In the cancer setting, 12 pediatric patients with neuroblastoma have received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with NEUPOGEN®; in this population, NEUPOGEN® was well-tolerated. There was one report of palpable splenomegaly associated with NEUPOGEN® therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo controlled trials of NEUPOGEN® use following myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in the responses between elderly and younger patients.

Clinical studies of NEUPOGEN® in other approved indications (ie, bone marrow transplant recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

ADVERSE REACTIONS

Cancer Patients Receiving Myelosuppressive Chemotherapy

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

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

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

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

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27% to 58% of 98 patients receiving blinded NEUPOGEN® therapy following cytotoxic chemotherapy; increases were generally mild-to-moderate. Transient decreases in blood pressure (< 90/60 mmHg), which did not require clinical treatment, were reported in 7 of 176 patients in phase 3 clinical studies following administration of NEUPOGEN®. Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11 of 375 cancer patients receiving NEUPOGEN® in clinical studies; the relationship to NEUPOGEN® therapy is unknown. No evidence of interaction of NEUPOGEN® with other drugs was observed in the course of clinical trials (see PRECAUTIONS).

There has been no evidence for the development of antibodies or of a blunted or diminished response to NEUPOGEN® in treated patients, including those receiving NEUPOGEN® daily for almost 2 years.

Patients With Acute Myeloid Leukemia

In a randomized phase 3 clinical trial, 259 patients received NEUPOGEN® and 262 patients received placebo postchemotherapy. Overall, the frequency of all reported adverse events was similar in both the NEUPOGEN® and placebo groups (83% vs 82% in

Induction 1; 61% vs 64% in Consolidation 1). Adverse events reported more frequently in the NEUPOGEN®-treated group included: petechiae (17% vs 14%), epistaxis (9% vs 5%), and transfusion reactions (10% vs 5%). There were no significant differences in the frequency of these events.

There were a similar number of deaths in each treatment group during induction (25 NEUPOGEN® vs 27 placebo). The primary causes of death included infection (9 vs 18), persistent leukemia (7 vs 5), and hemorrhage (6 vs 3). Of the hemorrhagic deaths, 5 cerebral hemorrhages were reported in the NEUPOGEN® group and one in the placebo group. Other serious nonfatal hemorrhagic events were reported in the respiratory tract (4 vs 1), skin (4 vs 4), gastrointestinal tract (2 vs 2), urinary tract (1 vs 1), ocular (1 vs 0), and other nonspecific sites (2 vs 1). While 19 (7%) patients in the NEUPOGEN® group and 5 (2%) patients in the placebo group experienced severe or fatal hemorrhagic events, overall, hemorrhagic adverse events were reported at a similar frequency in both groups (40% vs 38%). The time to transfusion-independent platelet recovery and the number of days of platelet transfusions were similar in both groups.

Cancer Patients Receiving Bone Marrow Transplant

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

Generally, adverse events observed in nonrandomized studies were similar to those seen in randomized studies, occurred in a minority of patients, and were of mild-to-moderate severity. In one study (n = 45), 3 serious adverse events reported by the investigator were considered possibly related to NEUPOGEN®. These included 2 events of renal insufficiency and one event of capillary leak syndrome. The relationship of these events to NEUPOGEN® remains unclear since they occurred in patients with culture-proven infection with clinical sepsis who were receiving potentially nephrotoxic antibacterial and antifungal therapy.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy

In clinical trials, 126 patients received NEUPOGEN® for PBPC mobilization. In this setting, NEUPOGEN® was generally well-tolerated. Adverse events related to NEUPOGEN® consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (33%). Headache was reported related to NEUPOGEN® in 7% of patients. Transient increases in alkaline phosphatase related to NEUPOGEN® were reported in 21% of the patients who had serum chemistries measured; most were mild-to-moderate.

All patients had increases in neutrophil counts during mobilization, consistent with the biological effects of NEUPOGEN®. Two patients had a WBC count > 100,000/mm^3. No 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; 5 patients (out of 126) had decreased platelet counts to < 50,000/mm^3. Anemia and thrombocytopenia have been reported to be related to leukapheresis; however, the possibility that NEUPOGEN® mobilization may contribute to anemia or thrombocytopenia has not been ruled out.

Patients With Severe Chronic Neutropenia

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with non-narcotic analgesics. Generalized musculoskeletal pain was also noted in higher frequency in patients treated with NEUPOGEN®. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently, and thrombocytopenia (< 50,000/mm^3) was noted in 12% of patients with palpable spleens. Fewer than 3% of all patients underwent splenectomy, and most of these had a prestudy history of splenomegaly. Fewer than 6% of patients had thrombocytopenia (< 50,000/mm^3) during NEUPOGEN® therapy, most of whom had a pre-existing history of thrombocytopenia. In most cases, thrombocytopenia was managed by NEUPOGEN® dose reduction or interruption. An additional 5% of patients had platelet counts between 50,000 to 100,000/mm^3. There were no associated serious hemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with NEUPOGEN®, but was associated with thrombocytopenia in 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. Other adverse events infrequently observed and possibly related to NEUPOGEN® therapy were: injection site reaction, rash, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of some pre-existing skin disorders (eg, psoriasis).

Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with NEUPOGEN® for SCN (see WARNINGS, PRECAUTIONS: Pediatric Use). As of 31 December 1997, data were available from a postmarketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years. Based on analysis of these data, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. A life-table analysis of these data revealed that the cumulative risk of developing leukemia or MDS by the end of the 8th year of NEUPOGEN® treatment in a patient with congenital neutropenia was 16.5 % (95% C.I. = 9.8%, 23.3%); this represents an annual rate of approximately 2%. Cytogenetic abnormalities, most commonly involving chromosome 7, have been reported in patients treated with NEUPOGEN® who had previously documented normal cytogenetics. It is unknown whether the development of cytogenetic abnormalities, MDS, or AML is related to chronic daily NEUPOGEN® administration or to the natural history of congenital neutropenia. It is also unknown if the rate of conversion in patients who have not received NEUPOGEN® is different from that of patients who have received NEUPOGEN®. Routine monitoring through regular CBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see LABORATORY MONITORING).

OVERDOSAGE

In cancer patients receiving NEUPOGEN® as an adjunct to myelosuppressive chemotherapy, it is recommended, to avoid the potential risks of excessive leukocytosis, that NEUPOGEN® therapy be discontinued if the ANC surpasses 10,000/mm^3 after the

chemotherapy-induced ANC nadir has occurred. Doses of NEUPOGEN® that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit.

The maximum tolerated dose of NEUPOGEN® has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg/day in the phase 3 study of nonmyeloablative chemotherapy. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

In NEUPOGEN® clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

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

DOSAGE AND ADMINISTRATION

NEUPOGEN® is supplied in either vials or in prefilled syringes with UltraSafe® Needle Guards. Following administration of NEUPOGEN® from the prefilled syringe, the UltraSafe® Needle Guard should be activated to prevent accidental needle sticks. To activate the UltraSafe® Needle Guard, place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.** The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

Cancer Patients Receiving Myelosuppressive Chemotherapy

The recommended starting dose of NEUPOGEN® is 5 mcg/kg/day, administered as a single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. A CBC and platelet count should be obtained before instituting NEUPOGEN® therapy, and monitored twice weekly during therapy. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir.

NEUPOGEN® should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. NEUPOGEN® should not be administered in the period 24 hours before the administration of chemotherapy (see PRECAUTIONS). NEUPOGEN® should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of NEUPOGEN® therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. NEUPOGEN® therapy should be discontinued if the ANC surpasses 10,000/mm^3 after the expected chemotherapy-induced neutrophil nadir (see PRECAUTIONS). In phase 3 trials, efficacy was observed at doses of 4 to 8 mcg/kg/day.

Cancer Patients Receiving Bone Marrow Transplant

The recommended dose of NEUPOGEN® following BMT is 10 mcg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion. For patients receiving

BMT, the first dose of NEUPOGEN® should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

During the period of neutrophil recovery, the daily dose of NEUPOGEN® should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count	NEUPOGEN® Dose Adjustment
When ANC > 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
then: If ANC remains > 1000/mm^3 for 3 more consecutive days	Discontinue NEUPOGEN®
then: If ANC decreases to < 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to < 1000/mm^3 at any time during the 5 mcg/kg/day administration, NEUPOGEN® should be increased to 10 mcg/kg/day, and the above steps should then be followed.

Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients

The recommended dose of NEUPOGEN® for the mobilization of PBPC is 10 mcg/kg/day SC, either as a bolus or a continuous infusion. It is recommended that NEUPOGEN® be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of NEUPOGEN® administration and leukapheresis schedule have not been established, administration of NEUPOGEN® for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective (see CLINICAL EXPERIENCE for schedules used in clinical trials). Neutrophil counts should be monitored after 4 days of NEUPOGEN®, and NEUPOGEN® dose modification should be considered for those patients who develop a WBC count > 100,000/mm^3.

In all clinical trials of NEUPOGEN® for the mobilization of PBPC, NEUPOGEN® was also administered after reinfusion of the collected cells (see CLINICAL EXPERIENCE).

Patients With Severe Chronic Neutropenia

NEUPOGEN® should be administered to those patients in whom a diagnosis of congenital, cyclic, or idiopathic neutropenia has been definitively confirmed. Other diseases associated with neutropenia should be ruled out.

Starting Dose:
Congenital Neutropenia: The recommended daily starting dose is 6 mcg/kg BID SC every day.

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 mcg/kg as a single injection SC every day.

Dose Adjustments:
Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patients' clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of NEUPOGEN® were: 6.0 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg

(idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of NEUPOGEN® ≥ 100 mcg/kg/day.

Dilution

If required, NEUPOGEN® may be diluted in 5% dextrose. NEUPOGEN® diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), NEUPOGEN® is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes.

Dilution of NEUPOGEN® to a final concentration of less than 5 mcg/mL is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

Storage

NEUPOGEN® should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe 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; if particulates or discoloration are observed, the container should not be used.

HOW SUPPLIED

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

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

Vials

Single-dose, preservative-free vials containing 300 mcg (1 mL) of Filgrastim (300 mcg/mL). Dispensing packs of 10 (NDC 55513-530-10).

Single-dose, preservative-free vials containing 480 mcg (1.6 mL) of Filgrastim (300 mcg/mL). Dispensing packs of 10 (NDC 55513-546-10).

Prefilled Syringes (SingleJect®)

Single-dose, preservative-free, prefilled syringes with 27 gauge, ½ inch needles with an UltraSafe® Needle Guard, containing 300 mcg (0.5 mL) of Filgrastim (600 mcg/mL). Dispensing packs of 10 (NDC 55513-924-10).

Single-dose, preservative-free, prefilled syringes with 27 gauge, ½ inch needles with an UltraSafe® Needle Guard, containing 480 mcg (0.8 mL) of Filgrastim (600 mcg/mL). Dispensing packs of 10 (NDC 55513-209-10).

NEUPOGEN® should be stored at 2° to 8°C (36° to 46°F). Avoid shaking.

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