NEUPOGEN® (Filgrastim)

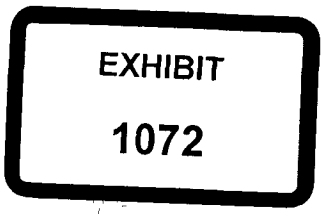
DESCRIPTION

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. Each single-use vial of NEUPOGEN contains 300 mcg/mL of 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 formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol, and 0.004% Tween® 80. The quantitative composition (per mL) of NEUPOGEN is:

Filgrastim	300 mcg
Acetate	0.59 mg
Sorbitol	50.0 mg
Tween® 80	0.004%
Sodium	0.035 mg
Water for Injection USP q.s. ad	1.0 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 five of the eight 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 dose 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.

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.