital neutropenia*:* the recommended daily starting dose is 0,6 MU (6 µg)/kg twice daily, subcutaneously.
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 adjustments: NEUPOGEN should be administered daily, by subcutaneous injection, to increase and sustain the average neutrophil count above 1,5 x 10^9/l. Long-term daily administration is required to maintain an adequate neutrophil count. After one or two weeks of therapy, the initial dose may be doubled, or halved, depending on the patient's response. Subsequently, the dose may be individually adjusted every 1 - 2 weeks to maintain the average neutrophil count between 1,5 x 10^9/l and 10 x 10^9/l.
A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials 97 % of patients who responded had a complete response at doses ≤ 24 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.

Paediatric use in severe chronic neutropenia.
The safety and efficacy in neonates have not been established.

Paediatric use in severe chronic neutropenia and Cancer setting
Sixty five percent of the patients studied in the severe chronic neutropenia (SCN) trial program were under 18 years old. 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.

Peripheral blood progenitor cell mobilisation
The 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, to accelerate haematopoietic recovery:
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 6 consecutive days. For infusions, NEUPOGEN should be diluted in 20 ml of 5 % glucose solution (refer to instructions on dilution). Timing of leukopheresis: a total of three consecutive collections are recommended, on days 5, 6 and 7.
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. Leukopheresis should be performed during the period when the ANC rises from < 0,5 x 10^9/l to > 5,0 x 10^9/l.
For patients who have not had extensive chemotherapy, one leukopheresis is often sufficient. In other circumstances, additional leukopheresis are recommended.
Paediatric Use

The safety and efficacy of NEUPOGEN have not been assessed in normal donors below 16 years undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation.
Geriatric Use
The safety and efficacy of NEUPOGEN have not been assessed in normal donors above 60 years. undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation.

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. Leukopheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipients' bodyweight.

Patients with 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 x 10^9/l). In clinical studies, > 90 % of patients responded to 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 of NEUPOGEN to maintain a normal neutrophil count should be established. Initial dose adjustment to 3 x weekly 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 x 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 x 10^9/l, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC ≥ 2,0 x 10^9/l. If myelosuppressive medication is discontinued and there is no recurrence of neutropenia, NEUPOGEN dosing should be reduced, and then stopped.

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. The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.
Refer to Pharmacokinetics in Special Populations.
Dilutions
If required, NEUPOGEN may be diluted in 5 % glucose. Diluted NEUPOGEN may be adsorbed to glass and plastic materials. Dilution to a final concentration less than 0,2 MU (2 µg)/ml is not recommended at any time. For patients treated with NEUPOGEN diluted to concentration below 1,5 MU (15 µg)/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 NEUPOGEN less than 30 MU (300 µg) should be given with 0,2 ml of 20 % human albumin solution added.
When diluted in 5 % glucose solution, NEUPOGEN is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Incompatibilities
NEUPOGEN should not be diluted with saline solutions.
NEUPOGEN vials and pre-filled syringes contain no preservatives and are for single dose use only.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Cancer patients
Administration of NEUPOGEN at the recommended dosage is frequently associated with musculoskeletal pain, specifically in medullar bones, that was mild to moderate in 10 %, and severe in 3 % of patients. Less frequent adverse events include urinary abnormalities (predominantly mild or moderate dysuria).
NEUPOGEN did not increase the incidence of clinical adverse events associated with cytotoxic chemotherapy. Adverse events reported included nausea and vomiting, alopecia, diarrhoea,

neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnoea, headache, cough, skin rash, chest pain, generalised weakness, sore throat, stomatitis, constipation and unspecified pain.
Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase (LDH), alkaline phosphatase, serum uric acid and gamma-glutamyl transpeptidase occurred with NEUPOGEN in approximately 50 %, 35 %, 25 % and 10 % of patients, respectively, at recommended doses. Transient decreases in blood pressure have been reported.
Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with NEUPOGEN has not been established.
Symptoms suggestive of allergic-type have been reported in rare cases; approximately half of these were associated with the initial dose. Overall, reports were more common after *IV* administration. In some cases, re-challenge resulted in a recurrence of symptoms.
Rare events (less than 1 in 7 000) 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 leukaemia, 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.
Pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, and pulmonary infiltrates have been reported; in some cases, leading to respiratory failure or ARDS (Adult Respiratory Distress Syndrome, an acute lung injury), which may be fatal.

Frequency	**Body System**	**Undesirable Effect**
Very Common (≥ 10 %)	Gastrointestinal disorders	Nausea Vomiting
	Investigations	Increased GGT Increased alkaline phosphatase Increased LDH
Common (1 – 10 %)	General disorders and administration site disorders	Fatigue Generalised weakness Mucosal inflammation
	Nervous system disorders	Headache
	Gastrointestinal disorders	Constipation Diarrhoea
	Metabolic and nutrition disorders	Anorexia
	Musculoskeletal disorders	Chest pain Musculoskeletal pain
	Respiratory disorders	Pharyngolaryngeal pain
	Skin and subcutaneous tissue	Alopecia Skin rash
Uncommon (< 1 %)	General disorders and administration site disorders	Unspecified pain
Very Rare (< 0,01 %)	Immune system disorders	Allergic reaction
	Musculoskeletal disorders	Rheumatoid arthritis exacerbation
	Respiratory disorders	Pulmonary infiltrates
	Skin and subcutaneous disorders	Sweet's syndrome Cutaneous vasculitis
	Renal and urinary disorders	Urinary abnormalities

Severe chronic neutropenia (SCN) patients
Adverse reactions related to NEUPOGEN therapy in SCN patients occur infrequently and the frequency of these events tend to decrease with time.
The most frequent clinical events attributable to NEUPOGEN were bone pain, and general musculoskeletal pain.
Other events seen, include splenic enlargement, which is generally not progressive, and thrombocytopenia.
Headache and diarrhoea have been reported in some patients shortly after starting NEUPOGEN

therapy. Anaemia and epistaxis have also been reported.
Transient increases, with no clinical symptoms, were observed in serum uric acid, lactic dehydrogenase, and alkaline phosphatase.
Transient, moderate decreases in non-fasting blood glucose have also been seen.
Adverse events infrequently observed, and possibly related to NEUPOGEN therapy in SCN patients, were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis, rash and exacerbation of some pre-existing skin disorders eg. psoriasis.
During long term use cutaneous vasculitis has been reported, very rarely. There have been very few instances of proteinuria/haematuria.

Frequency	**Body System**	**Undesirable Effect**
Very Common (≥ 10 %)	Blood and lymphatic system disorders	Anaemia Splenomegaly
	Investigations	Decreased glucose Increased alkaline phosphatase Increased LDH
	Metabolic and nutrition disorders	Hyperuricaemia
	Musculoskeletal disorders	Musculoskeletal pain
Common (1 – 10 %)	Nervous system disorders	Headache
	Gastrointestinal disorders	Diarrhoea
	Hepatobiliary disorders	Hepatomegaly
	Musculoskeletal disorders	Osteoporosis
	Skin and subcutaneous tissue	Alopecia Rash Cutaneous vasculitis
	Blood and lymphatic system disorders	Thrombocytopenia
	General disorders and administration site disorders	Unspecified pain
Uncommon (< 1 %)	Renal and urinary disorders	Haematuria Proteinuria
	Blood and lymphatic system disorders	Spleen disorders

In Normal Donors undergoing peripheral blood progenitor cell mobilisation with filgrastim
Frequently reported
Musculoskeletal and Connective Tissue Disorders: mild to moderate transient musculo-skeletal pain.
Blood and Lymphatic System Disorders: Leukocytosis (WBC > 50 x 10^9/l) was observed in 41 % of donors and transient thrombocytopenia (platelets < 100 x 10^9/l) following filgrastim and leukopheresis 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 (haemoptysis, pulmonary infiltrates) have been reported.
Less frequently
Blood and Lymphatic System: Isolated cases of splenic rupture. See: SIDE EFFECTS AND SPECIAL PRECAUTIONS.
Nervous System Disorders: headaches have been reported in PBPC donor studies.
Musculoskeletal and Connective Tissue Disorders: Exacerbation of arthritic symptoms.
Laboratory Abnormalities: Transient, minor increases in alkaline phosphatase, LDH, SGOT and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae. Symptoms suggestive of severe allergic reactions have been reported.

Frequency	Body System	Undesirable Effect
Very Common (>10 %)	Nervous system disorders Blood and lymphatic system disorders Musculoskeletal disorders	Headache Leucocytosis Thrombocytopenia Musculoskeletal pain
Common (1 – 10 %)	Investigations Blood and lymphatic system disorders	Increased alkaline phosphatase Increased LDH 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	Haemoptysis Pulmonary infiltrates Rheumatoid arthritis exacerbation

Patients with HIV infection
In clinical studies, the only adverse events that were consistently considered to be related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. The incidence of these events was similar to that reported in cancer patients.
Splenic enlargement was reported to be related to NEUPOGEN therapy in < 3 % of patients. In all cases this was mild or moderate on physical examination and the clinical course was benign; no patient had a diagnosis of hypersplenism and no patient 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
Very Common (>10 %)	Musculoskeletal disorders	Musculoskeletal pain Bone pain Myalgia
Common (1 – 10 %)	Blood and lymphatic system disorders	Splenic enlargement

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 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.
Rare cases (≥ 0,01 % and < 0,1 %) of Sweet's syndrome (acute febrile dermatosis) have been reported.
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.

SPECIAL PRECAUTIONS
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 leukaemia, has 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.
Other special precautions
Monitoring of bone density may be indicated in patients with underlying osteoporotic bone disease who undergo therapy with NEUPOGEN for more than 6 months.

The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of adult respiratory distress syndrome (ARDS). NEUPOGEN should be discontinued and appropriate treatment given.
Known cases of Hereditary Fructose Intolerance (HFI). 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 caution is advised.

Cancer patients
Leucocytosis: White blood cell counts of 100 x 10^9/l or greater, have been observed in less than 5 % of patients receiving NEUPOGEN at doses above 0,3 MU (3 µg)/kg/day. No adverse events 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 x 10^9/l after the expected nadir, NEUPOGEN should be discontinued immediately. However, during the period of administration of NEUPOGEN for peripheral blood progenitor cell mobilisation, discontinuation of NEUPOGEN is appropriate if the leukocyte counts rise to > 70 x 10^9/l.

Risks associated with increased doses of chemotherapy: Special caution should be used when treating patients with high dose chemotherapy, because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).
Treatment with NEUPOGEN alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.
The use of NEUPOGEN-mobilised peripheral blood progenitor cells has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

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

Special precautions in severe chronic neutropenia patients (SCN)

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 decrease of the NEUPOGEN dose in patients who develop thrombocytopenia, i.e. platelets consistently < 100 000/mm^3. Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.
Transformation to leukaemia or myelodysplastic syndrome: Special care should be taken in the diagnosis of severe chronic neutropenias to distinguish it from other haematologic 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 of myelodysplastic syndromes (MDS) or leukaemia in patients with severe chronic neutropenia treated with NEUPOGEN. This observation has only been made in patients with congenital neutropenia (Kostmann's syndrome). MDS and leukaemia's are natural complications of the disease and are of uncertain relation to NEUPOGEN therapy.
A subset 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 occurs. It is currently unclear whether long-term treatment of patients with severe chronic neutropenia will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended that morphologic and cytogenetic bone marrow examinations be performed in patients at regular intervals (approximately every 12 months).
Other special precautions:
Causes of transient neutropenia, such as viral infections, should be excluded.
Splenic enlargement is a direct effect of treatment with NEUPOGEN. A significant number of patients 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, but in some of the patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.
Haematuria/proteinuria occurred in a small number of patients. Regular urinanalysis should be performed to monitor this event.
The safety and efficacy in neonates and patients with auto-immune neutropenia of infancy have not been established.

Special precautions In Peripheral Blood Progenitor Cell Mobilisation

In patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell (PBPC) transplantation
Mobilisation: There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells means 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 PBPCs to achieve the recommended minimum yield (≥ 2,0 x 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 peripheral blood progenitor cell transplantation is envisaged, it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients *before* the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment, not requiring progenitor support, should be considered.

Assessment of progenitor cell yields: In assessing the number of progenitor cells harvested in patients treated with 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. Currently the minimum yield of $CD34^+$ cells is not well defined. The recommendation of a minimum yield of ≥ 2,0 x 10^6 $CD34^+$ cells/kg is based on published experience resulting in adequate haematological reconstitution. Yields in excess of this appear to correlate with more rapid recovery, and those below with slower recovery.

In normal donors undergoing peripheral blood progenitor cell mobilisation (PBPC) prior to allogeneic peripheral blood progenitor cell transplantation
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. Transient thrombocytopenia (platelets < 100 x 10^9/l) following filgrastim administration and leukapheresis was observed in 35 % of subjects studied. Among these, two cases of platelets < 50 x 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 x 10^9/l prior to leukapheresis; in general apheresis should not be performed if platelets < 75 x 10^9/l. Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.
NEUPOGEN administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/l. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.
A risk of promotion of a malignant clone cannot 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.
The safety and efficacy of NEUPOGEN have not been assessed in normal donors < 16 years or > 60 years.
There have been isolated cases of splenic rupture in both healthy donors and cancer patients following administration of granulocyte-colony stimulating factors (G-CSFs). Therefore, spleen size should be carefully monitored (e.g. clinical examination and ultrasound). A diagnosis of splenic rupture should be considered in donors reporting left upper abdominal pain or shoulder tip pain.

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

Special precautions in patients with HIV infection

Blood cell count: 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 doses of NEUPOGEN. It is recommended that the ANC be measured daily for the first 2 - 3 days of NEUPOGEN administration. Thereafter, it is recommended that the ANC be measured at least twice per week for the first 2 weeks and subsequently, once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 µg) of filgrastim, there will 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 be taken for ANC measurement immediately prior to any scheduled dosing with NEUPOGEN.

Risks 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 also 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 infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition. The effect of NEUPOGEN on neutropenia due to bone marrow infiltrating infection, or malignancy, have not been well established.

Other special precautions
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 NEUPOGEN in subjects with sickle cell disease. Physicians should exercise caution when considering the use of NEUPOGEN in patients with sickle cell disease, and only after careful evaluation of the potential risks and benefits.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
The effects of NEUPOGEN overdosage have not been established. Discontinuation of NEUPOGEN therapy usually results in a 50 % decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days. Treatment is symptomatic and supportive.

IDENTIFICATION
NEUPOGEN 30 is a clear, colourless liquid, practically free from particles, supplied either in colourless glass vials with rubber stoppers or in colourless glass syringes with tip caps and plunger stoppers containing 30 million units, equivalent to 300 µg of filgrastim.
NEUPOGEN 48 is a clear, colourless liquid, practically free from particles, supplied in colourless glass syringes with tip caps and plunger stoppers containing 48 million units, equivalent to 480 µg of filgrastim.

PRESENTATION

NEUPOGEN: 1,0 ml vial containing 30 MU: Packs of 5

NEUPOGEN 30 MU: 0,5 ml pre-filled syringe containing 30 MU: Packs of 5

NEUPOGEN 48 MU: 0,5 ml pre-filled syringe containing 48 MU: Packs of 5

STORAGE INSTRUCTIONS
NEUPOGEN should be stored between 2 – 8 ˚C.
NEUPOGEN should not be used after the expiry date shown on the pack.
Diluted NEUPOGEN solutions should not be prepared more than 24 hours before administration and should be stored between 2 - 8˚C.
Accidental exposure to freezing temperatures does not adversely affect the stability of NEUPOGEN.
NEUPOGEN vials and syringes are for single dose use only.
Keep out of reach of children.

REGISTRATION NUMBERS

NEUPOGEN (vial):	Z/30.4/190
NEUPOGEN 30 MU (0,5 ml pre-filled syringes):	32/30.4/0032
NEUPOGEN 48 MU (0,5 ml pre-filled syringes):	32/30.4/0033

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