NEUPOGEN® (Filgrastim)

DESCRIPTION

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, which has been selected as the name for recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF).

NEUPOGEN® is a 175 amino acid protein manufactured by recombinant DNA technology.[1] NEUPOGEN® is produced by *Escherichia coli* (*E coli*) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. NEUPOGEN® 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 NEUPOGEN® is produced in *E coli*, the product is nonglycosylated and thus differs from G-CSF isolated from a human cell.

NEUPOGEN® is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing Filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single use vials and prefilled syringes. The single use vials contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 1.0 mL or 1.6 mL, respectively. The single use prefilled syringes contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 0.5 mL or 0.8 mL, respectively. See table below for product composition of each single use vial or prefilled syringe.

	300 mcg/ 1.0 mL Vial	480 mcg/ 1.6 mL Vial	300 mcg/ 0.5 mL Syringe	480 mcg/ 0.8 mL Syringe
Filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
Acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
Sorbitol	50.0 mg	80.0 mg	25.0 mg	40.0 mg
Tween® 80	0.004%	0.004%	0.004%	0.004%
Sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg
Water for Injection USP q.s. ad	1.0 mL	1.6 mL	0.5 mL	0.8 mL

CLINICAL PHARMACOLOGY

Colony-stimulating Factors

Colony-stimulating factors are glycoproteins which act on hematopoietic 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 which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation,[2,3] differentiation,[2,4] and selected end-cell functional activation (including enhanced phagocytic ability,[5] priming of the cellular metabolism associated with respiratory burst,[6] antibody dependent killing,[7] and the increased expression of some functions associated

with cell surface antigens[8]). G-CSF is not species specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage.

Preclinical Experience

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a preclinical toxicology program which included single-dose acute, repeated-dose subacute, subchronic, and chronic studies. Single-dose administration of Filgrastim by the oral, intravenous (IV), subcutaneous (SC), or intraperitoneal (IP) routes resulted in no significant toxicity in mice, rats, hamsters, or monkeys. Although no deaths were observed in mice, rats, or monkeys at dose levels up to 3450 mcg/kg or in hamsters using single doses up to approximately 860 mcg/kg, deaths were observed in a subchronic (13-week) study in monkeys. In this study, evidence of neurological symptoms was seen in monkeys treated with doses of Filgrastim greater than 1150 mcg/kg/day for up to 18 days. Deaths were seen in 5 of the 8 treated animals and were associated with 15- to 28-fold increases in peripheral leukocyte counts, and neutrophil-infiltrated hemorrhagic foci were seen in both the cerebrum and cerebellum. In contrast, no monkeys died following 13 weeks of daily IV administration of Filgrastim at a dose level of 115 mcg/kg. In an ensuing 52-week study, one 115 mcg/kg dosed female monkey died after 18 weeks of daily IV administration of Filgrastim. Death was attributed to cardiopulmonary insufficiency.

In subacute, repeated-dose studies, changes observed were attributable to the expected pharmacological actions of Filgrastim (ie, dose-dependent increases in white cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). In all species, histopathologic examination 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. A dose-dependent increase in serum alkaline phosphatase was observed in rats, and may reflect increased activity of osteoblasts and osteoclasts. Changes in serum chemistry values were reversible following discontinuation of treatment.

In rats treated at doses of 1150 mcg/kg/day for 4 weeks (5 of 32 animals) and for 13 weeks at doses of 100 mcg/kg/day (4 of 32 animals) and 500 mcg/kg/day (6 of 32 animals), articular swelling of the hind legs was observed. Some degree of hind leg dysfunction was also observed; however, symptoms reversed following cessation of dosing. In rats, osteoclasis and osteoanagenesis were found in the femur, humerus, coccyx, and hind legs (where they were accompanied by synovitis) after IV treatment for 4 weeks (115 to 1150 mcg/kg/day), and in the sternum after IV treatment for 13 weeks (115 to 575 mcg/kg/day). These effects reversed to normal within 4 to 5 weeks following cessation of treatment.

In the 52-week chronic, repeated-dose studies performed in rats (IP injection up to 57.5 mcg/kg/day), and cynomolgus monkeys (IV injection of up to 115 mcg/kg/day), changes observed were similar to those noted in the subacute studies. Expected pharmacological actions of Filgrastim included dose-dependent increases in white cell counts, increased circulating segmented neutrophils and alkaline phosphatase levels, and increased myeloid:erythroid ratios in the bone marrow. Decreases in platelet counts were also noted in primates. In no animals tested were hemorrhagic complications observed. Rats displayed dose-related swelling of the hind limb, accompanied by some degree of hind limb dysfunction; osteopathy was noted microscopically. Enlarged spleens (both

species) and livers (monkeys), reflective of ongoing extramedullary granulopoiesis, as well as myeloid hyperplasia of the bone marrow, were observed in a dose-dependent manner.

Pharmacologic Effects of NEUPOGEN®

In phase 1 studies involving 96 patients with various nonmyeloid malignancies, NEUPOGEN® administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day.[9-11] This increase in neutrophil counts was observed whether NEUPOGEN® was administered IV (1 to 70 mcg/kg twice daily),[9] SC (1 to 3 mcg/kg once daily),[11] or by continuous SC infusion (3 to 11 mcg/kg/day).[10] With discontinuation of NEUPOGEN® therapy, neutrophil counts returned to baseline, in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine [fMLP] as the chemotaxin) activity in vitro.

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

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier 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® 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 IV infusion of 20 mcg/kg of NEUPOGEN® over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively. Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. The volume of distribution averaged 150 mL/kg in both normal subjects and cancer patients. The elimination half-life, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of NEUPOGEN® were approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily IV doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for IV administration (231 minutes, following doses of 34.5 mcg/kg) and for SC administration (210 minutes, following NEUPOGEN® doses of 3.45 mcg/kg). Continuous 24-hour IV infusions of 20 mcg/kg over an 11- to 20-day period produced steady-state serum concentrations of NEUPOGEN® with no evidence of drug accumulation over the time period investigated.

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

CLINICAL EXPERIENCE

Cancer Patients Receiving Myelosuppressive Chemotherapy

NEUPOGEN® has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens. In a phase 3 clinical trial in small cell lung cancer, patients received SC administration of NEUPOGEN® (4 to 8 mcg/kg/day, days 4 to 17) or placebo. In this study, the benefits of NEUPOGEN® therapy were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased IV antibiotic usage. No difference in survival or disease progression was demonstrated.

In the phase 3, randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer, patients were randomized to receive NEUPOGEN® (n = 99) or placebo (n = 111) starting on day 4, after receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide. A total of 210 patients were evaluated for efficacy and 207 evaluated for safety. Treatment with NEUPOGEN® resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia; the incidence of at least one infection over all cycles of chemotherapy was 76% (84/111) for placebo-treated patients, versus 40% (40/99) for NEUPOGEN®-treated patients ($p < 0.001$). The following secondary analyses were also performed. The requirements for in-patient hospitalization and antibiotic use were also significantly decreased during the first cycle of chemotherapy; incidence of hospitalization was 69% (77/111) for placebo-treated patients in cycle 1, versus 52% (51/99) for NEUPOGEN®-treated patients ($p = 0.032$). The incidence of IV antibiotic usage was 60% (67/111) for placebo-treated patients in cycle 1, versus 38% (38/99) for NEUPOGEN®-treated patients ($p = 0.003$). The incidence, severity, and duration of severe neutropenia (absolute neutrophil count [ANC] < 500/mm^3) following chemotherapy were all significantly reduced. The incidence of severe neutropenia in cycle 1 was 84% (83/99) for patients receiving NEUPOGEN® versus 96% (106/110) for patients receiving placebo ($p = 0.004$). Over all cycles, patients randomized to NEUPOGEN® had a 57% (286/500 cycles) rate of severe neutropenia versus 77% (416/543 cycles) for patients randomized to placebo. The median duration of severe neutropenia in cycle 1 was reduced from 6 days (range 0 to 10 days) for patients receiving placebo to 2 days (range 0 to 9 days) for patients receiving NEUPOGEN® ($p < 0.001$). The mean duration of neutropenia in cycle 1 was 5.64 ± 2.27 days for patients receiving placebo versus 2.44 ± 1.90 days for patients receiving NEUPOGEN®. Over all cycles, the median duration of neutropenia was 3 days for patients randomized to placebo versus 1 day for patients randomized to NEUPOGEN®. The median severity of neutropenia (as measured by ANC nadir) was 72/mm^3 (range 0/mm^3 to 7912/mm^3) in cycle 1 for patients receiving NEUPOGEN® versus 38/mm^3 (range 0/mm^3 to 9520/mm^3) for patients receiving placebo ($p = 0.012$). The mean severity of neutropenia in cycle 1 was 496/mm^3 ± 1382/mm^3 for patients receiving NEUPOGEN® versus 204/mm^3 ± 953/mm^3 for patients receiving placebo. Over all cycles, the ANC nadir for patients randomized to NEUPOGEN® was 403/mm^3, versus 161/mm^3 for patients randomized to placebo. Administration of NEUPOGEN® resulted in an earlier ANC nadir following chemotherapy than was experienced by patients receiving placebo (day 10 vs day 12). NEUPOGEN® was well-tolerated when given SC daily at doses of 4 to 8 mcg/kg for up to 14 consecutive days following each cycle of chemotherapy (see ADVERSE REACTIONS).

Several other phase 1/2 studies, which did not directly measure the incidence of infection, but which did measure increases in neutrophils, support the efficacy of NEUPOGEN®. The regimens are presented to provide some background on the clinical experience with NEUPOGEN®. No claim regarding the safety or efficacy of the chemotherapy regimens is made. The effects of NEUPOGEN® on tumor growth or on the anti-tumor activity of the chemotherapy were not assessed. The doses of NEUPOGEN® used in these studies are considerably greater than those found to be effective in the phase 3 study described above. Such phase 1/2 studies are summarized in the following table.

Type of Malignancy	Regimen	Chemotherapy Dose	No. Pts.	Trial Phase	NEUPOGEN® Daily Dosage[a]
Small Cell Lung Cancer	Cyclophosphamide Doxorubicin Etoposide	1 g/m^2/day 50 mg/m^2/day 120 mg/m^2/day x 3 q 21 days	210	3	4 - 8 mcg/kg SC days 4 - 17
Small Cell Lung Cancer[11]	Ifosfamide Doxorubicin Etoposide Mesna	5 g/m^2/day 50 mg/m^2/day 120 mg/m^2/day x 3 8 g/m^2/day q 21 days	12	1/2	5.75 - 46 mcg/kg IV days 4 - 17
Urothelial Cancer[12]	Methotrexate Vinblastine Doxorubicin Cisplatin	30 mg/m^2/day x 2 3 mg/m^2/day x 2 30 mg/m^2/day 70 mg/m^2/day q 28 days	40	1/2	3.45 - 69 mcg/kg IV days 4 - 11
Various Nonmyeloid Malignancies[13]	Cyclophosphamide Etoposide Cisplatin	2.5 g/m^2/day x 2 500 mg/m^2/day x 3 50 mg/m^2/day x 3 q 28 days	18	1/2	23 - 69 mcg/kg[b] IV days 8 - 28
Breast/Ovarian Cancer[14]	Doxorubicin[c]	75 mg/m^2 100 mg/m^2 125 mg/m^2 150 mg/m^2 q 14 days	21	2	11.5 mcg/kg IV days 2 - 9 5.75 mcg/kg IV days 10 - 12
Neuroblastoma	Cyclophosphamide Doxorubicin Cisplatin	150 mg/m^2 x 7 35 mg/m^2 90 mg/m^2 q 28 days (cycles 1,3,5)[d]	12	2	5.45 - 17.25 mcg/kg SC days 6 - 19

[a] NEUPOGEN® doses were those that accelerated neutrophil production. Doses which provided no additional acceleration beyond that achieved at the next lower dose are not reported.

[b] Lowest dose(s) tested in the study.

[c] Patients received doxorubicin at either 75, 100, 125, or 150 mg/m^2.

[d] Cycles 2,6 = cyclophosphamide 150 mg/m^2 x 7 and etoposide 280 mg/m^2 x 3.
Cycle 4 = cisplatin 90 mg/m^2 x 1 and etoposide 280 mg/m^2 x 3.

Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

In a randomized, double-blind, placebo-controlled, multi-center, phase 3 clinical trial, 521 patients (median age 54, range 16 to 89 years) were treated for de novo acute myeloid leukemia (AML). Following a standard induction chemotherapy regimen comprising daunorubicin, cytosine arabinoside, and etoposide[15] (DAV 3+7+5), patients received either NEUPOGEN® at 5 mcg/kg/day or placebo, SC, from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC 1000/mm^3 for 3 consecutive days or 10,000/mm^3 for 1 day) or for a maximum of 35 days.

Treatment with NEUPOGEN® significantly reduced the median time to ANC recovery and the median duration of fever, antibiotic use, and hospitalization following induction chemotherapy. In the NEUPOGEN®-treated group, the median time from initiation of chemotherapy to ANC recovery (ANC $\geq$ 500/mm^3) was 20 days (vs 25 days in the control group, $p = 0.0001$), the median duration of fever was reduced by 1.5 days ($p = 0.009$), and there were statistically significant reductions in the durations of IV antibiotic use and hospitalization. During consolidation therapy (DAV 2+5+5), patients treated with NEUPOGEN® also experienced significant reductions in the incidence of severe neutropenia, time to neutrophil recovery, the incidence and duration of fever, and in the durations of IV antibiotic use and hospitalization. Patients treated with a further course of standard (DAV 2+5+5) or high-dose cytosine arabinoside consolidation also experienced significant reductions in the duration of neutropenia.

There were no statistically significant differences between NEUPOGEN® and placebo groups in complete remission rate (69% NEUPOGEN® vs 68% placebo, $p = 0.77$), disease-free survival (median 342 days NEUPOGEN® [n = 178], 322 days placebo [n = 177], $p = 0.99$), time to progression of all randomized patients (median 165 days NEUPOGEN®, 186 days placebo, $p = 0.87$), or overall survival (median 380 days NEUPOGEN®, 425 days placebo, $p = 0.83$).

Cancer Patients Receiving Bone Marrow Transplant

In two separate randomized, controlled trials, patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) were treated with myeloablative chemotherapy and autologous bone marrow transplantation (ABMT). In one study (n = 54), NEUPOGEN® was administered at doses of 10 or 30 mcg/kg/day; a third treatment group in this study received no NEUPOGEN®. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the NEUPOGEN®-treated group versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group, [11 days in the combined treatment groups, $p = 0.004$]). In the second study (n = 44, 43 patients evaluable), NEUPOGEN® was administered at doses of 10 or 20 mcg/kg/day; a third treatment group in this study received no NEUPOGEN®. A statistically significant reduction in the median number of days of severe neutropenia occurred in the NEUPOGEN®-treated group versus the control group (21.5 days in the control group and 10 days in both treatment groups, $p < 0.001$). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group, 5 days in the 10 mcg/kg/day group, and 5.5 days in the 20 mcg/kg/day group, [5 days in the combined treatment groups, $p < 0.0001$]). Reductions in the number of days of hospitalization and antibiotic use were also seen, although these reductions were not statistically significant. There were no effects on red blood cell or platelet levels.

In a randomized, placebo-controlled trial, 70 patients with myeloid and nonmyeloid malignancies were treated with myeloablative therapy and allogeneic bone marrow transplant followed by 300 mcg/m^2/day of a Filgrastim product. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, $p < 0.001$) and time to recovery of ANC to $\geq 500/mm^3$ (21 days in the control group and 16 days in the treatment group, $p < 0.001$).

In three nonrandomized studies (n = 119), patients received ABMT and treatment with NEUPOGEN®. One study (n = 45) involved patients with breast cancer and malignant melanoma. A second study (n = 39) involved patients with HD. The third study (n = 35) involved patients with NHL, acute lymphoblastic leukemia (ALL), and germ cell tumor. In these studies, the recovery of the ANC to $\geq 500/mm^3$ ranged from a median of 11.5 to 13 days.

None of the conditioning regimens used in the ABMT studies included radiation therapy.

While these studies were not designed to compare survival, this information was collected and evaluated. The overall survival and disease progression of patients receiving NEUPOGEN® in these studies were similar to those observed in the respective control groups and to historical data.

Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients

All patients in the Amgen-sponsored trials received a similar mobilization/collection regimen: NEUPOGEN® was administered for 6 to 7 days, with an apheresis procedure on days 5, 6, and 7 (except for a limited number of patients receiving apheresis on days 4, 6, and 8). In a non-Amgen-sponsored study, patients underwent mobilization to a target number of mononuclear cells (MNC), with apheresis starting on day 5. There are no data on the mobilization of peripheral blood progenitor cells (PBPC) after days 4 to 5 that are not confounded by leukapheresis.

Mobilization: Mobilization of PBPC was studied in 50 heavily pretreated patients (median number of prior cycles = 9.5) with NHL, HD, or ALL (Amgen study 1). CFU-GM was used as the marker for engraftable PBPC. The median CFU-GM level on each day of mobilization was determined from the data available (CFU-GM assays were not obtained on all patients on each day of mobilization). These data are presented below.

The data from Amgen study 1 were supported by data from Amgen study 2 in which 22 pretreated breast cancer patients (median number of prior cycles = 3) were studied. Both the CFU-GM and CD34$^+$ cells reached a maximum on day 5 at > 10-fold over baseline and then remained elevated with leukapheresis.

Progenitor Cell Levels in Peripheral Blood by Mobilization Day						
	Overall Study 1 CFU-GM/mL		Study 2 CFU-GM/mL		Study 2 $CD34^+$ (x 10^4/mL)	
	No. Samples	Median (25% - 75%)	No. Samples	Median (25% - 75%)	No. Samples	Median (25% - 75%)
Day 1	11	18 (13 - 62)	20	42 (15 - 151)	20	0.13 (0.02 - 0.66)
Day 2	7	22 (3 - 61)	n/a	n/a	n/a	n/a
Day 3	10	138 (39 - 364)	n/a	n/a	n/a	n/a
Day 4	18	365 (158 - 864)	18	576 (108 - 1819)	17	2.11 (0.58 - 3.93)
Day 5	36	781 (391 - 1608)	21	960 (72 - 1677)	22	3.16 (1.08 - 6.11)
Day 6	46	505 (199 - 1397)	22	756 (70 - 3486)	22	2.67 (1.09 - 4.40)
Day 7	37	333 (111 - 938)	22	597 (118 - 2009)	21	2.64 (0.78 - 4.22)
Day 8	15	383 (94 - 815)	12	51 (10 - 746)	12	1.61 (0.38 - 4.31)

n/a = not available

In three studies of patients with prior exposure to chemotherapy, the median CFU-GM yield in the leukapheresis product ranged from 20.9 to 32.7 x 10^4/kg body weight (n = 105). In two of these studies where $CD34^+$ yields in the leukapheresis product were also determined, the median $CD34^+$ yields were 3.11 and 2.80 x 10^6/kg, respectively (n = 56). In an additional study of 18 chemotherapy-naive patients, the median CFU-GM yield was 123.4 x 10^4/kg.

Engraftment: Engraftment following NEUPOGEN®-mobilized PBPC is summarized for 101 patients in the table below. In all studies, a Cox regression model showed that the total number of CFU-GM and/or $CD34^+$ cells collected was a significant predictor of time to platelet recovery.

In a randomized, unblinded study of patients with HD or NHL undergoing myeloablative chemotherapy (Amgen study 3), 27 patients received NEUPOGEN®-mobilized PBPC followed by NEUPOGEN® and 31 patients received ABMT followed by NEUPOGEN®. Patients randomized to the NEUPOGEN®-mobilized PBPC group compared to the ABMT group had significantly fewer days of platelet transfusions (median 6 vs 10 days), a significantly shorter time to a sustained platelet count > 20,000/mm^3 (median 16 vs 23 days), a significantly shorter time to recovery of a sustained ANC ≥ 500/mm^3 (median 11 vs 14 days), significantly fewer days of red blood cell transfusions (median 2 vs 3 days) and a significantly shorter duration of posttransplant hospitalization.