

## PRODUCT MONOGRAPH

PrNEUPOGEN<sup>®</sup>

(filgrastim)

Sterile Solution for Injection  
(Subcutaneous or Intravenous Use Only)  
300 µg/mL

Hematopoietic Agent  
Granulocyte Colony Stimulating Factor

Manufactured by:  
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## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	5
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	13
DRUG INTERACTIONS .....	19
DOSAGE AND ADMINISTRATION.....	19
ACTION AND CLINICAL PHARMACOLOGY .....	24
STORAGE AND STABILITY.....	25
SPECIAL HANDLING INSTRUCTIONS .....	25
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	26
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>27</b>
PHARMACEUTICAL INFORMATION.....	27
CLINICAL TRIALS.....	27
DETAILED PHARMACOLOGY .....	33
TOXICOLOGY .....	35
REFERENCES .....	37
<b>PART III: CONSUMER INFORMATION.....</b>	<b>42</b>

# PrNEUPOGEN®

(filgrastim)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous (SC) or Intravenous (IV)	Sterile Solution for Injection / 300 µg/mL	Not Applicable <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### DESCRIPTION

NEUPOGEN® (filgrastim) is a recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF) produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein<sup>1</sup> 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*.

### INDICATIONS AND CLINICAL USE

NEUPOGEN® (filgrastim) is indicated for the following:

#### ***1. Cancer Patients Receiving Myelosuppressive Chemotherapy***

NEUPOGEN® (filgrastim) 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  $> 10 \times 10^9/L$  after expected chemotherapy-induced nadir.

## ***2. Patients with Acute Myeloid Leukemia***

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

## ***3. Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation***

NEUPOGEN<sup>®</sup> is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., 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).

## ***4. Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy***

NEUPOGEN<sup>®</sup> 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<sup>®</sup>, after myelosuppressive or myeloablative chemotherapy (see CLINICAL TRIALS, Clinical Experience).

## ***5. Patients with Severe Chronic Neutropenia***

NEUPOGEN<sup>®</sup> 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 CLINICAL TRIALS, Clinical Experience).

## ***6. Patients with HIV Infection***

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

## CONTRAINDICATIONS

NEUPOGEN<sup>®</sup> (filgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived products or to any component of the product. For a complete listing of the components, see the Dosage Forms, Composition and Packaging section of the product monograph.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN<sup>®</sup> (see **WARNINGS AND PRECAUTIONS: General**).
- Severe sickle cell crises, in some cases resulting in death, have been associated with the use of NEUPOGEN<sup>®</sup> in patients with sickle cell disorders (see **WARNINGS AND PRECAUTIONS: Hematologic**).

### General

#### **Splenic Rupture**

Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN<sup>®</sup>. Patients receiving NEUPOGEN<sup>®</sup> 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<sup>®</sup> (filgrastim) given simultaneously with cytotoxic chemotherapy have not been established. Studies in adult patients showed that an interaction between concurrent NEUPOGEN<sup>®</sup> 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<sup>®</sup> in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION).

The efficacy of NEUPOGEN<sup>®</sup> has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., 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<sup>®</sup> have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of NEUPOGEN<sup>®</sup> with chemotherapy and radiation therapy should be avoided.

#### **Carcinogenesis and Mutagenesis**

The carcinogenic potential of NEUPOGEN<sup>®</sup> has not been studied. NEUPOGEN<sup>®</sup> failed to

induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. NEUPOGEN<sup>®</sup> had no observed effect on the fertility of male or female rats, or on gestation at doses up to 500 µg/kg.

### **Growth Factor Potential**

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

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

Acute myeloid leukaemia (AML) has been reported to occur in the natural history of severe chronic neutropenia without cytokine therapy.<sup>2-4</sup> It is not known what, if any, additional risk may be imposed by NEUPOGEN<sup>®</sup> therapy.

### **Cardiovascular**

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

### **Hematologic**

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

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

In studies of NEUPOGEN<sup>®</sup> administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). As a result of the potential of receiving higher doses of chemotherapy (i.e., 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  $100 \times 10^9/L$  or greater were observed in approximately 2% of patients receiving NEUPOGEN<sup>®</sup> at doses above 5 and up to 115  $\mu\text{g}/\text{kg}/\text{day}$ . 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<sup>®</sup> therapy (see Monitoring and Laboratory Tests).

### **Hypersensitivity/Allergic Reactions**

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4,000 patients treated with NEUPOGEN<sup>®</sup>. 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<sup>®</sup> 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.

### **Cutaneous Vasculitis**

Cutaneous vasculitis has been reported in patients treated with NEUPOGEN<sup>®</sup>. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term NEUPOGEN<sup>®</sup> 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<sup>®</sup> at a reduced dose.

### **Immune**

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving NEUPOGEN<sup>®</sup> 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<sup>®</sup> and Neulasta<sup>®</sup>, the incidence of antibodies binding to NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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 crossreact 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 (NEUPOGEN<sup>®</sup>) may have allergic or hypersensitivity reactions to other *E.coli*-derived proteins.

### **Respiratory**

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN<sup>®</sup>, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving NEUPOGEN<sup>®</sup> who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, NEUPOGEN<sup>®</sup> 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<sup>®</sup>. The use of NEUPOGEN<sup>®</sup> for PBPC mobilization in healthy donors is not an approved indication.

### **Other**

#### ***Cancer Patients Receiving Myelosuppressive Chemotherapy***

##### **Premature Discontinuation of NEUPOGEN<sup>®</sup> Therapy**

A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of NEUPOGEN<sup>®</sup> therapy. However, for a sustained therapeutic response, NEUPOGEN<sup>®</sup> therapy should be continued following chemotherapy until the post nadir ANC reaches  $10 \times 10^9/L$ . Therefore, the premature discontinuation of NEUPOGEN<sup>®</sup> therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see 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.<sup>5</sup> When considering chemotherapy dose intensification with NEUPOGEN<sup>®</sup> 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,<sup>2-4</sup> which may be difficult to distinguish from myelodysplasia, before initiating NEUPOGEN<sup>®</sup> therapy. The safety and efficacy of NEUPOGEN<sup>®</sup> in the treatment of neutropenia or pancytopenia due to other haematopoietic disorders (e.g., 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<sup>®</sup> therapy.

Myelodysplasia (MDS), and acute myeloid leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy.<sup>6</sup> Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with NEUPOGEN<sup>®</sup> for 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<sup>®</sup> administration in patients with abnormal cytogenetics is unknown. If a patient with SCN develops abnormal cytogenetics, the risks and benefits of continuing NEUPOGEN<sup>®</sup> should be carefully considered (see ADVERSE REACTIONS).

### **Chronic Administration**

The safety and efficacy of chronic daily administration of NEUPOGEN<sup>®</sup> 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<sup>®</sup> is unclear, osteoporosis has been reported in approximately 7% of patients receiving NEUPOGEN<sup>®</sup> therapy for up to 4.5 years in clinical trials in patients with SCN. 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<sup>®</sup> therapy. Other infrequently observed adverse events included exacerbation of some pre-existing skin disorders (e.g., psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, haematuria/proteinuria, thrombocytopenia (platelets < 50 x 10<sup>9</sup>/L).

### ***Patients with HIV Infection***

#### **Risks Associated with Increased Doses of Myelosuppressive Medications**

Treatment with NEUPOGEN<sup>®</sup> 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<sup>®</sup> therapy, the patient may be at higher risk of developing thrombocytopenia (see 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<sup>®</sup> for treatment of neutropenia.

### **Special Populations**

**Pregnant Women:** NEUPOGEN<sup>®</sup> 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 embryoletality were observed in animals treated with NEUPOGEN<sup>®</sup> at 80 µg/kg/day. NEUPOGEN<sup>®</sup> administered to pregnant rabbits at doses of 80 µg/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 µg/kg/day. Reproductive studies in pregnant rats have shown that NEUPOGEN<sup>®</sup> 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 µg/kg/day.

In Segment III studies in rats, offspring of dams treated at greater than 20 µg/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 µg/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<sup>®</sup> has been demonstrated. NEUPOGEN<sup>®</sup> should be used during pregnancy only if the potential benefit justifies any potential theoretical risk to the fetus.

**Nursing Women:** It is not known whether NEUPOGEN<sup>®</sup> is excreted in human milk, therefore, NEUPOGEN<sup>®</sup> is not recommended for use in nursing women.

**Neonates:** The safety and efficacy of NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. In this population, NEUPOGEN<sup>®</sup> was well tolerated. There was one report of palpable splenomegaly

associated with NEUPOGEN<sup>®</sup> 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<sup>®</sup> post-chemotherapy in pediatric patients with AML has included 136 patients.<sup>7</sup> This interim analysis included children receiving intensive induction chemotherapy with NEUPOGEN<sup>®</sup>, 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<sup>®</sup> 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 CLINICAL TRIALS, Clinical Experience; INDICATIONS AND CLINICAL USAGE; Monitoring and Laboratory Tests; DOSAGE AND ADMINISTRATION).

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

Other serious long-term risks associated with daily administration of NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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.

## **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<sup>®</sup> therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when NEUPOGEN<sup>®</sup> 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<sup>®</sup> therapy) following marrow infusion.

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

After 4 days of NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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 (i.e., as clinically indicated but at least quarterly) is recommended. 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<sup>®</sup> therapy,
- Platelet counts were generally at the upper limits of normal prior to NEUPOGEN<sup>®</sup> therapy. With NEUPOGEN<sup>®</sup> therapy, platelet counts decreased but generally remained within normal limits (see 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<sup>®</sup> 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<sup>®</sup> therapy and at regular intervals (e.g., initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during NEUPOGEN<sup>®</sup> therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial doses of NEUPOGEN<sup>®</sup>. It is recommended that blood samples be drawn for ANC measurement prior to any scheduled dosing with NEUPOGEN<sup>®</sup>.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

See WARNINGS AND PRECAUTIONS regarding Splenic Rupture, ARDS, Allergic Reactions and Sick Cell Disease.

### **Clinical Trial Adverse Drug 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<sup>®</sup> (filgrastim) 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<sup>®</sup> 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 µg/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of NEUPOGEN<sup>®</sup> (3 to 10 µg/kg/day).

In the randomized, double-blind, placebo-controlled trial of NEUPOGEN<sup>®</sup> 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<sup>®</sup> at 4 to 8 µg/kg/day). Events are reported as exposure adjusted since patients remained on double-blind NEUPOGEN<sup>®</sup> a median of 3 cycles versus 1 cycle for placebo.

Event	% of Blinded Cycles with Events	
	NEUPOGEN <sup>®</sup>	Placebo
	Patient Cycles N=384	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<sup>®</sup> therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis, or other major systemic reactions to NEUPOGEN<sup>®</sup>.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27% to 58% of 98 patients receiving blinded NEUPOGEN<sup>®</sup> 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<sup>®</sup>. No evidence of interaction of NEUPOGEN<sup>®</sup> with other drugs was observed in the course of clinical trials (see WARNINGS AND PRECAUTIONS –Simultaneous Use with Chemotherapy).

The safety profile of NEUPOGEN<sup>®</sup> in the pediatric population is comparable to that seen in adult cancer patients receiving cytotoxic chemotherapy. Adverse events considered related to NEUPOGEN<sup>®</sup> administration by the investigators of 3 non-blinded studies included application site disorders, haematologic 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<sup>®</sup> studies.

#### ***Patients with Acute Myeloid Leukemia***

In a randomized phase 3 clinical trial involving 521 patients with de novo AML, 259 patients received NEUPOGEN<sup>®</sup> post-chemotherapy and 262 patients received placebo. NEUPOGEN<sup>®</sup> 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<sup>®</sup>. In the randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with NEUPOGEN<sup>®</sup> 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<sup>®</sup>. One event of erythema nodosum was reported moderate in severity and possibly related to NEUPOGEN<sup>®</sup>.

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

##### **NEUPOGEN<sup>®</sup> Mobilized PBPC Collection**

In clinical trials, 126 patients have received NEUPOGEN<sup>®</sup> for mobilization of PBPC. During the mobilization period, adverse events related to NEUPOGEN<sup>®</sup> 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<sup>®</sup> in 7% of patients. Mild-to-moderate transient increases in alkaline phosphatase levels were reported related to NEUPOGEN<sup>®</sup> 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<sup>®</sup>. Two patients had a WBC count greater than  $100 \times 10^9/L$  with WBC count increases during the mobilization period ranging from  $16.7 \times 10^9/L$  to  $138 \times 10^9/L$  above baseline. Eighty-eight percent of patients had an increase in WBC count between  $10 \times 10^9/L$  and  $70 \times 10^9/L$  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  $< 50 \times 10^9/L$ .

### **PBPC Transplantation Followed by NEUPOGEN<sup>®</sup>**

During the period of NEUPOGEN<sup>®</sup> administration post PBPC transplant, NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia ( $< 50 \times 10^9/L$ ) 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 ( $< 50 \times 10^9/L$ ) during NEUPOGEN<sup>®</sup> therapy, most of whom had a pre-study history. In most cases, thrombocytopenia was managed by NEUPOGEN<sup>®</sup> dose reduction or interruption. There were no associated, serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with NEUPOGEN<sup>®</sup>, 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<sup>®</sup> for SCN (see WARNINGS AND PRECAUTIONS, 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<sup>®</sup> 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<sup>®</sup>; 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. NEUPOGEN<sup>®</sup> 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<sup>®</sup>-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<sup>®</sup> in HIV-infected patients. The randomized study was not powered to address this issue and the possibility of an effect due to NEUPOGEN<sup>®</sup> on HIV replication cannot be entirely excluded.

As of 31 January 1996, an estimated 1.2 million patients worldwide have received NEUPOGEN<sup>®</sup> therapy across all indications. Of an estimated 150,000 HIV-infected patients receiving NEUPOGEN<sup>®</sup> 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<sup>®</sup> for neutropenia associated with HIV infection. Five deaths were reported in 106 post-marketing reports in patients receiving NEUPOGEN<sup>®</sup> 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<sup>®</sup>. It is notable, however, that randomized trials<sup>8-12</sup>, and non-randomized trials<sup>13-15</sup> demonstrated no increase in the known pulmonary toxicity of bleomycin when NEUPOGEN<sup>®</sup> was added to treatment.

In the randomized controlled study, the overall incidence of thrombocytopenia was 9.9% in the NEUPOGEN<sup>®</sup>-treated groups compared with 8.1% in the control group. Severe thrombocytopenia occurred in 7% of the NEUPOGEN<sup>®</sup>-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<sup>®</sup>-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<sup>®</sup> 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<sup>16</sup>, it is likely that the observed splenomegaly was associated with HIV disease and not related to NEUPOGEN<sup>®</sup>.

### **Post-Market Adverse Drug Reactions**

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

- Splenic rupture (see WARNINGS AND PRECAUTIONS: Splenic Rupture)
- Acute respiratory distress syndrome (ARDS) (see WARNINGS AND PRECAUTIONS: Respiratory)
- Alveolar hemorrhage and hemoptysis (see WARNINGS AND PRECAUTIONS: Respiratory)
- Allergic reactions (see WARNINGS AND PRECAUTIONS: Hypersensitivity/Allergic Reactions)
- Sick cell crisis (see WARNINGS AND PRECAUTIONS: Hematologic)
- Cutaneous vasculitis (see WARNINGS AND PRECAUTIONS: Cutaneous Vasculitis)
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Pseudogout (in patients treated with cancer)

## **DRUG INTERACTIONS**

### **Overview**

Interactions of NEUPOGEN<sup>®</sup> with other cytokines, including haematopoietic growth factors, have been observed in animal studies. The safety, efficacy, and possible interactions of NEUPOGEN<sup>®</sup> 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.

### **Drug-Drug Interactions**

Interactions with other drugs have not been established.

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory 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.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

#### ***Cancer Patients Receiving Myelosuppressive Chemotherapy***

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

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

NEUPOGEN<sup>®</sup> 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.

## **Recommended Dose and Dosage Adjustment**

### ***Cancer Patients Receiving Myelosuppressive Chemotherapy***

The recommended starting dose of NEUPOGEN<sup>®</sup> (filgrastim) in adult patients is 5 µg/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 µg/kg/day administered subcutaneously.

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

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

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

The recommended dose of NEUPOGEN<sup>®</sup> following bone marrow transplant is 10 µg/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<sup>®</sup> should be titrated against the neutrophil response as follows:

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

\* If ANC decreases to <  $1.0 \times 10^9/L$  at any time during the 5 µg/kg/day administration, NEUPOGEN<sup>®</sup> should be increased to 10 µg/kg/day, and the above steps should then be

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followed.

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

The recommended dose of NEUPOGEN<sup>®</sup> for PBPC mobilization is 10 µg/kg/day given as a single daily subcutaneous injection or a continuous 24-hour infusion. NEUPOGEN<sup>®</sup> 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<sup>®</sup>, 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<sup>+</sup> or GM-CFU, are not standardized and variations may exist between laboratories, and
- Factors other than NEUPOGEN<sup>®</sup> dosage, such as prior cytotoxic chemo- or radiotherapy, may affect the number and quality of progenitor cells mobilized and collected by leukapheresis.

The recommended dose of NEUPOGEN<sup>®</sup> following PBPC transplant is 5 µg/kg/day given either subcutaneously or as an intravenous infusion. The daily dose of NEUPOGEN<sup>®</sup> should be titrated according to the schedule provided above (***Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation***).

### ***Patients with HIV Infection***

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

In clinical trials, the maximum NEUPOGEN<sup>®</sup> dose did not exceed 10 µg/kg/day.

### ***Patients with Severe Chronic Neutropenia***

#### **Starting Dose**

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

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

#### **Dose Adjustments**

NEUPOGEN<sup>®</sup> may be administered subcutaneously as a single daily injection to increase and sustain the ANC above  $1.5 \times 10^9/L$ . 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  $1.5 \times 10^9/L$  and  $10 \times 10^9/L$ . WBC/ANC monitoring should be done more frequently (e.g., every other day) if the ANC reaches values above  $25 \times 10^9/L$ , and the dose reduced if the ANC remains greater than  $25 \times 10^9/L$  for 1 week. In the SCN post-marketing surveillance study, the median daily doses of NEUPOGEN<sup>®</sup> reported (median duration 4.4 years) were: Congenital Neutropenia 6.9 µg/kg; Cyclic Neutropenia 2.1 µg/kg; Idiopathic Neutropenia 1.2 µg/kg.

In clinical trials in patients with SCN, 91% of patients who responded to NEUPOGEN<sup>®</sup> therapy responded at doses of  $\leq 12 \mu\text{g/kg/day}$ . Ninety-seven percent of patients responded at doses of  $\leq 24 \mu\text{g/kg/day}$ . Therefore, patients with SCN who do not respond to the recommended starting dose should be treated with up to  $24 \mu\text{g/kg/day}$  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.

#### **Administration**

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

NEUPOGEN<sup>®</sup> should not be vigorously shaken.

In those situations in which the physician determines that the patient can safely and effectively self-administer NEUPOGEN<sup>®</sup>, 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.

### **Dilution**

If required, NEUPOGEN<sup>®</sup> may be diluted in 5% dextrose. NEUPOGEN<sup>®</sup> diluted to a concentration between 5 and 15 µg/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<sup>®</sup> is compatible with glass bottles, PVC and polyolefin intravenous bags and polypropylene syringes.

Dilution of NEUPOGEN<sup>®</sup> to a final concentration of < 5 µg/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.**

### **OVERDOSAGE**

The maximum tolerated dose of NEUPOGEN<sup>®</sup> (filgrastim) has not been determined. In dose ranging studies, 5 of 16 patients given  $\geq 69$  µg/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<sup>®</sup> clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts  $> 100 \times 10^9/L$  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<sup>®</sup> therapy should be discontinued if the ANC surpasses  $10 \times 10^9/L$  after the chemotherapy-induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of NEUPOGEN<sup>®</sup> 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.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **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.<sup>17-21</sup> 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.<sup>21,22</sup> NEUPOGEN<sup>®</sup> (filgrastim) is the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

### **Pharmacodynamics**

In phase 1 studies involving 96 patients with various non-myeloid malignancies, NEUPOGEN<sup>®</sup> administration resulted in a dose-dependent increase in neutrophil counts over the dose range of 1 to 70 µg/kg/day.<sup>23-25</sup> This increase in neutrophil counts was observed whether NEUPOGEN<sup>®</sup> was administered intravenously (1 to 70 µg/kg twice daily),<sup>23</sup> subcutaneously (1 to 3 µg/kg once daily),<sup>25</sup> or by continuous subcutaneous infusion (3 to 11 µg/kg/day).<sup>24</sup> With discontinuation of NEUPOGEN<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>. Increases in lymphocyte counts following NEUPOGEN<sup>®</sup> 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.

### **Pharmacokinetics**

Absorption and clearance of NEUPOGEN<sup>®</sup> follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous intravenous infusion of 20 µg/kg of NEUPOGEN<sup>®</sup> over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively.

Subcutaneous administration of 3.45 µg/kg and 11.5 µg/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<sup>®</sup> 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<sup>®</sup> doses of 34.5 µg/kg) and for subcutaneous administration (210 minutes, following NEUPOGEN<sup>®</sup> doses of 3.45 µg/kg). Continuous 24-hour intravenous infusions of 20 µg/kg over an 11 to 20 day period produced steady state serum concentrations of NEUPOGEN<sup>®</sup> 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 µg/kg/day NEUPOGEN<sup>®</sup> subcutaneously for 10 days. Peak concentrations of NEUPOGEN<sup>®</sup> of 3 to 117 ng/mL were reached after 4 to 12 hours with measurable NEUPOGEN<sup>®</sup> 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.

### **STORAGE AND STABILITY**

NEUPOGEN<sup>®</sup> should be stored in the refrigerator at 2 to 8 °C. Avoid vigorous shaking.

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

Prior to injection, NEUPOGEN<sup>®</sup> may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

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

### **SPECIAL HANDLING INSTRUCTIONS**

NEUPOGEN<sup>®</sup> should not be vigorously shaken.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

NEUPOGEN<sup>®</sup> (filgrastim) is a sterile, clear, colourless, preservative-free liquid for parenteral administration. Each single use vial of NEUPOGEN<sup>®</sup> contains 300 µg ( $3 \times 10^7$  units/mL) of filgrastim formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% Tween<sup>®</sup> 80.

The quantitative composition (per mL) of NEUPOGEN<sup>®</sup> is:

Filgrastim	300 µg
Acetate	0.59 mg
Sorbitol	50.0 mg
Tween <sup>®</sup> 80	0.004%
Sodium	0.035 mg
Water for Injection	1.0 mL
	USP q.s. ad

Filling and packaging operations for NEUPOGEN<sup>®</sup> are performed by Amgen Inc. or by an outside contractor licensed by Health Canada in accordance with good manufacturing practices.

### Availability of Dosage Forms

NEUPOGEN<sup>®</sup> (filgrastim) is available in 2 vial sizes; 1 mL and 1.6 mL.

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

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

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

## PART II: SCIENTIFIC INFORMATION

### 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<sup>®</sup> (filgrastim) is a sterile, clear, colourless, preservative-free liquid.

### CLINICAL TRIALS

#### Study Results

**Clinical Experience: Response to NEUPOGEN<sup>®</sup>**

*Cancer Patients Receiving Myelosuppressive Chemotherapy*

NEUPOGEN<sup>®</sup> 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<sup>®</sup> (4 to 8 µg/kg/day, days 4 to 17) or placebo. In this study, the benefits of NEUPOGEN<sup>®</sup> 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<sup>26</sup> patients were randomized to receive NEUPOGEN<sup>®</sup> (n=101) or placebo (n=110). Of the 211 patients enrolled, 207 patients were evaluable for safety (NEUPOGEN<sup>®</sup>, n=98; placebo, n=109) and 199 patients were evaluable for efficacy (NEUPOGEN<sup>®</sup>, n=95; placebo, n=104). NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> group.

Thus, treatment with NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> resulted in an earlier ANC nadir following chemotherapy than was experienced by patients receiving placebo (day 10 versus day 12). NEUPOGEN<sup>®</sup> was well

tolerated when given subcutaneously daily at doses of 4 to 8 µg/kg for up to 14 consecutive days following each cycle of chemotherapy (see ADVERSE REACTIONS).

In 36 patients receiving M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for treatment of transitional cell carcinoma of the urothelium,<sup>23</sup> 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<sup>®</sup> was administered, when compared to cycles of chemotherapy without NEUPOGEN<sup>®</sup>. The accelerated recovery of granulocyte counts during M-VAC cycles when NEUPOGEN<sup>®</sup> 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<sup>®</sup> was generally well tolerated at all doses treated (up to 115 µg/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,<sup>24</sup> patients were treated with NEUPOGEN<sup>®</sup> 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  $< 0.5 \times 10^9/L$ ) was reduced by NEUPOGEN<sup>®</sup> treatment independent of route.

The effect of NEUPOGEN<sup>®</sup> has also been studied in 12 patients receiving chemotherapy (doxorubicin, ifosfamide with Mesna, and etoposide) for small cell lung cancer.<sup>25</sup> Chemotherapy cycles without NEUPOGEN<sup>®</sup> were alternated with cycles in which NEUPOGEN<sup>®</sup> was administered following chemotherapy. There was a statistically significant reduction in the duration of both severe (ANC  $< 0.5 \times 10^9/L$ ) and moderate (ANC  $< 1.0 \times 10^9/L$ ) neutropenia between the NEUPOGEN<sup>®</sup> and no NEUPOGEN<sup>®</sup> 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<sup>®</sup> was well tolerated at doses of 1 to 45 µg/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<sup>®</sup>. The results indicated that NEUPOGEN<sup>®</sup> 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.<sup>27</sup>

#### ***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<sup>®</sup> significantly reduced the duration of neutropenia and the associated clinical consequences of fever, IV antibiotic use and hospitalization, following induction chemotherapy. In the NEUPOGEN<sup>®</sup>-treated group, the median duration of neutropenia (ANC < 0.5 x 10<sup>9</sup>/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<sup>®</sup> 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<sup>®</sup> was administered at doses of 10 or 30 µg/kg/day; a third treatment group in this study received no NEUPOGEN<sup>®</sup>. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 0.5 x 10<sup>9</sup>/L) occurred in the NEUPOGEN<sup>®</sup>-treated group versus the control group [23 days in the control group, 11 days in the 10 µg/kg/day group, and 14 days in the 30 µg/kg/day group, (11 days in the combined treatment groups; p=0.004)].

In the second study (n=44; 43 patients evaluable), NEUPOGEN<sup>®</sup> was administered at doses of 10 or 20 µg/kg/day; a third treatment group in this study received no NEUPOGEN<sup>®</sup>. A statistically significant reduction in the median number of days of severe neutropenia occurred in the NEUPOGEN<sup>®</sup>-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 µg/kg/day group, and 5.5 days in the 20 µg/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 µg/m<sup>2</sup>/day of NEUPOGEN<sup>®</sup>. 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 ≥ 0.5 x 10<sup>9</sup>/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<sup>®</sup>. 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 tumor. 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<sup>®</sup> 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 haemorrhagic complications and the need for platelet transfusions.

### **NEUPOGEN<sup>®</sup> Mobilized PBPC Collection**

In 4 studies (n=126), patients with NHL, HD, ALL, and breast cancer received NEUPOGEN<sup>®</sup> 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 were pheresed on days 4, 6, and 8). In 2 studies, the tested doses and schedules of NEUPOGEN<sup>®</sup> resulted in a greater number of PBPC in the pheresis product compared to the baseline leukapheresis product.

### **NEUPOGEN<sup>®</sup> Mobilized PBPC Therapy Followed by NEUPOGEN<sup>®</sup>**

In a randomized study of patients with HD or NHL undergoing myeloablative chemotherapy, 27 patients received NEUPOGEN<sup>®</sup> mobilized PBPC followed by NEUPOGEN<sup>®</sup> and 31 patients received ABMT plus NEUPOGEN<sup>®</sup>. Patients randomized to the NEUPOGEN<sup>®</sup> 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  $> 20 \times 10^9/L$ , (16 vs. 23 days;  $p=0.02$ ), a significantly shorter median time to recovery of a sustained ANC  $\geq 0.5 \times 10^9/L$  (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<sup>®</sup> 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 PBPC 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.<sup>28</sup> Untreated patients had a median ANC of  $0.210 \times 10^9/L$ . NEUPOGEN<sup>®</sup> therapy was adjusted to maintain the median ANC between  $1.5 \times 10^9/L$  and  $10 \times 10^9/L$ . A complete response was seen in 88% of patients (defined as a median ANC  $1.5 \times 10^9/L$  over 5 months of NEUPOGEN<sup>®</sup> therapy). Overall, complete response to NEUPOGEN<sup>®</sup> was observed in 1 to 2 weeks. The median ANC after 5 months of NEUPOGEN<sup>®</sup> therapy for all patients was  $7.46 \times 10^9/L$  (range 0.03 to  $30.88 \times 10^9/L$ ). In general, patients with congenital neutropenia responded to NEUPOGEN<sup>®</sup> 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  $\mu\text{g}/\text{kg}/\text{day}$ ) than for patients with idiopathic (0.6 to 11.5  $\mu\text{g}/\text{kg}/\text{day}$ ) or cyclic (0.5 to 6  $\mu\text{g}/\text{kg}/\text{day}$ ) neutropenia.

Overall, daily treatment with NEUPOGEN<sup>®</sup> 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<sup>®</sup> 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.<sup>27</sup>

### ***Patients with HIV Infection***

NEUPOGEN<sup>®</sup> 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  $< 0.5 \times 10^9/L$ ,  $p < 0.0001$ ) in NEUPOGEN<sup>®</sup>-treated patients. Three of 172 (1.7%) NEUPOGEN<sup>®</sup>-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<sup>®</sup>-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<sup>®</sup>-treated patients [ $p=0.17$ ,  $p=0.08$  (adjusted)].

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

In an open-label study to evaluate neutrophil function by *in vitro* chemiluminescence measurement, NEUPOGEN<sup>®</sup>-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<sup>®</sup>.

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<sup>®</sup> administration.

## **DETAILED PHARMACOLOGY**

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.<sup>17-21</sup> 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.<sup>21,22</sup> NEUPOGEN<sup>®</sup> (filgrastim) is the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

### **Pre-clinical Studies**

The results of all pre-clinical studies indicate that the pharmacologic effects are consistent with its role as a specific regulator of neutrophil production and function.

### **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,<sup>29,30</sup> differentiation,<sup>29,31</sup> and selected end-cell functional activation (including enhanced phagocytic ability,<sup>32</sup> priming of the cellular metabolism associated with respiratory burst,<sup>33</sup> antibody dependent killing,<sup>34</sup> and the increased expression of some functions associated with cell surface antigens<sup>35</sup>).

### **Pharmacologic Effects of NEUPOGEN<sup>®</sup>**

In phase 1 studies involving 96 patients with various non-myeloid malignancies, NEUPOGEN<sup>®</sup> administration resulted in a dose-dependent increase in neutrophil counts over the dose range of 1 to 70 µg/kg/day.<sup>23-25</sup> This increase in neutrophil counts was observed whether NEUPOGEN<sup>®</sup> was administered intravenously (1 to 70 µg/kg twice daily),<sup>23</sup> subcutaneously (1 to 3 µg/kg once daily),<sup>25</sup> or by continuous subcutaneous infusion (3 to 11 µg/kg/day).<sup>24</sup> With discontinuation of NEUPOGEN<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>. Increases in lymphocyte counts following NEUPOGEN<sup>®</sup> 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.

## **Pharmacokinetics**

Absorption and clearance of NEUPOGEN<sup>®</sup> follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous intravenous infusion of 20 µg/kg of NEUPOGEN<sup>®</sup> over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively.

Subcutaneous administration of 3.45 µg/kg and 11.5 µg/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<sup>®</sup> 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<sup>®</sup> doses of 34.5 µg/kg) and for subcutaneous administration (210 minutes, following NEUPOGEN<sup>®</sup> doses of 3.45 µg/kg). Continuous 24-hour intravenous infusions of 20 µg/kg over an 11 to 20 day period produced steady state serum concentrations of NEUPOGEN<sup>®</sup> 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 µg/kg/day NEUPOGEN<sup>®</sup> subcutaneously for 10 days. Peak concentrations of NEUPOGEN<sup>®</sup> of 3 to 117 ng/mL were reached after 4 to 12 hours with measurable NEUPOGEN<sup>®</sup> 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.

## **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 µg/kg/animal (862.5 µg/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<sub>50</sub> of r-metHuG-CSF in these species is in excess of 3,450 µg/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 osteoclasts 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 µg/kg, 5 of 8 (4 males and 1 female) monkeys given r-metHuG-CSF at 1,150 µg/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 haemorrhagic 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 µg/kg.

No hamsters or dogs died following 14 days of intravenous r-metHuG-CSF administration at doses up to 34.5 µg/animal (equivalent to 213.9 µg/kg based on group mean pre-study body weights) and 345 µg/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 µg/kg/day and death was associated with a gross exaggeration of granulopoietic activity.

## REFERENCES

1. Zsebo KM, Cohen AM, Murdock DC, Boone TC, Inque H, Chazin VR, Hines D, and Souza LM. Recombinant human granulocyte colony-stimulating factor: Molecular and biological characterization. *Immunobiol* 1986;172:175-184.
2. Alter BP. Hematology of Infancy and Childhood. WB Saunders Co. 1987;Chp 7:159-241.
3. Dale DC. Hematology. McGraw Hill. 1990;Chp 86:807-816.
4. Hutchinson RJ and Boxer LA. Hematology:Basic Principles and Practice. Churchill Livingstone. 1991;Chp 14:193-205.
5. Morris-Jones, PH. The late effects of cancer therapy in childhood. *Br. J. Cancer* 1991;64:1-2.
6. Schroeder TM and Kurth R. Spontaneous chromosomal breakage and high incidence of leukemia in inherited disease. *Blood* 1971;37:96-112.
7. Woods WG, Kobrinsky N, Buckley J, et al. Timed sequential induction therapy improves post-remission in pediatric acute myeloid leukemia (AML) [abstract]. *Med Pediatr Oncol* 1995;25:O147.
8. Bastion Y, Reyes F, Coiffier B, et al. Possible toxicity with the association of G-CSF and bleomycin. *Lancet* 1994;343:1221-1222.
9. Bertini M, Freilone R, Vitolo U, et al. P-VEBEC: A new 8-weekly schedule with or without rG-CSF for elderly patients with aggressive non-Hodgkin=s lymphoma. *Ann Oncol* 1994;5(10):895-900.
10. Fossa S, Kaye SB, Mead BM, et al. An MRC/EORTC randomized trial in poor prognosis metastatic teratoma comparing treatment with/without Filgrastim [abstract]. *Proc Ann Soc Clin Oncol* 1995;A656.
11. Ogawa M, Masaoka T, Mizoguchi H, et al. A phase II study of KRN 8601 rhG-CSF on neutropenia induced by chemotherapy for malignant lymphoma - a multi-institutional placebo controlled double-blind comparative study. *Gan To Kagaku Ryoho (Japan)*.Mar 1990;17(1):365-373.

12. Pettengell R, Gurney H, Radford JA, et al. G-CSF to prevent dose limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992;80(6):1430-1436.
13. Blanke C, Loehrer P, Einhorn L, and Nichols C. A phase II study of VP-16 plus ifosfamide plus cisplatin plus vinblastine plus bleomycin (VIP/VB) with Filgrastim for advanced stage testicular cancer [Meeting abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1994;13:723a.
14. Saxman SB, Nichols CR, Stephens AW and Einhorn LH. Pulmonary toxicity in patients with advanced germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Proc Am Soc Clin Oncol* 1995;14:A690.
15. Saxman SB, Nichols CR, Einhorn LH. Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* 1997;111(3):657-660.
16. Mathew A, Raviglione M, Nianjan U, et al. Splenectomy in patients with AIDS. *Amer J of Hem* 1989;32:184-189.
17. Zsebo KM, Yuschenkoff VN, Schiffer S, et al. Vascular endothelial cells and granulopoiesis: Interleukin-1 stimulates release of G-CSF and GM-CSF. *Blood* 1988;71:99-103.
18. Souza LM, Boone TC, Gabrilove J, et al. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. *Science* 1986;232:61-85.
19. Koeffler HP, Gasson I, Ranyard J, Souza LM, Shepard M, and Munker R. Recombinant human TNF stimulates production of granulocyte colony-stimulating factor. *Blood* 1987;70:55-59.
20. Seelentag WK, Mermoud JJ, Montesano R, and Vassalli P. Additive effects of Interleukin 1 and tumor necrosis factor-alpha on the accumulation of the three granulocyte and macrophage colony-stimulating factor mRNAs in human endothelial cells. *EMBO J* 1987;6:2261-2265.
21. Metcalf D. *The Haematopoietic colony stimulating factors*. Elsevier Sci Pub 1984;Chp 13:55-92.

22. Burgess AW and Metcalf D. Characterization of a serum factor stimulating the differentiation of myelomonocytic leukemic cells. *Int J Cancer* 1980;26:647-654.
23. Gabrilove JL, Jakubowski A, Fain K, et al. Phase 1 study of granulocyte colony-stimulating factor in patients with transitional cell carcinoma of the urothelium. *J Clin Invest* 1988;82:1454-1461.
24. Morstyn G, Souza L, Keech J, et al. Effect of granulocyte colony-stimulating factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988;26:667-672.
25. Bronchud MH, Scarffe JH, Thatcher N, et al. Phase 1/2 study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. *Br J Cancer* 1987;56:809-813.
26. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small cell lung cancer. *N Engl J Med* 1991;325:164-170.
27. Fazio MT and Glaspy JA. The impact of granulocyte colony-stimulating factor on quality of life in patients with severe chronic neutropenia. *Oncol Nurs Forum* 1991;18:1411-1414.
28. Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase 3 trial of recombinant human granulocyte colony-stimulating factor (Filgrastim) for treatment of severe chronic neutropenia. *Blood* 1993;81(10):2496-2502.
29. Welte K, Bonilla MA, Gillio AP, et al. Recombinant human G-CSF: Effects on hematopoiesis in normal and cyclophosphamide treated primates. *J Exp Med* 1987;165:941-948.
30. Duhrsen U, Villefal JL, Boyd J, et al. Effects of recombinant human granulocyte colony-stimulating factor on hematopoietic progenitor cells in cancer patients. *Blood* 1988;72:2074-2081.
31. Souza LM, Boone TC, Gabrilove J, et al. Recombinant human granulocyte colony-stimulating factor: Effects on normal and leukemic myeloid cells. *Science* 1986;232:61-65.
32. Weisbart RH, Kacena A, Schuh A, Golde DW. GM-CSF induces human neutrophil IgA-mediated phagocytosis by an IgA Fc receptor activation mechanism. *Nature* 1988;332:647-648.

33. Kitagawa S, Yuo A, Souza LM, Saito M, Milura Y, Takaku F. Recombinant human granulocyte colony-stimulating factor enhances superoxide release in human granulocytes stimulated chemotactic peptide. *Biochem Biophys Res Commun* 1987;144:1143.
34. Glaspy IA, Baldwin GC, Robertson PA, et al. Therapy for neutropenia in hairy cell leukemia with recombinant human granulocyte colony-stimulating factor. *Ann Int Med* 1988;109:789-795.
35. Yuo A, Kitagawa S, Ohsaka A, et al. Recombinant human granulocyte colony-stimulating factor as an activator of human granulocytes: potentiation of responses triggered by receptor-mediated agonists and stimulation of C3bi receptor expression and adherence. *Blood* 1989;74:2144-2149.
36. Taylor K, Jagannath S, Spitzer G, et al. Recombinant human granulocyte colony stimulating factor hastens granulocyte recovery after high-dose chemotherapy and autologous bone marrow transplantation in Hodgkin's disease. *J Clin Oncol* 1989;7:1791-1799.
37. Sheridan WP, Begley CG, Jutner CA, et al. Effect of peripheral-blood progenitor cell mobilized by Filgrastim (G-CSF) on platelet recovery after high-dose chemotherapy. *Lancet* 1992;339:640-644.
38. Masaoka T, et al. Recombinant human granulocyte colony-stimulating factor in allogeneic bone marrow transplantation. *Exp Hematol* 1989;17:1047-1050.
39. Sheridan WP, Wolf M, Lusk J. Granulocyte-colony stimulating factor and neutrophil recovery after high-dose chemotherapy and autologous bone marrow transplantation. *The Lancet II* 1989;891-895.
40. Alter B, Young N. Kostmann's Syndrome. *Aplastic Anemia - Acquired and Inherited*. 1993;22:391-394.
41. DeVries A, Peketh L, Joshua H. Leukemia and agranulocytosis in a member of a family with hereditary leukopenia. *Acta. Medica Orientalia*. 1958;17:25-32.
42. Gilman PA, Jackson DP, Guild HG. Congenital agranulocytosis: Prolonged survival and terminal acute leukemia. *Blood*. 1970;36(5):576-585.
43. Wong WY, Williams D, Slovak ML, et al. Terminal acute myelogenous leukemia in a

- patient with congenital agranulocytosis. *American Journal of Hematology*. 1993; 43:133-138.
44. Rosen RB, Kang S. Congenital agranulocytosis terminating in acute myelomonocytic leukemia. *Journal of Pediatrics*. 1979;94(3):406-408.
  45. Weetman RM, Boxer LA. Childhood neutropenia. *Pediatric Clinics of North America*. 1980;27(2):361-375.
  46. Woods WG, Roloff JS, Lukens JN, et al. The occurrence of leukemia in patients with Schwachman Syndrome. *Journal of Pediatrics*. 1981;99(3):425-428.
  47. Smith OP, Hann IM, Chessels JM, et al. Haematological abnormalities in Schwachman-Diamond syndrome. *British Journal of Haematology*. 1996;94:279-284.
  48. Mack DR, Forstner GG, Wilschanski M, et al. Schwachman Syndrome: Exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology*. 1996; 111:1593-1602.
  49. Medlock ES, Kaplan DL, Cecchini M, Ulich TR, del Castillo J, Andresen J. Granulocyte colony-stimulating factor crosses the placenta and stimulates fetal rat granulopoiesis. *Blood*. Feb 1993;81(4):916-922.
  50. Novales JS, Salva AM, Modanlou HD, Kaplan DL, del Castillo J, Andresen J, Medlock ES. Maternal administration of granulocyte colony-stimulating factor improves neonatal rat survival after a lethal group B streptococcal infection. *Blood*. Feb 1993;81(4):923-927.
  51. Calhoun DA, Rosa C, Christensen RD. Transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. *Am J Obstet Gynecol*. 1996;174(4):1306-1311.
  52. Calhoun DA, Harcum J, Christensen RD. A randomized, double-blind, placebo-controlled trial of recombinant human granulocyte colony-stimulating factor administration to women with an imminent preterm delivery. *Pediatric Research*. 1996;39(4):Abstract 1747.
  53. Calhoun DA, Christensen RD. Assessment of transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. *Journal of Investigative Medicine*. Jan 1996; 44(1):114a.

**PART III: CONSUMER INFORMATION****NEUPOGEN<sup>®</sup>**  
(filgrastim)

This leaflet is part III of a three-part "Product Monograph" published when NEUPOGEN<sup>®</sup> was approved for sale in Canada and is designed specifically for Consumers. It provides you (or your caregiver) with information and instructions on how NEUPOGEN<sup>®</sup> should be given. This leaflet is a summary and will not tell you everything about NEUPOGEN<sup>®</sup>. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What is NEUPOGEN<sup>®</sup>?**

NEUPOGEN<sup>®</sup> 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. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection.

**What is NEUPOGEN<sup>®</sup> used for?**

NEUPOGEN<sup>®</sup> is used to treat neutropenia (nu-tro-**peen**-ee-ah), a condition where the body makes too few neutrophils. 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.

**How does NEUPOGEN<sup>®</sup> work?**

NEUPOGEN<sup>®</sup> works by helping your body make more neutrophils. To make sure NEUPOGEN<sup>®</sup> 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.

**Who should not take NEUPOGEN<sup>®</sup>?**

Do not take NEUPOGEN<sup>®</sup> if you are:

- allergic to NEUPOGEN<sup>®</sup> (filgrastim) or any of its ingredients. Check below and the Product Monograph for a list of ingredients in NEUPOGEN<sup>®</sup>.
- allergic to other medicines made using the bacteria *E coli*. Ask your doctor if you are not sure.

**What is the medicinal ingredient in NEUPOGEN<sup>®</sup>?**  
filgrastim**What are the important nonmedicinal ingredients in NEUPOGEN<sup>®</sup>?**

Acetate, sorbitol, polysorbate (Tween<sup>®</sup>) 80, sodium

**What dosage forms does NEUPOGEN<sup>®</sup> come in?**

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

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

- Your spleen may become enlarged and can rupture while taking NEUPOGEN<sup>®</sup>. 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 a sickle cell disorder, make sure that you tell your doctor before you start taking NEUPOGEN<sup>®</sup> so that the potential risks and benefits can be discussed. In patients with sickle cell disorder, severe sickle cell crises have been associated with the use of NEUPOGEN<sup>®</sup>, resulting in death in some cases.

**What important information do I need to know about taking NEUPOGEN<sup>®</sup>?**

NEUPOGEN<sup>®</sup> may reduce your chance of getting an infection, but does not prevent all infections. An infection can still happen during the short time when your/your child's neutrophil levels are low. You must be alert and look for some of the 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<sup>®</sup>, tell your doctor or nurse immediately.

There is a possibility that you could have a reaction at an injection site. If there is a lump, swelling, or bruising at an injection site that does not go away, call your doctor.

If you have a sickle cell disorder, make sure that you tell your doctor before you start taking NEUPOGEN<sup>®</sup>. If you have a sickle cell crisis after getting NEUPOGEN<sup>®</sup>, tell your doctor right away.

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

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

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

**What about pregnancy or breastfeeding?**

NEUPOGEN<sup>®</sup> has not been studied in pregnant women, and its effects on unborn babies are not known. If you take NEUPOGEN<sup>®</sup> 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<sup>®</sup> can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast feeding, you should tell your doctor before using NEUPOGEN<sup>®</sup>.

### INTERACTIONS WITH THIS MEDICATION

Drug interactions between NEUPOGEN<sup>®</sup> 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<sup>®</sup>.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

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

#### Overdose:

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

#### Missed Dose:

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

### How to prepare and give a NEUPOGEN<sup>®</sup> injection

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

NEUPOGEN<sup>®</sup> is available as a liquid in vials. When you receive your NEUPOGEN<sup>®</sup>, always check to see that:

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

#### If you are using vials of NEUPOGEN<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>.

**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 of NEUPOGEN<sup>®</sup> from the refrigerator. Allow NEUPOGEN<sup>®</sup> to reach room temperature (this takes about 30 minutes). Vials should be used only once. **DO NOT SHAKE THE VIAL.** Shaking may damage the NEUPOGEN<sup>®</sup>. If the vial 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<sup>®</sup> vial and sterile disposable syringe and needle:



- Two alcohol swabs and one cotton ball or gauze pad

#### Alcohol Swabs



#### Cotton Ball



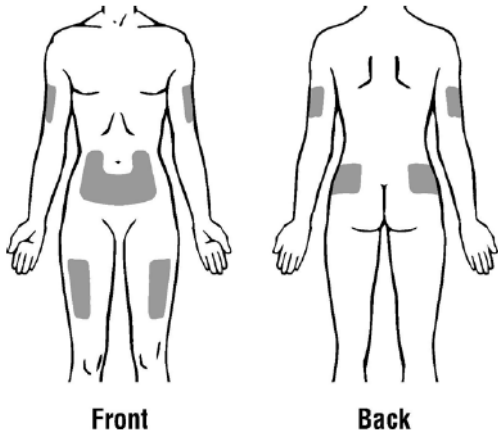
- Puncture-proof disposal container

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



#### Selecting and preparing the injection site

- Choose an injection site. Four recommended injection sites for NEUPOGEN<sup>®</sup> 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



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

- 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<sup>®</sup> IN VIALS

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

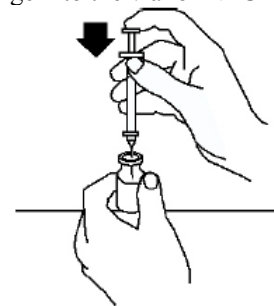


- Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.

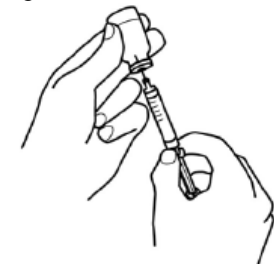
- Pull the needle cover straight off the syringe. Then, pull back the plunger and draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of NEUPOGEN<sup>®</sup> that your doctor prescribed.



- 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.
- Push the plunger of the syringe down and inject the air from the syringe into the vial of NEUPOGEN<sup>®</sup>.



- Keeping the needle in the vial, turn the vial upside down. Make sure that the NEUPOGEN<sup>®</sup> liquid is covering the tip of the needle.

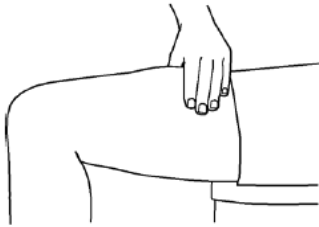


- Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with NEUPOGEN<sup>®</sup> liquid to the number (mL or cc) that matches the dose your doctor prescribed.
- Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the 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.

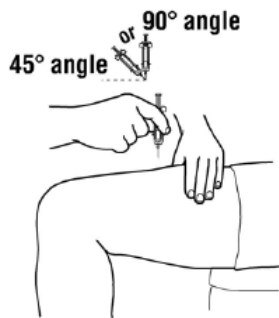
9. Keeping the tip of the needle in the liquid, once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of NEUPOGEN<sup>®</sup>. If there are still air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

### Injecting the dose of NEUPOGEN<sup>®</sup>

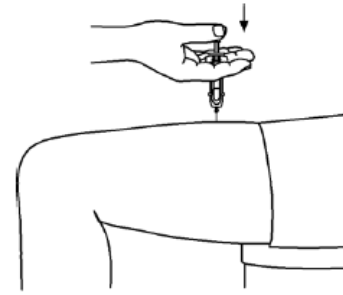
1. Slowly remove the syringe and needle from the vial.
2. Hold the syringe in the hand you will use to inject NEUPOGEN<sup>®</sup>. Use the other hand to pinch a fold of skin at the cleaned injection site.



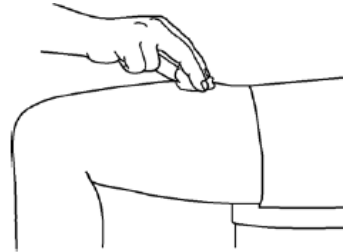
3. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



4. After the needle is inserted, let go of the skin. Pull the plunger back slightly. **If blood comes into the syringe, do not inject NEUPOGEN<sup>®</sup>, because the needle has entered a blood vessel.** Withdraw the syringe and discard it in the puncture-proof container. Repeat the steps to prepare a new syringe and choose and clean a new injection site. Remember to check again for blood before injecting NEUPOGEN<sup>®</sup>. If no blood appears, slowly push down on the plunger all the way, until all the NEUPOGEN<sup>®</sup> is injected.



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 a syringe, needle and vial only once. **DO NOT** put the needle cover (the cap) back on the needle. Discard the vial with any remaining NEUPOGEN<sup>®</sup> liquid.

### Disposal of syringes, needles and vials

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes, needles and vials. 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.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

#### What are possible serious side effects of NEUPOGEN<sup>®</sup>?

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking NEUPOGEN<sup>®</sup>. 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 your or your child's spleen is enlarged or ruptured.

- **Serious Allergic Reactions.** NEUPOGEN<sup>®</sup> 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<sup>®</sup> and call your doctor or seek emergency care right away. If you or your child has an allergic reaction during the injection of NEUPOGEN<sup>®</sup>, 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.

**What are the most common side effects of NEUPOGEN<sup>®</sup>?**

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-aspirin 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<sup>®</sup>, 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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
		Talk with your doctor or pharmacist	
Rare ≥ 0.01% and < 0.1%	<ul style="list-style-type: none"> <li>• 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)</li> <li>• Acute respiratory distress syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs).</li> </ul>		T
Very Rare <0.01%	<ul style="list-style-type: none"> <li>• Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder)</li> </ul>		T

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Very Common ≥ 10%	<ul style="list-style-type: none"> <li>• Bone Pain</li> </ul>		T

*This is not a complete list of side effects. For any unexpected effects while taking NEUPOGEN<sup>®</sup>, contact your doctor or pharmacist.*

**HOW TO STORE IT**

**How should NEUPOGEN<sup>®</sup> be stored?**

NEUPOGEN<sup>®</sup> should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Avoid shaking NEUPOGEN<sup>®</sup>. If NEUPOGEN<sup>®</sup> 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<sup>®</sup> can be left out at room temperature for up to 24 hours. Do not leave NEUPOGEN<sup>®</sup> in direct sunlight. If you have any questions about storage or how

to carry NEUPOGEN<sup>®</sup> when you travel, contact your doctor, nurse, or pharmacist.

#### **REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online:	<a href="http://www.healthcanada.gc.ca/medeffect">www.healthcanada.gc.ca/medeffect</a>
Toll-free telephone:	1-866-234-2345
Toll-free fax:	1-866-678-6789
Postage Paid Mail:	Canada Vigilance Program Health Canada AL 0701C Ottawa ON K1A 0K9

***NOTE: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.***

#### **MORE INFORMATION**

A copy of this document plus the full product monograph, prepared for health professionals, can be attained by contacting the sponsor, Amgen Canada Inc., at: 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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