PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNEUPOGEN®

filgrastim injection

Sterile Solution, 300 mcg / mL and 600 mcg / mL

Subcutaneous or Intravenous Use Only

Professed Standard

Hematopoietic Agent

Granulocyte Colony Stimulating Factor

Amgen Canada Inc.
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Mississauga, Ontario
L5N 0A4

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RECENT MAJOR LABEL CHANGES

Not Applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NEUPOGEN® (filgrastim injection) is indicated for:

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

  NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies (see Patients with Acute Myeloid Leukemia) receiving myelosuppressive anti-neoplastic drugs.

  NEUPOGEN is indicated in adult and pediatric patients with cancer receiving myelosuppressive chemotherapy. A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week (see Monitoring and Laboratory Tests) during NEUPOGEN therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, NEUPOGEN therapy was discontinued when the ANC was > 10 x 10^9/L after expected chemotherapy-induced nadir.

- **Patients with Acute Myeloid Leukemia**

  NEUPOGEN is indicated for the reduction in the duration of neutropenia, fever, antibiotic use and hospitalization, following induction and consolidation treatment for acute myeloid leukemia.

- **Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation**

  NEUPOGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients undergoing myeloablative therapy followed by bone marrow transplantation.

  A CBC and platelet count should be obtained at a minimum of 3 times per week following marrow infusion to monitor marrow reconstitution (see Monitoring and Laboratory Tests).

- **Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy**

  NEUPOGEN is indicated for the mobilization of autologous peripheral blood progenitor cells in order to accelerate haematopoietic recovery by infusion of such cells, supported by NEUPOGEN, after myelosuppressive or myeloablative chemotherapy (see 14 CLINICAL TRIALS).

- **Patients with Severe Chronic Neutropenia (SCN)**

  NEUPOGEN is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic or idiopathic neutropenia (see 14 CLINICAL TRIALS).

- **Patients with HIV Infection**

  NEUPOGEN is indicated in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (eg, between 2 x 10^9 and 10 x 10^9/L). NEUPOGEN therapy reduces the clinical sequelae associated with neutropenia (eg, bacterial infections) and increases the ability to deliver myelosuppressive medications used for the treatment of HIV and its associated complications (see 14 CLINICAL TRIALS). It is recommended that complete blood counts and platelet counts be monitored at regular intervals (eg, initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during NEUPOGEN therapy (see Monitoring and Laboratory Tests).

2 CONTRAINDICATIONS

NEUPOGEN is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, filgrastim, pegfilgrastim, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN (see 7 WARNINGS AND PRECAUTIONS, General).
- Severe sickle cell crises, in some cases resulting in death, have been associated with the use of NEUPOGEN in patients with sickle cell trait or sickle cell disease (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

4 DOSAGE AND ADMINISTRATION

NEUPOGEN is supplied in either vials or in prefilled syringes (SingleJect®) with UltraSafe® Needle Guards. Following administration of NEUPOGEN from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks. To activate the UltraSafe® Needle Guard, place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place.

NOTE: If an audible click is not heard, the needle guard may not be completely activated.

The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

4.1 Dosing Considerations

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

  NEUPOGEN should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. NEUPOGEN should not be administered in the period 24 hours before the administration of chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

- **Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation**

  NEUPOGEN should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

- **Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy**

  The first dose should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after PBPC infusion.

4.2 Recommended Dose and Dosage Adjustment

Cancer Patients Receiving Myelosuppressive Chemotherapy

The recommended starting dose of NEUPOGEN in adult patients is 5 mcg/kg/day, administered as a single daily injection by subcutaneous bolus injection, by short intravenous infusion (15 to 30 minutes), or by continuous subcutaneous or continuous intravenous infusion.

The recommended dose in pediatric oncology patients is 5 mcg/kg/day administered subcutaneously.

A CBC and platelet count should be obtained before instituting NEUPOGEN therapy, and monitored twice weekly during therapy. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir. Therapy should be discontinued if the ANC surpasses 10×10^9/L after the ANC nadir has occurred.

NEUPOGEN should be administered daily for up to 2 weeks, until the ANC has reached 10×10^9/L following the expected chemotherapy-induced neutrophil nadir. The duration of NEUPOGEN therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. NEUPOGEN therapy should be discontinued if the ANC surpasses 10×10^9/L after the expected chemotherapy-induced neutrophil nadir (see 7 WARNINGS AND PRECAUTIONS). In phase 3 trials, efficacy was observed at doses of 4 to 8 mcg/kg/day.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

The recommended dose of NEUPOGEN following bone marrow transplant is 10 mcg/kg/day given as an intravenous infusion of 4 or 24 hours, or as a continuous 24-hour subcutaneous infusion. During the period of neutrophil recovery, the daily dose of NEUPOGEN should be titrated against the neutrophil response as follows:

Table 1. NEUPOGEN Dose Adjustment Based on Absolute Neutrophil Count

Absolute Neutrophil Count	NEUPOGEN Dose Adjustment
When ANC > 1.0 x 10^9/L for 3 consecutive days	Reduce to 5 mcg/kg/day (*see below)
then:	
If ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue NEUPOGEN
If ANC decreases to < 1.0 x 10^9/L	Resume at 5 mcg/kg/day

*If ANC decreases to < 1.0 x 10^9/L at any time during the 5 mcg/kg/day administration, NEUPOGEN should be increased to 10 mcg/kg/day, and the above steps should then be followed.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

The recommended dose of NEUPOGEN for PBPC mobilization is 10 mcg/kg/day given as a single daily subcutaneous injection or a continuous 24-hour infusion. NEUPOGEN therapy should be given for at least 4 days before the first leukapheresis procedure, and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haematopoietic progenitor cells is obtained. For peripheral blood progenitor cells mobilized with NEUPOGEN, a schedule of leukapheresis collections on days 5, 6, and 7 of a 7-day treatment regimen has been found to be effective.

The target number of progenitor cells to be collected and reinfused is to be determined by the treating physician. The following should be considered:

- A minimum or optimal number of progenitor cells in the leukapheresis product, needed for adequate haematopoietic reconstitution, have not been determined. However, studies indicate that the infusion of higher numbers of progenitor cells appears to be associated with a shorter time to neutrophil and platelet recovery,
- Tests for quantifying the number of progenitor cells, measured as $CD34^+$ or GM-CFU, are not standardized and variations may exist between laboratories, and
- Factors other than NEUPOGEN dosage, such as prior cytotoxic chemo- or radio-therapy, may affect the number and quality of progenitor cells mobilized and collected by leukapheresis.

The recommended dose of NEUPOGEN following PBPC transplant is 5 mcg/kg/day given either subcutaneously or as an intravenous infusion. The daily dose of NEUPOGEN should be titrated according to the schedule provided in Table 1 (Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation).

Patients with HIV Infection

The recommended starting dose of NEUPOGEN is 1 mcg/kg/day or 300 mcg 3 times per week by subcutaneous injection until a normal neutrophil count is reached and can be maintained (ANC $\geq$ 2 x 10^9/L). Dose adjustments may be necessary as determined by the patient's ANC to maintain the ANC between 2 x 10^9 and 10 x 10^9/L.

When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. An initial dose of 300 mcg 3 times per week by subcutaneous injection is recommended. A further dose adjustment may be necessary to maintain the ANC between 2 x 10^9 and 10 x 10^9/L.

In clinical trials, the maximum NEUPOGEN dose did not exceed 10 mcg/kg/day.

Patients with Severe Chronic Neutropenia

Starting Dose

Congenital Neutropenia: The recommended daily starting dose is 12 mcg/kg subcutaneously (single or divided dose).

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 mcg/kg subcutaneously (single or divided dose).

Dose Adjustments

NEUPOGEN may be administered subcutaneously as a single daily injection to increase and sustain the ANC above 1.5 x 10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count. After 1 to 2 weeks of therapy, the initial dose may be doubled or halved. Subsequently, the dose may be individually adjusted not more than every 1 to 2 weeks to maintain the ANC between 1.5 x 10^9/L and 10 x 10^9/L. WBC/ANC monitoring should be done more frequently (eg, every other day) if the ANC reaches values above 25 x 10^9/L, and the dose reduced if the ANC remains greater than 25 x 10^9/L for 1 week. In the SCN post-marketing surveillance study, the median daily doses of NEUPOGEN reported (median duration 4.4 years) were: Congenital Neutropenia 6.9 mcg/kg; Cyclic Neutropenia 2.1 mcg/kg; Idiopathic Neutropenia 1.2 mcg/kg.

In clinical trials in patients with SCN, 91% of patients who responded to NEUPOGEN therapy responded at doses of $\leq$ 12 mcg/kg/day. Ninety-seven percent of patients responded at doses of $\leq$ 24 mcg/kg/day. Therefore, patients with SCN who do not respond to the recommended starting dose should be treated with up to 24 mcg/kg/day in order to determine if they will respond. In some cases, where higher doses were tried, an improvement in the ANC and the clinical condition was seen with a few patients only.

4.3 Reconstitution

Product does not need to be reconstituted.

Dilution

If required, NEUPOGEN may be diluted in 5% dextrose. NEUPOGEN diluted to a concentration between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) at a concentration of 2.0 mg/mL. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), NEUPOGEN is compatible with glass bottles, PVC and polyolefin intravenous bags and polypropylene syringes.

Dilution of NEUPOGEN to a final concentration of < 5 mcg/mL even in the presence of Albumin (Human) is not recommended at any time. **Do not dilute with saline at any time: product may precipitate.**

4.4 Administration

NEUPOGEN is intended for subcutaneous injection or intravenous use and should not be given by any other route of administration.

NEUPOGEN should not be vigorously shaken.

In those situations in which the physician determines that the patient can safely and effectively self-administer NEUPOGEN, the patient should be instructed as to the proper dosage and administration. If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

4.5 Missed Dose

NEUPOGEN should be injected at the same time each day. Patients who miss a dose should be advised to contact their doctor or nurse.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

The maximum tolerated dose of NEUPOGEN has not been determined. In dose ranging studies, 5 of 16 patients given ≥ 69 mcg/kg/day were withdrawn due to adverse experiences. In these and other clinical trials, only 2 of 253 patients on lower doses were withdrawn due to adverse events.

In NEUPOGEN clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts > 100 x 10^9/L have been reported in less than 2% of patients and were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leukocytosis, that NEUPOGEN therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the chemotherapy-induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of NEUPOGEN therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous (SC) or Intravenous (IV)	Sterile Solution for Injection / 300 mcg/mL and 600 mcg/mL	Acetate, polysorbate 80, sodium, sorbitol.

NEUPOGEN is a sterile, clear, colourless, preservative-free liquid for parenteral administration. The product is available in single use vials and prefilled syringes.

Each single use vial of NEUPOGEN contains 300 mcg/mL (3 x 10^7 units/mL) of filgrastim formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% Polysorbate 80.

Each NEUPOGEN prefilled syringe contains 600 mcg/mL (6 x 10^7 units/mL) of filgrastim formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% Polysorbate 80.

Availability of Dosage Forms

Vials

NEUPOGEN is available in 2 vial sizes; 1 mL and 1.6 mL.

The single use, preservative-free 1 mL vials contain 300 mcg of filgrastim (300 mcg/mL) and are supplied in boxes of 10.

The single use, preservative-free 1.6 mL vials contain 480 mcg of filgrastim (300 mcg/mL) and are supplied in boxes of 10.

NEUPOGEN: Use only 1 dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Prefilled Syringes (SingleJect®)

NEUPOGEN is available in 2 prefilled syringe sizes; 0.5 mL and 0.8 mL.

The single use, preservative free 0.5 mL prefilled syringes with an UltraSafe® Needle Guard contain 300 mcg of filgrastim (600 mcg/mL) and are supplied in boxes of 10.

The single use, preservative free 0.8 mL prefilled syringes with an UltraSafe® Needle Guard contain 480 mcg of filgrastim (600 mcg/mL) and are supplied in boxes of 10.

NEUPOGEN: Use only 1 dose per prefilled syringe. Discard unused portions. Do not save unused drug for later administration.

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of **PART I: HEALTH PROFESSIONAL INFORMATION.**

General

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN. Patients receiving NEUPOGEN who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Simultaneous Use with Chemotherapy

The safety and efficacy of NEUPOGEN given simultaneously with cytotoxic chemotherapy have not been established. Studies in adult patients showed that an interaction between concurrent NEUPOGEN and 5-fluorouracil (5-FU) is possible and can result in a paradoxical fall in ANC. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use NEUPOGEN in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see 4 DOSAGE AND ADMINISTRATION).

The efficacy of NEUPOGEN has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-FU or cytosine arabinoside.

The safety and efficacy of NEUPOGEN have not been evaluated in patients receiving concurrent radiation therapy, except for patients with breast or lung cancer. Simultaneous use of NEUPOGEN with chemotherapy and radiation therapy should be avoided.

Carcinogenesis and Mutagenesis

The carcinogenic potential of NEUPOGEN has not been studied. NEUPOGEN failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. NEUPOGEN had no observed effect on the fertility of male or female rats, or on gestation at doses up to 500 mcg/kg.

Growth Factor Potential

NEUPOGEN is a growth factor that primarily stimulates production of neutrophils. However, the possibility that NEUPOGEN can act as a growth factor for certain tumour types cannot be excluded. Randomized studies have demonstrated that treatment with NEUPOGEN following chemotherapy for acute myeloid leukemia (AML) does not adversely influence the outcome of treatment. The use of NEUPOGEN in chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) has not been fully investigated, and caution should be exercised in using this drug in patients with CML or MDS.

Tumour cells may be collected in the leukapheresis product, following PBPC mobilization by NEUPOGEN. The clinical significance and the effect of reinfusion of tumour cells with the leukapheresis product are still unknown and the possible contribution of clonogenic tumour cells to an eventual relapse has not been determined.

MDS and AML in Breast and Lung Cancer Patients

In the post-marketing observational study setting, findings showed that filgrastim is associated with an increased risk of MDS and AML in breast and lung cancer patients when used in conjunction with chemotherapy and/or radiotherapy. Monitor patients for signs and symptoms of MDS/AML in these settings.

Cardiovascular

Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11 of 375 cancer patients receiving NEUPOGEN in clinical studies; the relationship to NEUPOGEN therapy is unknown. However, patients with pre-existing cardiac conditions receiving NEUPOGEN should be monitored closely.

Aortitis

Aortitis has been reported in patients receiving filgrastim and may present with generalized signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known etiology.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after the administration of filgrastim or pegfilgrastim. CLS can cause circulatory shock and may be fatal, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity, and may be life-threatening if treatment is delayed. Patients who develop symptoms of

capillary leak syndrome should be closely monitored and receive treatment, which may include a need for intensive care.

Hematologic

Sickle Cell Crises

Severe sickle cell crises, in some cases resulting in death, have been associated with the use of NEUPOGEN in patients with sickle cell trait or sickle cell disease. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell trait and sickle cell disease should prescribe NEUPOGEN for such patients, and only after careful consideration of the potential risks and benefits.

The response to NEUPOGEN may be diminished in patients with reduced neutrophil precursors such as those previously treated with extensive dose chemotherapy or radiotherapy.

In studies of NEUPOGEN administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see 8 ADVERSE REACTIONS). As a result of the potential of receiving higher doses of chemotherapy (ie, full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and non-haematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet count is recommended.

Leukocytosis

Cancer Patients Receiving Myelosuppressive Chemotherapy

In all studies, including phase 1/2 dose ranging studies, WBC counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving NEUPOGEN at doses above 5 and up to 115 mcg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a complete blood count (CBC) is recommended twice per week during NEUPOGEN therapy (see Monitoring and Laboratory Tests).

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

During the period of administration of NEUPOGEN for PBPC mobilization in cancer patients, discontinuation of NEUPOGEN is appropriate if the leukocyte count rises to > 100 x 10^9/L (see Monitoring and Laboratory Tests).

Thrombocytopenia

Thrombocytopenia, including serious events, has been reported in patients receiving NEUPOGEN. Platelet counts should be monitored regularly (see Monitoring and Laboratory Tests).

Immune

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving NEUPOGEN has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies comparing NEUPOGEN and Neulasta, the incidence of antibodies binding to NEUPOGEN was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including timing of sampling, sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to NEUPOGEN with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against filgrastim may cross react with endogenous G-CSF, resulting in immune-mediated neutropenia; however, this has not been reported in clinical studies or in post-marketing experience. Patients who develop hypersensitivity to filgrastim may have allergic or hypersensitivity reactions to other *E.coli*-derived proteins.

Hypersensitivity / Allergic Reactions

Hypersensitivity, including serious allergic reactions and anaphylactic reactions occurring on initial or subsequent treatment have been reported in < 1 in 4,000 patients treated with NEUPOGEN. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving NEUPOGEN intravenously. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged. Do not administer NEUPOGEN to patients with a history of allergic reactions to filgrastim or pegfilgrastim (see 2 CONTRAINDICATIONS). If a serious allergic reaction or anaphylactic reaction occurs, appropriate therapy should be administered and NEUPOGEN should be permanently discontinued.

Cutaneous Vasculitis

Cutaneous vasculitis has been reported in patients treated with NEUPOGEN. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term NEUPOGEN therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue NEUPOGEN at a reduced dose.

Monitoring and Laboratory Tests

Cancer Patients Receiving Myelosuppressive Chemotherapy

A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during NEUPOGEN therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when NEUPOGEN was administered, and white blood cell (WBC) differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

A CBC and platelet count should be obtained at regular intervals (3 times per week during NEUPOGEN therapy) following marrow infusion.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

After 4 days of NEUPOGEN treatment for PBPC mobilization, neutrophil counts should be monitored. Monitoring of platelet and red blood cell counts is recommended during the leukapheresis period. Frequent CBCs and platelet counts are recommended (at least 3 times per week) following PBPC reinfusion.

Patients with Severe Chronic Neutropenia

During the initial 4 weeks of NEUPOGEN therapy, and for 2 weeks following any dose adjustment, a CBC with differential and platelet determination should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular CBCs (ie, as clinically indicated but at least quarterly) is recommended. Patients should be monitored for the possible occurrence of bone density changes while on long-term NEUPOGEN therapy. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment.

In clinical trials, the following laboratory results were observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of NEUPOGEN therapy,
- Platelet counts were generally at the upper limits of normal prior to NEUPOGEN therapy. With NEUPOGEN therapy, platelet counts decreased but generally remained within normal limits (see 8 ADVERSE REACTIONS),
- Early myeloid forms were noted in the peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients,
- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with NEUPOGEN therapy,

- As in other trials, increases were observed in serum uric acid, lactic dehydrogenase, and serum alkaline phosphatase.

Patients with HIV Infection

A CBC and platelet count should be obtained prior to starting NEUPOGEN therapy and at regular intervals (eg, initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during 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 blood samples be drawn for ANC measurement prior to any scheduled dosing with NEUPOGEN.

Renal

Glomerulonephritis

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

Respiratory

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving NEUPOGEN who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, NEUPOGEN should be withheld until resolution of ARDS or discontinued. Patients should receive appropriate medical management for this condition.

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing peripheral blood progenitor cell (PBPC) mobilization. Hemoptysis resolved with discontinuation of NEUPOGEN. The use of NEUPOGEN for PBPC mobilization in healthy donors is not an approved indication.

Other

Cancer Patients Receiving Myelosuppressive Chemotherapy

Premature Discontinuation of NEUPOGEN Therapy

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 be continued following chemotherapy until the post nadir ANC reaches 10 x 10^9/L. Therefore, the premature discontinuation of NEUPOGEN therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see 4 DOSAGE AND ADMINISTRATION).

Risks Associated with Increased Doses of Chemotherapy

Intensified doses of chemotherapeutic agents may lead to increased toxicities associated with these agents, including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the product monograph of the specific chemotherapy agents used). Increased exposure to alkylating agents, particularly if combined with radiotherapy, is known to be associated with the genesis of secondary malignancies. When considering chemotherapy dose intensification with NEUPOGEN support, clinicians should weigh the risk of secondary malignancy against the potential benefits of improved primary disease outcome.

Patients with Severe Chronic Neutropenia

Diagnosis of Congenital, Cyclic or Idiopathic Neutropenia

Care should be taken to confirm the diagnosis of congenital, cyclic or idiopathic neutropenia, which may be difficult to distinguish from myelodysplasia, before initiating NEUPOGEN therapy. The safety and efficacy of NEUPOGEN in the treatment of neutropenia or pancytopenia due to other haematopoietic disorders (eg, myelodysplastic syndrome) has not been established.

It is, therefore, essential that serial complete blood counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype, be performed prior to initiation of NEUPOGEN therapy.

Myelodysplasia (MDS), and acute myeloid leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with NEUPOGEN for aplastic anemia and severe chronic neutropenia (SCN). Based on available data, the risk of developing MDS, and AML has been confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics has been associated with the eventual development of myeloid leukaemia. The effect of continued NEUPOGEN administration in patients with abnormal cytogenetics is unknown. If a patient with SCN develops abnormal cytogenetics, the risks and benefits of continuing NEUPOGEN should be carefully considered (see 8 ADVERSE REACTIONS).

Chronic Administration

The safety and efficacy of chronic daily administration of NEUPOGEN in patients with SCN have been established in phase 1/2 clinical trials of 74 patients treated for up to 4.5 years, and in a phase 3 trial of 123 patients treated for up to 3.5 years.

Although the relationship to NEUPOGEN is unclear, osteoporosis has been reported in approximately 7% of patients receiving NEUPOGEN therapy for up to 4.5 years in clinical trials in patients with SCN. Decreased bone density and osteoporosis have also been seen in pediatric patients with SCN in the post-market setting. Patients with SCN, particularly those with congenital neutropenia and those with underlying osteoporotic bone disease, should be monitored for the possible occurrence of bone density changes while on long-term NEUPOGEN therapy. Other infrequently observed adverse events included exacerbation of some pre-existing skin disorders (eg, psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, haematuria/proteinuria, thrombocytopenia (platelets < 50 x 10^9/L).

Patients with HIV Infection

Risks 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 (see 8 ADVERSE REACTIONS) and anemia. Regular monitoring of blood counts is recommended.

Infections 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 infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition, in addition to administration of NEUPOGEN for treatment of neutropenia.

7.1 Special Populations

7.1.1 Pregnant Women

NEUPOGEN has been shown to cause adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose.

In rabbits, increased abortion and embryolethality were observed in animals treated with NEUPOGEN at 80 mcg/kg/day. NEUPOGEN administered to pregnant rabbits at doses of 80 mcg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, and decreased body weight, live births, and food consumption. External abnormalities were not observed in the fetuses of dams treated at 80 mcg/kg/day. Reproductive studies in pregnant rats have shown that NEUPOGEN was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily intravenous injection during the period of organogenesis at dose levels up to 575 mcg/kg/day.

In Segment III studies in rats, offspring of dams treated at greater than 20 mcg/kg/day exhibited a delay in external differentiation (detachment of auricles and descent of testes) and slight growth retardation, possibly due to lower body weight of females during rearing and nursing. Offspring of dams treated at 100 mcg/kg/day exhibited decreased body weights at birth, and a slightly reduced 4 day survival rate.

There are cases in the literature where the transplacental passage of NEUPOGEN has been demonstrated. NEUPOGEN should be used during pregnancy only if the potential benefit justifies any potential theoretical risk to the fetus.

7.1.2 Breast-feeding

It is not known whether NEUPOGEN is excreted in human milk, therefore, NEUPOGEN is not recommended for use in nursing women.

7.1.3 Pediatrics

Neonates

The safety and efficacy of NEUPOGEN in neonates have not been established.

Pediatrics (< 18 years of age)

Cancer Patients Receiving Myelosuppressive Chemotherapy

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

Twelve pediatric patients with neuroblastoma have received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with NEUPOGEN. In this population, NEUPOGEN was well tolerated. There was one report of palpable splenomegaly associated with NEUPOGEN therapy, however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

Patients with Acute Myeloid Leukemia

Published experience with the administration of NEUPOGEN post-chemotherapy in pediatric patients with AML has included 136 patients. This interim analysis included children receiving intensive induction chemotherapy with NEUPOGEN, and demonstrated that it had no detrimental impact on disease outcome in comparison to a similarly-treated historical control group.

Patients with Severe Chronic Neutropenia

NEUPOGEN is indicated for chronic administration to adults and pediatric patients with SCN to reduce the incidence and duration of the sequelae of neutropenia. In a phase 3 study, 120 patients with a median age of 12 years (range 1 to 76 years) were treated; 12 of these were infants (1 month to 2 years of age), 47 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age) (see 14 CLINICAL TRIALS; 1 INDICATIONS; Monitoring and Laboratory Tests; 4 DOSAGE AND ADMINISTRATION).

The most commonly reported adverse event in clinical trials was bone pain; splenomegaly has also been reported with chronic administration (see 8 ADVERSE REACTIONS). Pediatric patients with congenital types of neutropenia have been reported to develop MDS/AML or cytogenetic abnormalities while receiving chronic NEUPOGEN treatment. The relationship of these events to NEUPOGEN administration is unknown (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS).

Other serious long-term risks associated with daily administration of NEUPOGEN have not been identified in pediatric patients (ages 1 month to 17 years) with SCN. Regarding growth and development, long term follow-up data from the post-marketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of NEUPOGEN treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation, or endocrine function.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Dose-dependent musculoskeletal pain, specifically medullary bone pain, was the only consistently reported adverse event across all cancer patient populations. These events were usually mild-to-moderate, and most patients that experienced this effect were symptomatically controlled by non-narcotic analgesia.

Bone pain and pain in extremity occurred at a higher incidence in NEUPOGEN-treated patients as compared with placebo-treated patients across all indications.

See 7 WARNINGS AND PRECAUTIONS regarding Splenic Rupture, ARDS, Allergic Reactions and Sickle Cell Crises.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cancer Patients Receiving Myelosuppressive Chemotherapy

In clinical trials involving over 350 patients receiving NEUPOGEN following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2 and 3 trials, medullary bone pain, reported in 24% of patients, was the only consistently observed adverse reaction attributed to NEUPOGEN therapy. This bone pain was generally reported to be of mild-to-moderate severity, and could be controlled in most patients with non-narcotic analgesics. Infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 mcg/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of NEUPOGEN (3 to 10 mcg/kg/day).

In the randomized, double-blind, placebo-controlled trial of NEUPOGEN therapy following combination chemotherapy in patients (n = 207) with small cell lung cancer, the following adverse events were reported during blinded cycles of study medication (placebo or NEUPOGEN at 4 to 8 mcg/kg/day). Events are reported as exposure adjusted since patients remained on double-blind NEUPOGEN a median of 3 cycles versus 1 cycle for placebo.

Table 3. Adverse Events in the randomized, double-blind, placebo-controlled trial (n = 207)

Event	% of Blinded Cycles with Events	
	NEUPOGEN Patient Cycles N = 384	Placebo Patient Cycles N = 257
Nausea/Vomiting	57	64
Skeletal Pain	22	11
Alopecia	18	27
Diarrhea	14	23
Neutropenic Fever	13	35
Mucositis	12	20
Fever	12	11
Fatigue	11	16
Anorexia	9	11
Dyspnea	9	11
Headache	7	9
Cough	6	8
Skin Rash	6	9
Chest Pain	5	6
Generalized Weakness	4	7
Sore Throat	4	9
Stomatitis	5	10
Constipation	5	10
Pain (Unspecified)	2	7

In this study, there were no serious, life-threatening, or fatal adverse reactions attributed to NEUPOGEN therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis, or other major systemic reactions to NEUPOGEN.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27% to 58% of 98 patients receiving blinded NEUPOGEN therapy following cytotoxic chemotherapy. Increases were generally mild-to-moderate. Transient decreases in blood pressure (< 90/60 mmHg) which did not require clinical treatment, were reported in 7 of 176 patients in phase 3 clinical studies following administration of NEUPOGEN. No evidence of interaction of NEUPOGEN with other drugs was observed in the course of clinical trials (see 7 WARNINGS AND PRECAUTIONS, General, Simultaneous Use with Chemotherapy).

The safety profile of NEUPOGEN in the pediatric population is comparable to that seen in adult cancer patients receiving cytotoxic chemotherapy. Adverse events considered related to NEUPOGEN administration by the investigators of 3 non-blinded studies included application site disorders, hematologic disorders (including thrombocytopenia), musculoskeletal disorders, and a single case of vasculitis. Of these, musculoskeletal disorders are the most consistent adverse events seen in other NEUPOGEN studies.

Patients with Acute Myeloid Leukemia

In a randomized phase 3 clinical trial involving 521 patients with de novo AML, 259 patients received NEUPOGEN post-chemotherapy and 262 patients received placebo. NEUPOGEN was generally well tolerated, and most adverse experiences were considered to be the sequelae of the underlying malignancy or cytotoxic chemotherapy. The most frequently reported events were diarrhea, rash, and petechiae, and there were no significant differences between the treatment groups.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplantation. The most common events reported in both control and treatment groups included stomatitis, nausea and vomiting, generally of mild-to-moderate severity and were considered unrelated to NEUPOGEN. In the randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with NEUPOGEN than in controls: nausea (10% vs. 4%), vomiting (7% vs. 3%), hypertension (4% vs. 0%), rash (12% vs. 10%), and peritonitis (2% vs. 0%). None of these events were reported by the investigator to be related to NEUPOGEN. One event of erythema nodosum was reported moderate in severity and possibly related to NEUPOGEN.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

NEUPOGEN Mobilized PBPC Collection

In clinical trials, 126 patients have received NEUPOGEN for mobilization of PBPC. During the mobilization period, adverse events related to NEUPOGEN consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to NEUPOGEN in 7% of patients. Mild-to-moderate transient increases in alkaline phosphatase levels were reported related to NEUPOGEN in 21% of the patients who had serum chemistries evaluated during the mobilization phase.

All patients had increases in neutrophil counts consistent with the biological effects of NEUPOGEN. Two patients had a WBC count greater than 100 x 10^9/L with WBC count increases during the mobilization period ranging from 16.7 x 10^9/L to 138 x 10^9/L above baseline. Eighty-eight percent of patients had an increase in WBC count between 10 x 10^9/L and 70 x 10^9/L above baseline. No clinical sequelae were associated with any grade of leukocytosis.

Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts possibly related to the leukapheresis procedure. Only 5 patients had platelet counts < 50 x 10^9/L.

PBPC Transplantation Followed by NEUPOGEN

During the period of NEUPOGEN administration post PBPC transplant, NEUPOGEN was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high dose chemotherapy. Mild-to-moderate musculoskeletal pain was the most frequently reported adverse event related to NEUPOGEN reported in 15% of patients.

Patients with Severe Chronic Neutropenia

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was usually readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with NEUPOGEN. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia (< 50 x 10^9/L) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy, and most of these had a pre-study history of splenomegaly. Approximately 7% of patients had thrombocytopenia (< 50 x 10^9/L) during NEUPOGEN therapy, most of whom had a pre-study history. In most cases, thrombocytopenia was managed by NEUPOGEN dose reduction or interruption. There were no associated, serious hemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with NEUPOGEN, but was associated with thrombocytopenia in only 2% of patients. Anemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with NEUPOGEN for SCN (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Patients with Severe Chronic Neutropenia). As of December 31, 1997, data were available from a post-marketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years. Of these 531 patients, 32 were infants (1 month to 2 years of age), 200 were children (2 to 12 years of age), and 68 were adolescents (12 to 16 years of age). Based on analysis of these data, the risk of developing MDS, and AML was confined to the subset of patients with congenital neutropenia (Kostmann's syndrome, congenital agranulocytosis, and Shwachman-Diamond syndrome). A life table analysis of these data revealed that the cumulative risk of developing leukemia or MDS by the end of the eighth year of NEUPOGEN treatment in a patient with congenital neutropenia was 16.5% (95% C.I. = 9.8% to 23.3%); this represents an annual rate of approximately 2%. Leukemic transformation has also been documented in congenital neutropenia patients who have never received NEUPOGEN; it is unknown if the rate of conversion in untreated patients is different from that of treated patients. Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with NEUPOGEN who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, MDS, or AML is related to chronic daily NEUPOGEN administration or to the natural history of SCN. Routine monitoring through regular CBCs is recommended for all patients with SCN.

Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see Monitoring and Laboratory Tests).

Other adverse events infrequently observed and possibly related to NEUPOGEN therapy were: injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, and haematuria/proteinuria.

Patients with HIV Infection

In the multicenter, randomized, controlled trial, 172 of 258 patients were treated with NEUPOGEN. NEUPOGEN was generally well tolerated. The most frequently reported treatment-related adverse events in the 24-week treatment period were skeletal pain (14.5%), headache (6.4%), back pain and myalgia (5.8% each), and increased alkaline phosphatase (5.2%).

There were no new or unexpected treatment-related events seen in NEUPOGEN-treated patients. Adverse events observed in clinical trials were consistent with progression of HIV disease or events observed in other clinical settings.

There was no apparent increase or decrease in HIV replication and viral load as measured by quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Although prior *in vitro* and *in vivo* studies have not shown any increase in viral load following use of NEUPOGEN in HIV-infected patients. The randomized study was not powered to address this issue and the possibility of an effect due to NEUPOGEN on HIV replication cannot be entirely excluded.

As of 31 January 1996, an estimated 1.2 million patients worldwide have received NEUPOGEN therapy across all indications. Of an estimated 150,000 HIV-infected patients receiving NEUPOGEN to date, there have been 106 spontaneous adverse event reports received worldwide. No new adverse event patterns were identified in adults or children receiving NEUPOGEN for neutropenia associated with HIV infection. Five deaths were reported in 106 post-marketing reports in patients receiving NEUPOGEN for HIV infection. Three of 5 deaths were attributed to various manifestations of HIV disease progression. In the fourth case, the cause of death was not reported. In the fifth case, the physician reported that death in the context of ARDS occurred in the absence of fever and microbiological cause and was typical of bleomycin pulmonary toxicity. However, the physician reported that this may have been enhanced by NEUPOGEN. It is notable, however, that randomized trials, and non-randomized trials demonstrated no increase in the known pulmonary toxicity of bleomycin when NEUPOGEN was added to treatment.

In the randomized controlled study, the overall incidence of thrombocytopenia was 9.9% in the NEUPOGEN-treated groups compared with 8.1% in the control group. Severe thrombocytopenia occurred in 7% of the NEUPOGEN-treated patients and 3.5% of control patients in the controlled, randomized study. During this study, mean platelet count decreased at week 2 in the NEUPOGEN-treated patients, but returned to baseline by week 3 and remained stable thereafter. In the post-marketing experience of HIV-infected patients which includes an estimated 150,000 patients worldwide, 10 of 106 spontaneous reports of adverse reactions were for thrombocytopenia. Of these, 3 cases were reported as serious.

Because adverse events of thrombocytopenia in HIV-infected individuals are multifactorial and may be attributed to the natural progression of HIV disease and associated infections, and because of the inconsistent occurrence of thrombocytopenia in a small number of patients in the aforementioned clinical trials, no definitive relationship between NEUPOGEN therapy in HIV-infected patients and thrombocytopenia can be established.

In one study, 16 of 24 patients (66.7%) were reported to have splenomegaly during an observation period of 49-701 days. However, no baseline measurements of spleen size were made for comparison to on-study values. In 3 other uncontrolled clinical trials, only 1 of 297 patients (0.3%) had a report of splenomegaly. Since splenomegaly is a common clinical finding in 72% of patients with AIDS sometime during the course of their disease it is likely that the observed splenomegaly was associated with HIV disease and not related to NEUPOGEN.

Clinical Experience Relevant to all Indications

Adverse reactions listed under specific indications can also be seen across all indications.

In combined clinical trials involving a total of 1834 patients, the following adverse reactions which are not presented in the adverse reaction sections by indication above, occurred with ≥ 5% higher incidence in Neupogen treated patients compared to controls: paresthesia, erythema, oropharyngeal pain, decreased appetite, oral pain, malaise, edema peripheral, sepsis, bronchitis, upper respiratory tract infection, urinary tract infection, muscle spasms, dizziness, hypoesthesia, insomnia, hypersensitivity, hemoglobin decreased, rash maculo-papular and transfusion reaction.

8.5 Post-Market Adverse Reactions

In addition to the events listed above, reports of serious adverse reactions have been identified post-market in patients receiving NEUPOGEN, including:

- Splenomegaly (enlarged spleen) and splenic rupture (see 7 WARNINGS AND PRECAUTIONS, General, Splenic Rupture)
- Aortitis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Capillary Leak Syndrome (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Acute respiratory distress syndrome (ARDS) (see 7 WARNINGS AND PRECAUTIONS, Respiratory)
- Sickle cell crisis (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Leukocytosis (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Allergic reactions, including anaphylactic reactions (see 7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity / Allergic Reactions)
- Cutaneous vasculitis (see 7 WARNINGS AND PRECAUTIONS, Immune)
- Glomerulonephritis (see 7 WARNINGS AND PRECAUTIONS, Renal)
- Alveolar hemorrhage (manifesting as pulmonary infiltrates and hemoptysis) (see 7 WARNINGS AND PRECAUTIONS, Respiratory)
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Chondrocalcinosis pyrophosphate (in patients treated for cancer)

- Decreased bone density and osteoporosis (in pediatric patients with SCN receiving chronic treatment with NEUPOGEN)
- Bone Pain
- Extramedullary hematopoiesis

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

No serious drug interactions have been identified.

9.2 Drug Interactions Overview

Interactions of NEUPOGEN with other cytokines, including haematopoietic growth factors, have been observed in animal studies. The safety, efficacy, and possible interactions of NEUPOGEN used in combination with other cytokines have not been characterized in clinical trials. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

9.3 Drug-Behavioural Interactions

No drug-behavioural interactions have been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Filgrastim is a human granulocyte colony stimulating factor (G-CSF) produced by recombinant DNA technology. G-CSF regulates the production of neutrophils within the bone marrow; endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts, and endothelial cells. G-CSF is a colony stimulating factor which has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of other haematopoietic cell types. NEUPOGEN (filgrastim) is the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

Colony Stimulating Factors

Colony stimulating factors are glycoproteins which act on haematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and some end-cell functional activation.

Endogenous G-CSF is a lineage-specific colony stimulating factor with selectivity for the neutrophil lineage. G-CSF is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

10.2 Pharmacodynamics

In phase 1 studies involving 96 patients with various non-myeloid malignancies, NEUPOGEN administration resulted in a dose-dependent increase in neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether NEUPOGEN was administered intravenously (1 to 70 mcg/kg twice daily), subcutaneously (1 to 3 mcg/kg once daily), or by continuous subcutaneous infusion (3 to 11 mcg/kg/day). With discontinuation of NEUPOGEN therapy, neutrophil counts returned to baseline, in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic [measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine (fMLP) as the chemotaxin] activity *in vitro*.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving NEUPOGEN, however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of NEUPOGEN. Increases in lymphocyte counts following NEUPOGEN administration have been reported in some normal subjects and cancer patients.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

10.3 Pharmacokinetics

Information generated and published by independent investigators suggests that filgrastim binds to the G-CSF receptor (G-CSFR) on the surface of the neutrophils, and the drug-receptor complex is internalized to the endosomal compartments, and either recycled or degraded; the receptor-mediated processes appear to be an important mode of disposition (elimination) for filgrastim. In general, linear and nonlinear filgrastim pharmacokinetics may be observed in relation to the receptor-mediated disposition and this involves the filgrastim serum concentration, changes in cell number precursors and circulating neutrophils – complex manifestations which also relate to the filgrastim dosage regimen and the biological effects upon multiple doses.

Over the wide range of doses of NEUPOGEN examined (3.45 – 69.0 mcg/kg) in the early clinical trials for NEUPOGEN, absorption and clearance, in general, approximated first-order pharmacokinetics, showing an apparent positive linear correlation between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous intravenous infusion of 20 mcg/kg of NEUPOGEN over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. The volume of distribution averaged 150 mL/kg in normal subjects and cancer patients. The elimination half-life, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of NEUPOGEN were approximately 0.5 to 0.7 mL/min/kg. Single parenteral doses or daily intravenous doses, over a 14 day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following NEUPOGEN doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following NEUPOGEN doses of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20 day period produced steady state serum concentrations of NEUPOGEN with no evidence of drug accumulation over the time period investigated.

Special Populations and Conditions

Pediatrics:

In a study of 15 children with neuroblastoma, 5 children were treated at each of the 3 dose levels; 5, 10, and 15 mcg/kg/day NEUPOGEN subcutaneously for 10 days. Peak concentrations of NEUPOGEN of 3 to 117 ng/mL were reached after 4 to 12 hours with measurable NEUPOGEN concentrations for the entire 24-hour dosing interval. Mean elimination half-life of 5.8 hours and 4.5 hours were found on day 1 and on day 10, respectively.

Geriatrics:

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

11 STORAGE, STABILITY, AND DISPOSAL

NEUPOGEN should be stored in the refrigerator at 2 °C to 8 °C. Avoid vigorous shaking. Keep the container in the outer carton to protect from light.

Accidental exposure to room temperature (up to 30 °C) or exposure to freezing temperatures does not adversely affect the stability of the product.

NEUPOGEN may be allowed to reach room temperature for a maximum of 14 days. Any vial or prefilled syringe left at room temperature for greater than 14 days should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

12 SPECIAL HANDLING INSTRUCTIONS

NEUPOGEN should not be vigorously shaken.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Filgrastim
Chemical name:	recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF)
Molecular formula and molecular mass:	filgrastim consists of 175 amino acids with a molecular weight 18,800 daltons
Structural formula:	Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli (E. coli)* bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Filgrastim has a molecular weight of 18,800 Daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because filgrastim is produced in *E. coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Product Characteristics

NEUPOGEN® (filgrastim injection) is a sterile, clear, colourless, preservative-free liquid.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Cancer Patients Receiving Myelosuppressive Chemotherapy

NEUPOGEN has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens for a number of cancer types. In a phase 3 clinical trial in small cell lung cancer, patients received subcutaneous administration of NEUPOGEN (4 to 8 mcg/kg/day, days 4 to 17) or placebo. In this study, the benefits of NEUPOGEN therapy were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased antibiotic usage.

In the phase 3, randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer patients were randomized to receive NEUPOGEN (n = 101) or placebo (n = 110). Of the 211 patients enrolled, 207 patients were evaluable for safety (NEUPOGEN, n = 98; placebo, n = 109) and 199 patients were evaluable for efficacy (NEUPOGEN, n = 95; placebo, n = 104). NEUPOGEN was started on day 4, after patients received standard dose chemotherapy with cyclophosphamide, doxorubicin and etoposide.

The incidence of febrile neutropenia during cycle 1 was significantly reduced by 51% in the NEUPOGEN group as compared to the placebo group (28% versus 57%, respectively; $p < 0.001$). The difference in the cumulative incidence of febrile neutropenia over all 6 cycles between the placebo group (77%) and the NEUPOGEN group (40%) was statistically significant ($p < 0.001$). The incidence of culture confirmed infections was reduced by 50% from 13% to 6.5%.

The absolute neutrophil nadir (severity) and duration of severe neutropenia [days with absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L] were significantly reduced in all 6 cycles for patients receiving NEUPOGEN compared to placebo ($p < 0.005$). For all treatment cycles combined, the median duration of severe neutropenia was 6 days per cycle in the placebo group compared to 1 day per cycle in the NEUPOGEN group.

Thus, treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, as well as the severity and duration of severe neutropenia following chemotherapy.

In-patient hospitalization and antibiotic use were evaluated as secondary endpoints (clinical sequelae) to neutropenia. The incidence of febrile neutropenia with hospitalization during cycle 1 was significantly reduced by 50% in the NEUPOGEN group compared to the placebo group (26% versus 55%; $p < 0.001$). Over all 6 cycles there was a 45% reduction in the mean number of days of hospitalization in the NEUPOGEN group compared to the placebo group. Furthermore, there was an overall 47% reduction in the mean number of days of intravenous antibiotic use.

Administration of NEUPOGEN resulted in an earlier ANC nadir following chemotherapy than was experienced by patients receiving placebo (day 10 versus day 12). NEUPOGEN was well tolerated when given subcutaneously daily at doses of 4 to 8 mcg/kg for up to 14 consecutive days following each cycle of chemotherapy (see 8 ADVERSE REACTIONS).

In 36 patients receiving M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for treatment of transitional cell carcinoma of the urothelium, both the severity ($p = 0.0001$) and the duration of granulocytopenia (absolute granulocyte count $< 1.0 \times 10^9$/L; $p = 0.0001$) were reduced during cycles of chemotherapy in which NEUPOGEN was administered, when compared to cycles of chemotherapy without NEUPOGEN. The accelerated recovery of granulocyte counts during M-VAC cycles when NEUPOGEN was administered resulted in clinically and statistically significant increases in the number of patients eligible to receive planned doses of methotrexate and vinblastine on schedule on cycle day 14 ($p = 0.0001$). NEUPOGEN was generally well tolerated at all doses treated (up to 115 mcg/kg/day) when administered as a 15 to 30 minute intravenous infusion on days 4 to 11 of the 21-day M-VAC cycle.

In 45 patients treated with melphalan for a variety of advanced malignancies, patients were treated with NEUPOGEN at several doses and using 3 routes of administration (subcutaneous bolus, intravenous, and subcutaneous infusion). This was a dose finding study without controls. A dose-dependent effect on maximum ANC was demonstrated in this study [p = 0.004 (non-parametric test of ordered responses)]. Descriptive analysis showed that the period of severe neutropenia (ANC < 0.5 x 10^9/L) was reduced by NEUPOGEN treatment independent of route.

The effect of NEUPOGEN has also been studied in 12 patients receiving chemotherapy (doxorubicin, ifosfamide with Mesna, and etoposide) for small cell lung cancer. Chemotherapy cycles without NEUPOGEN were alternated with cycles in which NEUPOGEN was administered following chemotherapy. There was a statistically significant reduction in the duration of both severe (ANC < 0.5 x 10^9/L) and moderate (ANC < 1.0 x 10^9/L) neutropenia between the NEUPOGEN and no NEUPOGEN groups for cycles 1 and 2 [p = 0.01 in each case (Wilcoxon signed-rank test)]. The duration of febrile neutropenia and hospitalization was also reduced. NEUPOGEN was well tolerated at doses of 1 to 45 mcg/kg/day, given as a continuous infusion on days 4 through 17 of a 21-day chemotherapy cycle.

Sixty-three pediatric patients with advanced neuroblastoma and acute lymphoblastic leukemia (ALL) have received up to 6 cycles of chemotherapy followed with NEUPOGEN. The results indicated that NEUPOGEN is efficacious in reducing the incidence and duration of neutropenia and febrile neutropenia in pediatric patients receiving cytotoxic chemotherapy. These results are comparable to those seen in previous studies involving recombinant stimulating factors as an adjunct to chemotherapy in both adults and children.

Patients with Acute Myeloid Leukemia

In a double-blind, placebo-controlled, multi-center, randomized phase 3 clinical trial, 521 patients (median age 54, range 16-89 yrs) with de novo acute myeloid leukemia received 1 or 2 courses of induction chemotherapy and then, if in remission, 1 or 2 courses of consolidation chemotherapy.

Treatment with NEUPOGEN significantly reduced the duration of neutropenia and the associated clinical consequences of fever, IV antibiotic use and hospitalization, following induction chemotherapy. In the NEUPOGEN-treated group, the median duration of neutropenia (ANC < 0.5 x 10^9/L) was reduced by 5 days during the first course of induction therapy (p = 0.0001); fever was reduced by 1.5 days (p = 0.009); the use of IV antibiotics by 3.5 days (p = 0.0001), and the median duration of hospitalization was reduced by 5 days (p = 0.0001). NEUPOGEN had a similar impact on the duration of neutropenia in subsequent cycles, with reductions in fever, IV antibiotic use and hospitalization. In this trial, the remission rate, time to disease progression and overall survival were similar in both treatment groups.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

In 2 separate randomized, controlled trials, patients with Hodgkin's and non-Hodgkin's lymphoma were treated with myeloablative chemotherapy and autologous bone marrow transplantation (ABMT). In one study (n = 54), NEUPOGEN was administered at doses of 10 or 30 mcg/kg/day; a third treatment group in this study received no NEUPOGEN. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 0.5 x 10^9/L)

occurred in the NEUPOGEN-treated group versus the control group [23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group, (11 days in the combined treatment groups; p = 0.004)].

In the second study (n = 44; 43 patients evaluable), NEUPOGEN was administered at doses of 10 or 20 mcg/kg/day; a third treatment group in this study received no NEUPOGEN. A statistically significant reduction in the median number of days of severe neutropenia occurred in the NEUPOGEN-treated group versus the control group (21.5 days in the control group and 10 days in both treatment groups; p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study [13.5 days in the control group, 5 days in the 10 mcg/kg/day group, and 5.5 days in the 20 mcg/kg/day group, (5 days in the combined treatment groups; p < 0.0001)]. Reductions in the number of days of hospitalization and antibiotic use were also seen, although these reductions were not statistically significant. There were no effects on red blood cell or platelet levels.

In a randomized, placebo-controlled trial, 70 patients with myeloid and non-myeloid malignancies were treated with myeloablative therapy and allogeneic bone marrow transplant followed by 300 mcg/m^2/day of NEUPOGEN. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group; p < 0.001) and time to recovery of ANC to $\geq 0.5 \times 10^9$/L (21 days in the control group and 16 days in the treatment group; p < 0.001).

In 3 non-randomized studies (n = 119), patients received ABMT and treatment with NEUPOGEN. One study (n = 45) involved patients with breast cancer and malignant melanoma. A second study (n = 39) involved patients with Hodgkin's disease (HD). The third study (n = 35) involved patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukaemia (ALL), and germ cell tumour. In these studies, the recovery of the ANC to $\geq 0.5 \times 10^9$/L ranged from a median of 11.5 to 13 days.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

Use of NEUPOGEN either alone, or after chemotherapy, mobilizes haematopoietic progenitor cells into the peripheral blood. These autologous peripheral blood progenitor cells may be harvested and infused after high dose chemotherapy, either in place of, or in addition to bone marrow transplantation. Infusion of peripheral blood progenitor cells accelerates the rate of neutrophil and platelet recovery reducing the risk of hemorrhagic complications and the need for platelet transfusions.

NEUPOGEN Mobilized PBPC Collection

In 4 studies (n = 126), patients with NHL, HD, ALL, and breast cancer received NEUPOGEN for 6 to 7 days to mobilize haematopoietic progenitor cells into the circulating blood pool where they were collected by 3 aphereses on days 5, 6, and 7 (except for 13 patients in one study who where pheresed on days 4, 6, and 8). In 2 studies, the tested doses and schedules of NEUPOGEN resulted in a greater number of PBPC in the pheresis product compared to the baseline leukapheresis product.

NEUPOGEN Mobilized PBPC Therapy Followed by NEUPOGEN

In a randomized study of patients with HD or NHL undergoing myeloablative chemotherapy, 27 patients received NEUPOGEN mobilized PBPC followed by NEUPOGEN and 31 patients received ABMT plus NEUPOGEN. Patients randomized to the NEUPOGEN mobilized PBPC group compared to the ABMT group had significantly fewer median days of platelet transfusions, (6 vs. 10 days; $p < 0.001$), a significantly shorter median time to a sustained platelet count > 20 x 10^9/L, (16 vs. 23 days; $p = 0.02$), a significantly shorter median time to recovery of a sustained ANC $\geq$ 0.5 x 10^9/L (11 vs. 14 days; $p = 0.005$), and a significantly shorter duration of hospitalization (17 vs. 23 days; $p = 0.002$).

Overall, therapy with NEUPOGEN mobilized peripheral blood progenitor cells provided rapid and sustained haematologic recovery. Long-term (limited to 100 days) follow up haematology data from patients treated with PBPCT alone or in combination with bone marrow, was compared to historical data from patients treated with ABMT alone (1 study only). This retrospective analysis indicated that engraftment is durable.

Patients with Severe Chronic Neutropenia

In the phase 3 trial in patients with severe chronic neutropenia (SCN), patients with diagnoses of congenital, cyclic and idiopathic neutropenia were evaluated. Untreated patients had a median ANC of 0.210 x 10^9/L. NEUPOGEN therapy was adjusted to maintain the median ANC between 1.5 x 10^9/L and 10 x 10^9/L. A complete response was seen in 88% of patients (defined as a median ANC 1.5 x 10^9/L over 5 months of NEUPOGEN therapy). Overall, complete response to NEUPOGEN was observed in 1 to 2 weeks. The median ANC after 5 months of NEUPOGEN therapy for all patients was 7.46 x 10^9/L (range 0.03 to 30.88 x 10^9/L). In general, patients with congenital neutropenia responded to NEUPOGEN therapy with a lower median ANC than patients with idiopathic or cyclic neutropenia.

Dosing requirements were generally higher for patients with congenital neutropenia (2.3 to 40 mcg/kg/day) than for patients with idiopathic (0.6 to 11.5 mcg/kg/day) or cyclic (0.5 to 6 mcg/kg/day) neutropenia.

Overall, daily treatment with NEUPOGEN resulted in clinically and statistically significant reductions in the incidence and duration of fever, infection, and oropharyngeal ulcers. As a result, there also were decreases in requirements for antibiotic use and hospitalization. Additionally, patients treated with NEUPOGEN reported fewer episodes of diarrhea, nausea, fatigue and sore throat. These clinical findings may translate into improvements in the quality of life in these patients.

Patients with HIV Infection

NEUPOGEN has been shown to be safe and effective in preventing and treating neutropenia in patients with HIV infection. In a randomized, controlled, multicenter trial of 258 patients, a statistically significant reduction was observed in the incidence of grade 4 neutropenia (ANC < 0.5 x 10^9/L, $p < 0.0001$) in NEUPOGEN-treated patients. Three of 172 (1.7%) NEUPOGEN-treated patients and 19 of 86 (22.1%) untreated patients experienced confirmed grade 4 neutropenia.

In this randomized study, 85 patients had a total of 128 new or worsening bacterial infections, during the 168 day study period. Of these, a total of 26 events were graded as severe bacterial infections (WHO toxicity grade 3 or higher). The incidence of bacterial infections was decreased by 31% [p = 0.07, p = 0.03 (adjusted for number of prior opportunistic infections and baseline CD4 count)] and the incidence of severe bacterial infections was decreased by 54% [p = 0.005, p = 0.002 (adjusted)] in NEUPOGEN-treated patients when compared with untreated patients. In addition, the total number of hospitalizations or prolonged hospitalizations due to a bacterial infection for all groups in this study, was 24 events in 21 patients, for a total duration of 392 days. Days of hospitalization for bacterial infection were decreased by 45% [p = 0.05, p = 0.03 (adjusted)]. A 28% decrease in the number of days of IV antibacterial medications was seen in NEUPOGEN-treated patients [p = 0.17, p = 0.08 (adjusted)].

In 3 open-label non-randomized clinical studies, the response to NEUPOGEN (ANC > 2 x 10^9/L) was observed in a median of 2 - 9 days with either daily or intermittent dosing (see 4 DOSAGE AND ADMINISTRATION). NEUPOGEN therapy was titrated to maintain ANCs between 2 x 10^9 and 10 x 10^9/L.

In the randomized controlled trial, there was a 12% increase in the number of days patients were able to receive full or high-dose myelosuppressive medications. In a multicenter, non-comparative study of 200 patients, NEUPOGEN allowed more than 80% of patients to increase or maintain dosing of ganciclovir, zidovudine, trimethoprim/sulfamethoxazole and pyrimethamine, or to add 1 or more medications to their therapy. The number of these 4 medications received per patient increased by approximately 20% during NEUPOGEN therapy.

In an open-label study to evaluate neutrophil function by *in vitro* chemiluminescence measurement, NEUPOGEN-treated patients had increased oxidase-myeloperoxidase activity and potentially greater microbial killing capacity.

In the randomized controlled study, 13 deaths (5%) were reported on study. There were 13 additional deaths within 30 days of study completion. The leading causes of death were HIV-associated complications and AIDS progression. There were no other patterns observed for cause of death. In 3 uncontrolled studies, 16 of the 32 deaths were reported as AIDS progression, the other 16 deaths were attributed to HIV-associated complications. In these clinical studies, all deaths were reported by the investigator as not related or unlikely to be related to NEUPOGEN.

In clinical trials, changes in HIV viral load were evaluated by a quantitative HIV-1 RNA RT-Polymerase Chain Reaction (PCR) analyses and by measurement of HIV-1 p24 antigen levels. These studies did not show any evidence of increased HIV replication associated with NEUPOGEN administration.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Recombinant human granulocyte colony stimulating factor (r-metHuG-CSF) was administered to monkeys, dogs, hamsters, rats and mice as part of a comprehensive pre-clinical toxicology program which included both single-dose acute, repeated dose subacute and chronic studies.

Single-dose administration of r-metHuG-CSF by the oral, intravenous, subcutaneous, or intraperitoneal route resulted in no significant toxicity in mice, rats or hamsters at doses up to 115 mcg/kg/animal (862.5 mcg/kg based on group mean pre-study body weights). The increased leukocyte counts observed in monkeys on day 7 was an expected result of the pharmacological activity of r-metHuG-CSF and this had returned to control values by day 14. Consequently, the single-dose LD_{50} of r-metHuG-CSF in these species is in excess of 3,450 mcg/kg, which is at least 50- to 600-fold greater than the highest anticipated human clinical dose.

In the subacute, repeated-dose studies, the changes observed with r-metHuG-CSF can be attributed to the anticipated pharmacological actions of the protein. In rats, hamsters, dogs and monkeys, increased granulopoiesis was evidenced by dose-dependent increases in total white blood cell counts, an increased proportion of segmented neutrophils in the circulation, and an increase in the myeloid to erythroid ratio in the bone marrow. In the 14-day monkey study and 13-week rat study, platelet counts were reduced in the 2 high dose groups. In all species, histopathologic examinations of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis. Increased spleen weights were seen in all species and appeared to be dose-related.

Few significant changes in blood biochemistry values were observed in rats, hamsters, dogs, or monkeys. However, a dose-dependent increase in serum alkaline phosphatase was observed in rats. This increase may be reflective of increased activity of osteoblasts and osteoclasts, as published evidence indicates that osteoclasts are derived from haematopoietic precursors. The stimulatory effect of r-metHuG-CSF on granulopoiesis may, therefore, produce an imbalance in the normal equilibrium between osteoclasts and osteoblasts. The finding of increased osteoclasis and osteoanagenesis in the hind legs (which account for 30% of haematopoiesis in rats) is consistent with this hypothesis. Changes noted in serum chemistry values were readily reversible upon discontinuation of treatment and do not appear to be of serious toxicological consequence.

Whereas rats survived 13 weeks of daily administration of r-metHuG-CSF at dose levels up to 575 mcg/kg, 5 of 8 (4 males and 1 female) monkeys given r-metHuG-CSF at 1,150 mcg/kg died within 18 days. Death was preceded by signs of neurological toxicity and was associated with 15- to 28-fold increases in peripheral leukocyte counts and neutrophil-infiltrated hemorrhagic foci in both the cerebrum and cerebellum. In contrast, no monkeys died following 13 weeks of daily intravenous administration of r-metHuG-CSF at a dose level of 115 mcg/kg.

No hamsters or dogs died following 14 days of intravenous r-metHuG-CSF administration at doses up to 34.5 mcg/animal (equivalent to 213.9 mcg/kg based on group mean pre-study body weights) and 345 mcg/kg, respectively. One monkey in the control group died in the 14-day study. Consequently, the lethal dose of r-metHuG-CSF is greater than 115 mcg/kg/day and death was associated with a gross exaggeration of granulopoietic activity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNEUPOGEN® (pronounced *nu-po-gen*)

filgrastim injection

Read this carefully before you start taking **NEUPOGEN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NEUPOGEN**.

Serious Warnings and Precautions

- Your spleen may become enlarged and can rupture while taking NEUPOGEN. A ruptured spleen can cause death. Call your doctor right away if you or your child has pain in the left upper stomach area or left shoulder tip area.
- If you have sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking NEUPOGEN so that the potential risks and benefits can be discussed. In patients with sickle cell trait or sickle cell disease, severe sickle cell crises have been associated with the use of NEUPOGEN, resulting in death in some cases.

What is NEUPOGEN used for?

NEUPOGEN is used to treat neutropenia (nu-tro-**peen**-ee-ah), a condition where the body makes too few neutrophils. Neutropenia predisposes your body to infections and prevents you from fighting them. Your doctor has decided to prescribe Neupogen for you to increase the number of neutrophils (**nu-**tro-fils), which will fight infections.

Neutropenia may be a long-standing condition where your body does not make enough neutrophils, or it may be caused by drugs used to treat cancer. In some cases, your body may make enough neutrophils, but as part of your treatment for cancer, your doctor may want to increase the number of certain blood cells (CD34 cells) and collect them. The cells are collected using a process called apheresis (ay-fer-**ree**-sis). These collected cells are given back to you after you receive very high doses of treatment for cancer to make your blood counts get back to normal more quickly.

NEUPOGEN is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *E coli*. G-CSF is a substance naturally produced by the body.

How does NEUPOGEN work?

NEUPOGEN works by helping your body make more neutrophils. To make sure NEUPOGEN is working, your doctor will ask that you have regular blood tests to count the number of neutrophils you have. It is important that you follow your doctor's instructions about getting these tests.

What are the ingredients in NEUPOGEN?

Medicinal ingredients: filgrastim

Non-medicinal ingredients: acetate, polysorbate 80, sodium, sorbitol

The needle cover on the single use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

NEUPOGEN comes in the following dosage forms:

NEUPOGEN is available in 2 vial sizes: 1 mL and 1.6 mL. The preservative-free single use vials contain 300 mcg/mL of filgrastim.

NEUPOGEN is available in 2 prefilled syringe sizes: 0.5 mL and 0.8 mL. The preservative-free single use prefilled syringes contain 600 mcg/mL of filgrastim.

Do not use NEUPOGEN if you are:

- allergic to NEUPOGEN (filgrastim) or any of its ingredients.
- allergic to other medicines made using the bacteria *E coli*. Ask your doctor if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NEUPOGEN. Talk about any health conditions or problems you may have, including:

- If you have common signs or symptoms of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you/your child has any of these signs or symptoms during treatment with NEUPOGEN, tell your doctor or nurse immediately. NEUPOGEN may reduce your chance of getting an infection, but does not prevent all infections. An infection can still happen during the short time when you/your child's neutrophil levels are low.
- If there is a lump, swelling, or bruising at an injection site that does not go away, call your doctor. There is a possibility that you could have a reaction at an injection site.
- If you have a sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking NEUPOGEN. If you have a sickle cell crisis after getting NEUPOGEN, tell your doctor right away.

Other warnings you should know about:

Make sure your doctor knows about all medicines, and herbal or vitamin supplements you are taking before starting NEUPOGEN. If you are taking lithium you may need more frequent blood tests.

If you/your child are receiving NEUPOGEN because you are also receiving chemotherapy, the last dose of NEUPOGEN should be injected at least 24 hours before your next dose of chemotherapy.

Talk to your doctor if you experience unusual bleeding or bruising while taking NEUPOGEN following chemotherapy, as this could mean a decrease of platelets which reduces the ability of blood to clot.

If you have any questions, you should talk to your doctor.

Pregnancy or breastfeeding and NEUPOGEN

NEUPOGEN has not been studied in pregnant women, and its effects on unborn babies are not known. If you take NEUPOGEN while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if NEUPOGEN can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breastfeeding, you should tell your doctor before using NEUPOGEN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NEUPOGEN:

Drug interactions between NEUPOGEN and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into the blood stream. You should discuss your treatment with your doctor before using NEUPOGEN.

How to take NEUPOGEN:

If you are giving someone else NEUPOGEN injections, it is important that you know how to inject NEUPOGEN, how much to inject, and how often to inject NEUPOGEN.

NEUPOGEN is available as a liquid in vials or in prefilled syringes. When you receive your NEUPOGEN, always check to see that:

- The name NEUPOGEN appears on the package and vial or prefilled syringe label.
- The expiration date on the vial or prefilled syringe label has not passed. **Do not use a vial or prefilled syringe after the date on the label.**
- The NEUPOGEN liquid in the vial or in the prefilled syringe is clear and colourless. **Do not use NEUPOGEN** if the contents of the vial or prefilled syringe appear discoloured or cloudy, or if the vial or prefilled syringe appears to contain lumps, flakes, or particles.

If you are using vials of NEUPOGEN only use the syringe that your doctor prescribes.

Your doctor or nurse will give you instructions on how to measure the correct dose of NEUPOGEN. This dose will be measured in milliliters. You should only use a syringe that is marked in tenths of milliliters, or mL (for example, 0.2 mL). The doctor or nurse may refer to an mL as a cc (1 mL = 1 cc). If you do not use the correct syringe, you or your child could receive too much or too little NEUPOGEN.

Only use disposable syringes and needles. Use the syringes only once and dispose of them as instructed by your doctor or nurse.

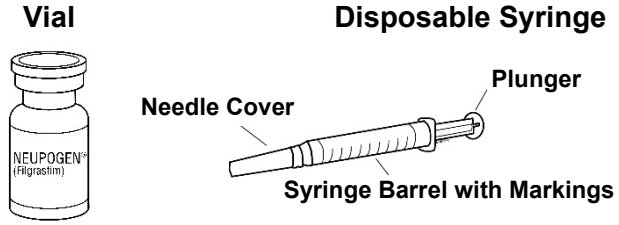
IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

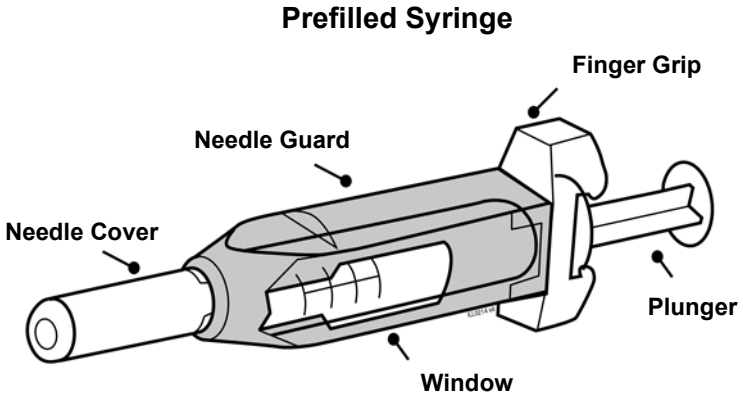
1. Find a clean flat working surface, such as a table.

2. Remove the vial or prefilled syringe of NEUPOGEN from the refrigerator. Allow NEUPOGEN to reach room temperature (this takes about 30 minutes). Vials or prefilled syringes should be used only once. DO NOT SHAKE THE VIAL OR PREFILLED SYRINGE. Shaking may damage the NEUPOGEN. If the vial or prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

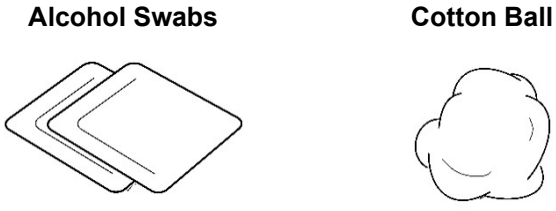
3. Assemble the supplies you will need for an injection:
   - NEUPOGEN vial and sterile disposable syringe and needle:



   - Or NEUPOGEN prefilled syringe with transparent (clear) plastic orange needle guard attached:

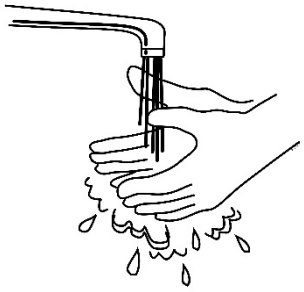


   - Two alcohol swabs and one cotton ball or gauze pad



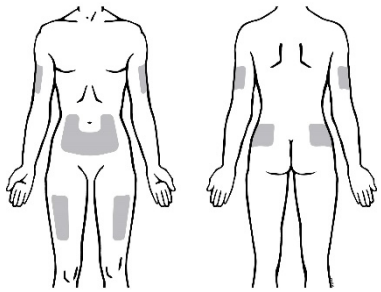
   - Puncture-proof disposal container

4. Clean your work surface thoroughly and wash your hands with soap and warm water.



Selecting and preparing the injection site (for vials and prefilled syringes)

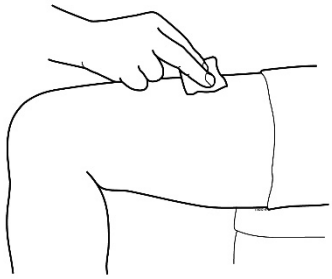
1. Choose an injection site. Four recommended injection sites for NEUPOGEN are:
   - The outer area of your upper arms
   - The abdomen, except for the two inch area around your navel
   - The front of your middle thighs
   - The upper outer areas of your buttocks



Front **Back**

2. Choose a new site each time you inject NEUPOGEN. Choosing a new site can help avoid soreness at any one site. Do not inject NEUPOGEN into an area that is tender, red, bruised, hard or that has scars or stretch marks.

3. Clean the injection site with a new alcohol swab. Use a circular motion from the inside to the outside of the injection site.

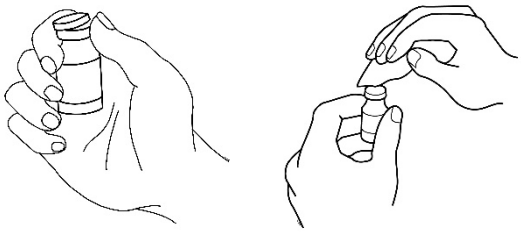


HOW TO PREPARE THE DOSE OF NEUPOGEN IN VIALS OR PREFILLED SYRINGES

If you are using NEUPOGEN in a vial, follow the instructions in Section A. If you are using NEUPOGEN in a prefilled syringe, go to Section B.

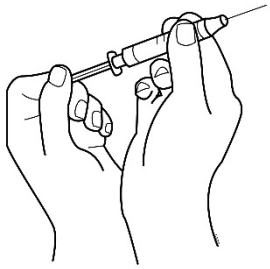
Section A. Preparing the dose using NEUPOGEN in a vial

1. Take the cap off the vial. Clean the rubber stopper with one alcohol swab.



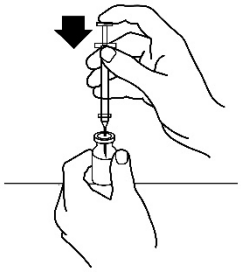
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.

3. Pull the needle cover straight off the syringe. Then, pull back the plunger and draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of NEUPOGEN that your doctor prescribed.

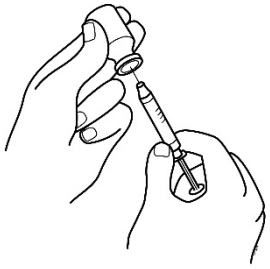


4. Keep the vial on your flat working surface and insert the needle straight down through the rubber stopper. Do not put the needle through the rubber stopper more than once.

5. Push the plunger of the syringe down and inject the air from the syringe into the vial of NEUPOGEN.



6. Keeping the needle in the vial, turn the vial upside down. Make sure that the NEUPOGEN liquid is covering the tip of the needle.



7. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with NEUPOGEN liquid to the number (mL or cc) that matches the dose your doctor prescribed.

8. Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe.

9. Keeping the tip of the needle in the liquid, once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of NEUPOGEN. If there are still air bubbles, repeat the steps above to remove them.

10. Check again to make sure that you have the correct dose of NEUPOGEN in the syringe. It is important that you use the exact dose prescribed by your doctor. Remove the syringe from the vial but **do not lay it down** or let the needle touch anything.

Section B. Preparing the dose using NEUPOGEN in a prefilled syringe

1. Remove the syringe from the package and the tray. Check to see that the plastic orange needle guard is covering the barrel of the glass syringe. DO NOT push the orange needle guard over the needle cover before injection. This may activate or lock the needle guard. If the orange needle guard is covering the needle that means it has been activated. DO NOT use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new syringe from the package.

2. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cover straight off.

3. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

4. Push the plunger up to the number (mL) on the syringe that matches the dose of NEUPOGEN that your doctor prescribed.

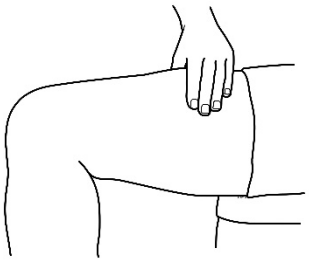
5. Check again to make sure the correct dose of NEUPOGEN is in the syringe.

6. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

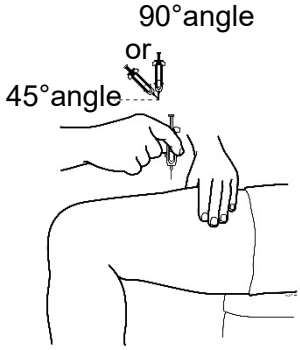
Injecting the dose of NEUPOGEN (for vials and prefilled syringes)

1. For injecting the dose of NEUPOGEN from a vial, slowly remove the syringe and needle from the vial. For injecting the dose of NEUPOGEN from a prefilled syringe, pick up the prefilled syringe from the clean flat working surface by grabbing the sides of the needle guard with your thumb and finger.

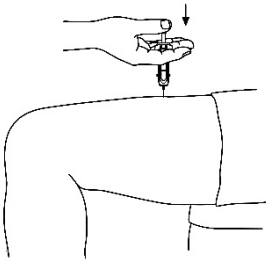
2. Hold the syringe in the hand you will use to inject NEUPOGEN. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: If using a prefilled syringe with a needle guard, hold the syringe barrel through the needle guard windows when giving the injection.



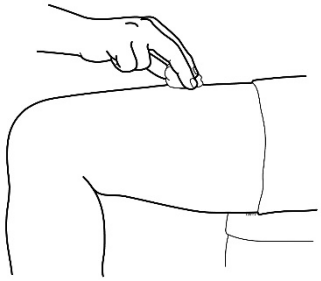
3. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



4. After the needle is inserted, let go of the skin. Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.



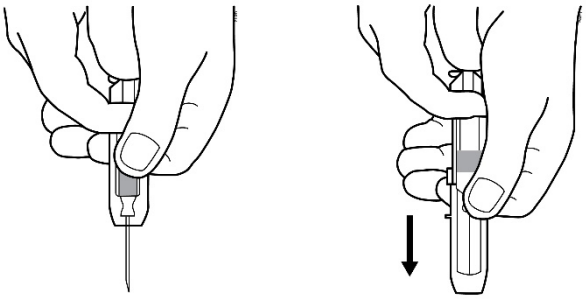
5. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



6. Use the prefilled syringe with the needle guard or a syringe, needle and vial only once. If you are using a syringe needle, DO NOT put the needle cover (the cap) back on the needle. Discard the vial with any remaining NEUPOGEN liquid.

Activating the Needle Guard for the prefilled syringe after the injection has been given

1. After injecting NEUPOGEN® from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the orange needle guard with your free hand and slide the orange needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



2. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

Disposal of syringes, needles, vials and needle guards

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes, needles, vials and needle guards. There may be special provincial or local laws for disposal of used needles and syringes.

- Place all used needles, needle covers, syringes, and vials (empty or unused contents) into a "Sharps" container given to you by your doctor or pharmacist or in a hard-plastic container with a screw-on cap, or a metal container with a plastic lid, such as a coffee can, labeled "used syringes." If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard-plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off**. Do not throw the container in the household trash. Do not recycle.**

- **Always** keep the container out of the reach of children.

Usual dose:

Your doctor will determine you/your child's correct dose based on you/your child's body weight.

Overdose:

You must always use the correct dose of NEUPOGEN. Too little NEUPOGEN may not protect you against infections, and too much NEUPOGEN may cause too many neutrophils to be in your blood.

If you think you, or a person you are caring for, have taken too much NEUPOGEN, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

NEUPOGEN should be injected at the same time each day. If you miss a dose contact your doctor or nurse.

What are possible serious side effects from using NEUPOGEN?

These are not all the possible side effects you may experience when taking NEUPOGEN. If you experience any side effects not listed here, tell your healthcare professional.

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking NEUPOGEN. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you or your child has pain in the left upper stomach area or left shoulder tip area. This pain could mean you or your child's spleen is enlarged or ruptured.
- **Serious Allergic Reactions.** NEUPOGEN can cause serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating. If you or your child starts to have any of these symptoms, stop using NEUPOGEN and call your doctor or seek emergency care right away. If you or your child has an allergic reaction during the injection of NEUPOGEN, stop the injection right away.
- **A serious lung problem called acute respiratory distress syndrome (ARDS).** Call your doctor or seek emergency care right away if you or your child has shortness of breath, trouble breathing or a fast rate of breathing.
- **Sickle Cell Crisis.** Call your doctor or seek emergency care right away if you or your child experiences severe pain in bones, chest, gut or joints.
- **Kidney injury (glomerulonephritis)** has been seen in patients who received NEUPOGEN. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.

What are the most common side effects of NEUPOGEN?

The most common side effect you/your child may experience is aching in the bones and muscles. This aching can usually be relieved by taking a non-acetylsalicylic acid pain reliever such as acetaminophen.

Some people experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in NEUPOGEN, or it may be a local reaction. If you are giving an injection to a child, look for signs of redness, swelling, or itching at the site of injection because they may not be able to tell you they are experiencing a reaction. If you notice any signs of a local reaction, call your doctor. **If at any time a serious allergic reaction occurs, immediately call a doctor or emergency services (for example, call 911).**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON ≥ 0.1% and < 1%			
Bone Pain		√	
Acute respiratory distress syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs)		√	√
Alveolar hemorrhage and hemoptysis (including the following symptoms: bleeding from the lungs and coughing of blood)		√	√
Low platelet counts (thrombocytopenia) (including the following symptoms: easy bruising and increased bleeding).		√	
Capillary Leak Syndrome (including the following symptoms: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness)		√	
RARE ≥ 0.01% and < 0.1%			
Extramedullary hematopoiesis (production of blood cell components [red blood cells, white blood cells, and/or platelets] outside of the typical site of production [bone marrow]). This may result in an enlarged spleen, liver, or pink, red, or blue/purple spots or bumps on the skin.		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE < 0.01%			
Splenomegaly (including the following symptoms: pain in the left upper stomach area or left shoulder tip area)		√	
Osteoporosis in children with severe chronic neutropenia (including decreased bone density, making them weak, more brittle and likely to break)		√	
Allergic reactions (including the following symptoms: rash over the whole body, shortness of breath, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, weakness, sweating; severe redness or swelling or itching at injection site)		√	√
Cutaneous Vasculitis (including the following signs: inflammation of the blood vessels in the skin)		√	
Sweet's Syndrome (including the following symptoms: plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever)		√	
Kidney Injury (glomerulonephritis) (including the following symptoms: puffiness in the face or ankles, blood in urine or brown coloured urine, or urinating less often than usual).		√	√
***FREQUENCY NOT KNOWN**			
Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder)		√	
Pseudogout (including the following symptoms in patients treated for cancer: pain and swelling of the joints, similar to gout)		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
**Abnormal number of immature bone marrow cells (myelodysplastic syndrome) that could lead to a type of cancer (acute myeloid leukemia) (including the following symptoms: fever, bone pain, bruising, difficulty breathing, bleeding and a general feeling of tiredness).		√	√

*Reported in the post-marketing setting where the incidence is not known.

**Adverse events in breast and lung cancer patients receiving chemotherapy and/or radiotherapy

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

- NEUPOGEN should be stored in the refrigerator at 2 °C to 8 °C (36 °F to 46 °F), but not in the freezer. Avoid shaking NEUPOGEN.
- If NEUPOGEN is accidentally frozen, allow it to thaw in the refrigerator before giving the next dose. However, if it is frozen a second time, do not use it and contact your doctor or nurse for further instructions.
- NEUPOGEN can be left out at room temperature for up to 14 days. Keep the container in the outer carton to protect from light. Do not leave NEUPOGEN in direct sunlight.
- If you have any questions about storage or how to carry NEUPOGEN when you travel, contact your doctor, nurse, or pharmacist.

Keep out of reach and sight of children.

If you want more information about NEUPOGEN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's web site (www.amgen.ca), or by calling Amgen Canada Inc., at: 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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