| | | Amgen-sponsored Study 1 N = 13 | Amgen-sponsored Study 2 N = 22 | Amgen-sponsored Study 3 N = 27 | Non-Amgen-sponsored Study N = 39 |
|---|---|---|---|---|---|
| Median PBPC/kg Collected | MNC | $9.5 \times 10^8$ | $9.5 \times 10^8$ | $8.1 \times 10^8$ | $10.3 \times 10^8$ |
| | $CD34^+$ | n/a | $3.1 \times 10^6$ | $2.8 \times 10^6$ | $6.2 \times 10^6$ |
| | GFU-GM | $63.9 \times 10^4$ | $25.3 \times 10^4$ | $32.6 \times 10^4$ | n/a |
| Days to ANC ≥ 500/mm$^3$ | Median | 9 | 10 | 11 | 10 |
| | Range | 8 - 10 | 8 - 15 | 9 - 38 | 7 - 40 |
| Days to Plt. ≥ 20,000/mm$^3$ | Median | 10 | 12.5 | 16 | 15.5 |
| | Range | 7 - 16 | 10 - 30 | 8 - 52 | 7 - 63 |

n/a = not available

Three of the 101 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm$^3$ by day 28. In clinical trials of NEUPOGEN® for the mobilization of PBPC, NEUPOGEN® was administered to patients at 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm$^3$) was reached. The rate of engraftment of these cells in the absence of NEUPOGEN® posttransplantation has not been studied.

***Patients With Severe Chronic Neutropenia***

Severe chronic neutropenia (SCN) (idiopathic, cyclic, and congenital) is characterized by a selective decrease in the number of circulating neutrophils and an enhanced susceptibility to bacterial infections.

The daily administration of NEUPOGEN® has been shown to be safe and effective in causing a sustained increase in the neutrophil count and a decrease in infectious morbidity in children and adults with the clinical syndrome of SCN.[16] In the phase 3 trial, summarized in the following table, daily treatment with NEUPOGEN® resulted in significant beneficial changes in the incidence and duration of infection, fever, antibiotic use, and oropharyngeal ulcers. In this trial, 120 patients with a median age of 12 years (range 1 to 76 years) were treated.

| Overall Significant Changes in Clinical Endpoints Median Incidence[a] (events) or Duration (days) per 28-day Period | | | |
|---|---|---|---|
| | Control Patients[b] | NEUPOGEN® -treated Patients | p-value |
| Incidence of Infection | 0.50 | 0.20 | < 0.001 |
| Incidence of Fever | 0.25 | 0.20 | < 0.001 |
| Duration of Fever | 0.63 | 0.20 | 0.005 |
| Incidence of Oropharyngeal Ulcers | 0.26 | 0.00 | < 0.001 |
| Incidence of Antibiotic Use | 0.49 | 0.20 | < 0.001 |

[a] Incidence values were calculated for each patient, and are defined as the total number of events experienced divided by the number of 28-day periods of exposure (on-study). Median incidence values were then reported for each patient group.

[b] Control patients were observed for a 4-month period.

The incidence for each of these 5 clinical parameters was lower in the NEUPOGEN® arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. All 3 diagnostic groups showed favorable trends in favor of treatment. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although NEUPOGEN® substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

As a result of the lower incidence and duration of infections, there was also a lower number of episodes of hospitalization (28 hospitalizations in 62 patients in the treated group vs 44 hospitalizations in 60 patients in the control group over a 4-month period [p = 0.0034]). Patients treated with NEUPOGEN® also reported a lower number of episodes of diarrhea, nausea, fatigue, and sore throat.

In the phase 3 trial, untreated patients had a median ANC of 210/mm$^3$ (range 0 to 1550/mm$^3$). NEUPOGEN® therapy was adjusted to maintain the median ANC between 1500 and 10,000/mm$^3$. Overall, the response to NEUPOGEN® was observed in 1 to 2 weeks. The median ANC after 5 months of NEUPOGEN® therapy for all patients was 7460/mm$^3$ (range 30 to 30,880/mm$^3$). NEUPOGEN® dosing requirements were generally higher for patients with congenital neutropenia (2.3 to 40 mcg/kg/day) than for patients with idiopathic (0.6 to 11.5 mcg/kg/day) or cyclic (0.5 to 6 mcg/kg/day) neutropenia.

## INDICATIONS AND USAGE

### *Cancer Patients Receiving Myelosuppressive Chemotherapy*

NEUPOGEN® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (see CLINICAL EXPERIENCE). A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week (see LABORATORY MONITORING) 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 ≥ 10,000/mm$^3$ after the expected chemotherapy-induced nadir.

### *Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy*

NEUPOGEN® is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

### *Cancer Patients Receiving Bone Marrow Transplant*

NEUPOGEN® is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation (see CLINICAL EXPERIENCE). It is recommended that CBCs and platelet counts be obtained at a minimum of 3 times per week (see LABORATORY MONITORING) following marrow infusion to monitor the recovery of marrow reconstitution.

***Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy***

NEUPOGEN® is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care (see CLINICAL EXPERIENCE).

***Patients With Severe Chronic Neutropenia***

NEUPOGEN® is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (see CLINICAL EXPERIENCE). It is essential that serial CBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of NEUPOGEN® therapy (see WARNINGS). The use of NEUPOGEN® prior to confirmation of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

## CONTRAINDICATIONS

NEUPOGEN® is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, Filgrastim, or any component of the product.

## WARNINGS

***Allergic Reactions***

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with NEUPOGEN®. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving NEUPOGEN® IV. 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.

***SPLENIC RUPTURE***

**RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF COLONY-STIMULATING FACTORS, INCLUDING NEUPOGEN®, FOR PERIPHERAL BLOOD PROGENITOR CELL (PBPC) MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. INDIVIDUALS RECEIVING NEUPOGEN® WHO REPORT ABDOMINAL OR SHOULDER TIP PAIN, PARTICULARLY HEALTHY DONORS RECEIVING NEUPOGEN® FOR PBPC MOBILIZATION, SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.**

### *Adult Respiratory Distress Syndrome (ARDS)*

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

### *Sickle Cell Disease*

Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/β+ thalassemia) who received NEUPOGEN® for PBPC mobilization or following chemotherapy. One of these cases was fatal. NEUPOGEN® should be used with caution in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits. Patients with sickle cell disease who receive NEUPOGEN® should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crisis, supportive care should be administered, and interventions to ameliorate the underlying event, such as therapeutic red blood cell exchange transfusion, should be considered.

### *Patients With Severe Chronic Neutropenia*

The safety and efficacy of NEUPOGEN® in the treatment of neutropenia due to other hematopoietic disorders (eg, myelodysplastic syndrome [MDS]) have not been established. Care should be taken to confirm the diagnosis of SCN before initiating NEUPOGEN® therapy.

MDS and AML have been reported to occur in the natural history of congenital neutropenia without cytokine therapy.[17] Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with NEUPOGEN® for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia (see ADVERSE REACTIONS). Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of NEUPOGEN® on the development of abnormal cytogenetics and the effect of continued NEUPOGEN® administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing NEUPOGEN® should be carefully considered.

## PRECAUTIONS

### General

### Simultaneous Use With Chemotherapy and Radiation Therapy

The safety and efficacy of NEUPOGEN® given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use NEUPOGEN® in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION).

The efficacy of NEUPOGEN® has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelosuppressive doses of antimetabolites such as 5-fluorouracil.

The safety and efficacy of NEUPOGEN® have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of NEUPOGEN® with chemotherapy and radiation therapy should be avoided.

**Potential Effect on Malignant Cells**

NEUPOGEN® is a growth factor that primarily stimulates neutrophils. However, the possibility that NEUPOGEN® can act as a growth factor for any tumor type cannot be excluded. In a randomized study evaluating the effects of NEUPOGEN® versus placebo in patients undergoing remission induction for AML, there was no significant difference in remission rate, disease-free, or overall survival (see CLINICAL EXPERIENCE).

The safety of NEUPOGEN® in chronic myeloid leukemia (CML) and myelodysplasia has not been established.

When NEUPOGEN® is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well-studied, and the limited data available are inconclusive.

**Leukocytosis**

***Cancer Patients Receiving Myelosuppressive Chemotherapy***

White blood cell counts of 100,000/mm$^3$ or greater were observed in approximately 2% of patients receiving NEUPOGEN® at doses above 5 mcg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a CBC is recommended twice per week during NEUPOGEN® therapy (see LABORATORY MONITORING).

**Premature Discontinuation of NEUPOGEN® Therapy**

***Cancer Patients Receiving Myelosuppressive Chemotherapy***

A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of NEUPOGEN® therapy. However, for a sustained therapeutic response, NEUPOGEN® therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm$^3$. Therefore, the premature discontinuation of NEUPOGEN® therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see DOSAGE AND ADMINISTRATION).

***Immunogenicity***

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

several factors including timing of sampling, sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to NEUPOGEN® with the incidence of antibodies to other products may be misleading.

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

**Other**

In studies of NEUPOGEN® administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). Because of the potential of receiving higher doses of chemotherapy (ie, full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and nonhematologic 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. Furthermore, care should be exercised in the administration of NEUPOGEN® in conjunction with other drugs known to lower the platelet count.

There have been rare reports (< 1 in 7000 patients) of cutaneous vasculitis in patients treated with NEUPOGEN®. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term NEUPOGEN® therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue NEUPOGEN® at a reduced dose.

**Information for Patients and Caregivers**

Patients should be referred to the "Information for Patients and Caregivers" labeling included with the package insert in each dispensing pack of NEUPOGEN® vials or NEUPOGEN® prefilled syringes. The "Information for Patients and Caregivers" labeling provides information about neutrophils and neutropenia and the safety and efficacy of NEUPOGEN®. It is not intended to be a disclosure of all known or possible effects.

**Laboratory Monitoring**

***Cancer Patients Receiving Myelosuppressive Chemotherapy***

A CBC and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during NEUPOGEN® therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when NEUPOGEN® was administered, and 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 Bone Marrow Transplant***

Frequent CBCs and platelet counts are recommended (at least 3 times per week) following marrow transplantation.

***Patients With Severe Chronic Neutropenia***

During the initial 4 weeks of NEUPOGEN® therapy and during the 2 weeks following any dose adjustment, a CBC with differential and platelet count should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet count should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular CBCs (ie, as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment (see WARNINGS, ADVERSE REACTIONS).

In clinical trials, the following laboratory results were observed:

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

**Drug Interaction**

Drug interactions between NEUPOGEN® and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

**Pregnancy Category C**

NEUPOGEN® has been shown to have adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose. Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of NEUPOGEN® on the developing fetus or the reproductive capacity of the mother is unknown. However, the scientific literature describes transplacental passage of NEUPOGEN® when administered to pregnant rats during the latter part of gestation[18] and apparent transplacental passage of NEUPOGEN®

when administered to pregnant humans by ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation).[19] NEUPOGEN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

**Nursing Mothers**

It is not known whether NEUPOGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if NEUPOGEN® is administered to a nursing woman.

**Pediatric Use**

In a phase 3 study to assess the safety and efficacy of NEUPOGEN® in the treatment of SCN, 120 patients with a median age of 12 years were studied. Of the 120 patients, 12 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). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 531 patients in the surveillance study as of 31 December 1997, 32 were infants, 200 were children, and 68 were adolescents (see CLINICAL EXPERIENCE, INDICATIONS AND USAGE, LABORATORY MONITORING, DOSAGE AND ADMINISTRATION).

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic NEUPOGEN® treatment. The relationship of these events to NEUPOGEN® administration is unknown (see WARNINGS, ADVERSE REACTIONS).

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of NEUPOGEN® treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

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