

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103353/000

Summary Basis of Approval

Redacted documents transferred from CBER



February 20, 1991

Our Reference Nos.: 90-0066 and 90-0067

N. Kirby Alton, Ph.D.
Amgen, Inc.
Amgen Center
Thousand Oaks, CA 91320-1789

Dear Dr. Alton:

Enclosed is a product license which authorizes Amgen, Inc., U.S. License No. 1080, to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce, Filgrastim.

Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

Your establishment license application is also amended to include the manufacture of Filgrastim with the stipulation that filling and finishing of final product will only be performed at the Rochester, MI location of Parke-Davis under a contractual arrangement. All Filgrastim manufacturing operations performed at Parke-Davis shall be under your direct supervision and control as specified in your establishment license application. The Thousand Oaks facility is not approved to fill or finish final product at this time.

You are requested to submit samples of each future lot of the product together with protocols showing results of all applicable tests. No lots of product shall be shipped for distribution until notification of release is received from the Director, Center for Biologics Evaluation and Research.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of the final sterile filtration of the bulk solution into final containers. Results of ongoing stability studies should be submitted at regular intervals as specified in your letter of January 4, 1991. The first three production lots should be entered into your ongoing stability program.

Any changes in the manufacturing, testing, packaging, or labeling of the product or in the manufacturing facilities will require the submission of an amendment to either your product or establishment license application for our review and written approval prior to implementation.

Page 2 - Dr. Alton

We acknowledge receipt of your written commitments of January 8, 1991 to acquire additional data so that process specifications can be set for the percentage of the reduced form of Filgrastim.

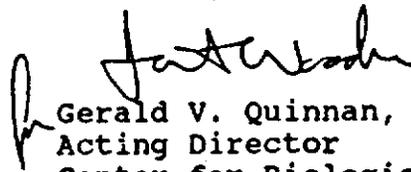
You are requested to submit adverse experience reports in accordance with the requirements for postmarketing reporting of adverse drug experiences (21 CFR 314.80) until such time that specific reporting requirements for biological products become effective. All experience reports should be prominently labeled as "BIOLOGICAL PRODUCT" and be submitted to the attention of Biostatistics and Epidemiology, HFB-250, Office of Biological Product Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information.

In addition, advertising and promotional labeling should be submitted for review and approval prior to the initial publication of any advertisement and prior to the initial dissemination of any promotional labeling. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed license to the Acting Director, Division of Product Certification, HFB-240, Center for Biologics Evaluation and Research.

Sincerely yours,



Gerald V. Quinnan, Jr., M.D.
Acting Director
Center for Biologics
Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FEB 20 1991

Our Reference No: 90-0067

N. Kirby Alton, Ph.D.
Amgen, Inc.
Amgen Center
Thousand Oaks, CA 91320-1789

Dear Dr. Alton:

This is in response to your letter of February 19, 1991 which petitions the Food and Drug Administration to grant a waiver of the requirement for adequate and well-controlled studies to substantiate certain labeling statements included in the proposed package insert for Filgrastim in accordance with 21 CFR 201.58.

Your request is granted with the following stipulation. The inclusion of information in the package insert concerning Phase I and Phase II trials is for the purpose of providing a broader clinical experience of Filgrastim to the physician. Any advertising and promotional labeling claims should be based only on the results of Phase III study data.

Sincerely yours,

Gerald V. Quinnan, Jr., M.D.
Acting Director
Center for Biologics
Evaluation and Research

PREPARED BY:HFB-240:RJOHNSON-LEVA:mn 2/20/91

SUMMARY BASIS OF APPROVAL

Reference Number:

PLA #90-0067
ELA #90-0066

Drug Generic Name:

Filgrastim

Applicant:

Amgen Inc.
Amgen Center
Thousand Oaks, CA 91320

Drug Trade Name:

Neupogen

I. INDICATION FOR USE

Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. Studies have demonstrated an acceleration in the recovery of neutrophil counts following a variety of chemotherapy regimens for a number of cancer types. In a single phase III study, response to treatment with Filgrastim decreased the incidence of infection, decreased the incidence of hospitalization and length of hospitalization, and decreased intravenous antibiotic usage. Neupogen is the Amgen, Inc. trademark for Filgrastim, which has been selected as the name for recombinant human granulocyte colony stimulating factor (G-CSF).

Filgrastim is contraindicated in patients with known hypersensitivity to *E. coli* derived products. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of Filgrastim is not recommended in the period 24 hours before to 24 hours after the administration of cytotoxic chemotherapy. Filgrastim is a growth factor that primarily stimulates neutrophils. However, the possibility that it can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Therefore, because of the possibility of tumor growth, caution should be exercised in using this drug in any malignancy with myeloid characteristics.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSE

Filgrastim is supplied as a preservative-free injectable solution in 1.0 mL and 1.6 mL volumes containing 0.30 mg of filgrastim per 1 mL. Each milliliter of injectable solution contains 0.30 mg of filgrastim; 0.59 mg acetate; 0.50 mg mannitol; 0.004% Tween 80; 0.035 mg sodium; and 1.0 mL Water for Injection. The pH of Filgrastim is 4.0. The formulation does not contain a preservative. Each vial delivers only a single dose. The unused portion of any vial should be discarded.

Route of Administration and Recommended Dose

The recommended starting dose of Filgrastim is 5 mcg/kg/day, administered as a single daily subcutaneous or intravenous injection. The selected dosage regimen should be maintained for up to two weeks or until the white blood cell count has reached 10×10^9 cells per liter following the expected chemotherapy induced neutrophil nadir. Regular monitoring of white blood cell counts (twice weekly) is recommended in order to avoid excessive leukocytosis (Absolute Neutrophil Count $>10 \times 10^9/L$). The duration of treatment to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Doses may be increased in increments of 5 mcg/kg/day for each chemotherapy cycle, according to the duration and severity of the ANC nadir.

III. MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

Filgrastim is manufactured by recombinant DNA technology. It is produced in E. coli bacteria which have been genetically engineered by the insertion of a human granulocyte colony stimulating factor gene.

E. coli from a master seed lot containing the gene for filgrastim are grown in a fermenter, in medium optimized for product synthesis, to a specified cell density. The cells are harvested and lysed and product extracted. The product is allowed to oxidize to its native state and is purified by several chromatographic and filtration steps. Formulation is in an acetate buffer with mannitol and Tween 80. The highly purified

bulk product consists of a 175 amino acid recombinant-derived protein with a molecular weight of 18,800 daltons. The process has been described in sufficient detail and validated to yield purified Filgrastim which contains an N-terminal methionine and lacks O-linked glycosylation.

Raw materials and packaging components are obtained from approved vendors and evaluated by Quality Assurance personnel according to established written procedures prior to acceptance for use in manufacture.

Manufacturing controls and in-process testing at multiple stages are performed to assure product purity, identity, strength, and quality. The purified bulk filgrastim is tested for identity and purity by SDS-PAGE, amino acid analysis, N-terminal sequence analysis, peptide mapping, HPLC, isoelectric focusing, and Western blot analysis. The product is also tested for the presence of *E. coli* proteins and DNA. The final product is tested to ensure the identity, quality, safety, purity, strength, potency, and excipient chemical content of the final dosage form. Potency is determined by a cell proliferation assay. The National Institute for Biological Standards and Control interim reference reagent for G-CSF was used to determine a potency value of 1×10^6 u/mg.

The product is manufactured through the formulated bulk stage by Amgen Inc. at its facilities located in Thousand Oaks, California. The formulated bulk product is shipped under controlled conditions to Parke-Davis, a Division of Warner Lambert in Rochester, Michigan. Under the direct supervision and control of Amgen personnel, the formulated bulk product is sterile-filtered, filled into final containers, labeled, and packaged as specified in the establishment license application. The final labeled product is shipped under controlled conditions to Amgen, Inc. in Thousand Oaks, California. A written contract between Amgen and Parke-Davis outlines responsibilities for each key manufacturing step, assuring adequate supervision and control of the process.

The consistency of the manufacturing process is demonstrated through detailed laboratory analyses of multiple production lots. Samples of all lots, along with the test result protocols, are submitted to the Center for Biologics Evaluation and Research for lot release.

B. Stability Studies

The stability of the Filgrastim 0.30 mg/mL dosage form, at the recommended storage conditions of 2-8°C (36-46°F), has been verified. Stability studies are ongoing with multiple lots of final product; formulations at 1.0, 1.6, and 2.0 mL volumes are included in the studies, and product is maintained at various temperatures above and below the recommended storage temperatures. Amgen has committed to providing updates on ongoing stability studies to CBER at 3 month intervals. Data from these ongoing studies support a 24-month dating period from the date of manufacture for the 0.30 mg/mL dosage form stored at 2-8°C. The date of manufacture shall be defined as the date of the last sterile filtration.

C. Validation

Utility systems, manufacturing equipment, manufacturing processes, and analytical methodologies used in the production have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of utility and process equipment and regular monitoring of environmental conditions within the production facilities.

D. Labeling

The container label, package labels, and package insert have been reviewed for compliance with 21 CFR 201.56, 201.57, 610.60, 610.61, and 610.62, and have been found to be satisfactory. The product trade name, Filgrastim, is not known to conflict with that of any other drug. A patient information insert will accompany each package in order to provide adequate instructions for home administration.

E. Establishment Inspection

A pre-license inspection of Amgen's production facility in Thousand Oaks, California, was conducted on November 5-8, 1990. Facilities and procedures were found to be in compliance with current Good Manufacturing Practices.

F. Environmental Assessment (EA)

An Environmental Assessment was submitted by Amgen Inc. as part of the establishment and product license applications. The procedures followed comply with the

guidelines published by the National Institutes of Health for research involving recombinant DNA molecules. In addition, all applicable federal, state, and local environmental regulations are observed. The licensing of Filgrastim is not expected to have any adverse effect on the environment.

IV. PHARMACOLOGY

A. Background

Human granulocyte colony stimulating factor (G-CSF) regulates the production of neutrophils within the bone marrow. Endogenous human G-CSF is produced by monocytes, fibroblasts and endothelial cells. It has been shown to have minimal direct effect on the production of other hematopoietic cell types. Filgrastim is a 175 amino acid recombinant-derived protein with molecular weight of 18,800 daltons. It is produced by *E. coli* bacteria into which the human granulocyte colony stimulating factor gene has been inserted. The protein expressed is non-glycosylated and has an N-terminal methionine which is necessary for expression in *E. coli*.

Filgrastim is not species restricted and has efficiently stimulated the generation of neutrophilic granulocyte colonies from the marrow cells of all mammalian species so far examined. The similarity of the biological response to Filgrastim in rabbits, mice, rats, hamsters, dogs, and cynomolgus monkeys and the binding of iodinated human G-CSF to murine tissues indicate species crossreactivity of the human material.

B. Pharmacologic Activity

Administration of Filgrastim results in a dose-dependent increase in circulating neutrophil counts over the dose range of 1-70 mcg/kg/day. This increase is observed whether administration is intravenous, subcutaneous or continuous subcutaneous infusion. Termination of therapy results in the decline of circulating neutrophil counts to pretreatment levels within 1-7 days.

C. Pharmacokinetics

Absorption and clearance of Filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence when measured in human subjects. Availability, as measured by area under the

curve (AUC) determination, was similar for both subcutaneous and intravenous administration. Continuous intravenous infusions of 20 mcg/kg of Filgrastim 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 of Filgrastim is 3.5 hours for both normal subjects and cancer patients, with clearance rates of approximately 0.5-0.7 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 for doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes for doses of 3.45 mcg/kg). Continuous intravenous infusion for 24 hours at 20 mcg/kg over an 11 to 20 day period produced steady-state serum concentrations without drug accumulation, indicative of clearance mechanisms not being saturated. There was no evidence that high doses or repeat dosing caused substantial alteration in distribution or elimination kinetics.

D. Clinical Pharmacology Studies

A Phase I single dose placebo-controlled study in normal healthy volunteer males (21) was conducted to determine the safety, pharmacodynamic effects and pharmacokinetic profile of Filgrastim.

Intravenously administered Filgrastim resulted in a dose-dependent and rapidly reversible increase in ANC when administered as single doses of 0.575 to 3.45 mcg/kg. Filgrastim was well tolerated with no clinically important adverse events recorded. Filgrastim showed first order pharmacokinetics with an elimination half-life of 160 minutes.

The effect of Filgrastim on increasing ANC was highly specific. Minor increases seen in monocyte, eosinophil, basophil and white blood cell precursor counts were clinically insignificant. The most frequently reported adverse event was bone pain, which was generally mild to moderate in severity.

E. Tissue Distribution/Excretion

Intravenous Administration

Sixty-four rats were injected intravenously with 5.75 mcg/kg ¹²⁵I-Filgrastim; blood and tissue samples were obtained for the determination of total, trichloroacetic acid (TCA)-insoluble, and immune-precipitable radioactivity at intervals for up to 24 hours. Urine and fecal collections were made for up to 72 hours.

Plasma clearance of labelled product was biphasic. The results showed a half-life during the alpha-phase of approximately 0.7 hours for total, TCA-insoluble and immune-precipitable radioactivity. In contrast, the beta phase half-lives varied and were 5.5, 6.4, and 3.8 hours for total, TCA-insoluble and immune-precipitable radioactivity, respectively.

Tissue distribution studies revealed highest initial (10 minutes) concentrations of radioactivity (in descending order) in plasma, adrenals, blood, kidneys, thyroid, liver, bone marrow, trachea, spleen, and hypophysis. After one hour, only bone marrow and thyroid showed a further increase in concentration. At later intervals, all tissues, with the exception of thyroid, gastrointestinal tract, and trachea displayed a time-dependent decrease. The increased radioactivity observed in the thyroid and G.I. tract most likely represent iodide trapping and gastric/biliary secretion of iodide and labelled degradation products. Very little radioactivity was detected in brain, eye, thymus, adipose tissue, and skeletal muscle at any time point. With the exception of large concentrations of radioactivity in the ovaries, there were very few sex-related differences.

The cumulative excretion of radioactivity showed that more than 60% of the administered dose was eliminated in the urine within 12 hours in both sexes. At 24 hours, 90% of the administered radioactivity was found in urine and ~5% was found in feces.

Subcutaneous Administration

Similar studies were done in thirty-six male rats using subcutaneous administration. At the 5.75 mcg/kg subcutaneous dose, maximum plasma radioactivity was only 5-10% of that following intravenous administration. At later intervals,

plasma radioactivity declined in a biphasic manner with distribution half-lives of 3.7, 1.1, and 1.6 hours for total, acid-insoluble, and immune-precipitable radioactivity, respectively. The longer clearance times relative to those observed after intravenous administration may reflect a balance between clearance from plasma and continued absorption from the site of administration. Results obtained from the larger doses were similar, and the resulting areas under the curves (AUCs) were directly proportional to dose. Thus, elimination pathways were not saturated within the dose range studied.

The tissue distribution studies of the 5.75 mcg/kg dose of ¹²⁵I-Filgrastim showed highest initial (30 minutes) radioactive concentrations at the injection site, thyroid, kidneys, adrenals, gastric contents, plasma, and bone marrow. Between 2 and 4 hours, radioactivity at the injection site and adrenals declined slowly, while that in the thyroid, gastric contents, kidneys, plasma, bone marrow, spleen, and urinary bladder increased. Thereafter, with the exception of the thyroid, radioactivity decreased gradually in all tissues. After 48 hours three percent of the radioactivity was observed at the injection site. One percent of the radioactivity was observed in other tissues and ninety-six percent was observed in the thyroid at this same timepoint. As noted following intravenous administration, very little radioactivity was detected in the brain, eye, or skeletal muscle at any time point. At 12 hours after injection, 50.3% of the administered radioactivity was present in the urine. At 144 hours, 84.9% was in urine and 8.4% was in feces.

Regardless of the administration route, >50% of the administered radioactivity was found in urine within 12 hours, and cumulative excretion continued at a slower rate thereafter in both urine and feces. Radioactivity was retained at the subcutaneous injection site and resulted in a bioavailability of only 10-30% relative to intravenous administration. Prolonged accumulation was not observed in any of the major tissues with either intravenous or subcutaneous administration.

F. Toxicity Studies

The safety of Filgrastim was evaluated in acute, subacute and chronic toxicology studies in 5 animal species and are summarized in the following table:

Toxicology Studies

| <u>Study</u> | <u>Species</u> | <u>No.†</u> | <u>Route</u> | <u>Dose (mcg/kg/day)</u> | <u>Duration</u> |
|--------------|----------------|-------------|--------------|--------------------------|-----------------|
| Acute | Mouse | 192 | po, iv, ip | 34.5, 345, 3450 | Single dose |
| Acute | Rat | 192 | po, iv, ip | 34.5, 345, 3450 | Single dose |
| Acute | Hamster | 120 | sc | 0.86, 8.6, 86, 860 | Single dose |
| Acute | Monkey | 20 | iv | 345, 1150, 3450 | Single dose |
| Subacute | Hamster | 270 | sc | 7.13, 71.3, 213.9 | 2 weeks |
| Subacute | Dog | 30 | iv | 1.15, 11.5, 115, 345 | 2 weeks |
| Subacute | Monkey | 15 | iv | 11.5, 57.5, 287.5, 1150 | 2 weeks |
| Subacute | Rat | 168 | iv | 1.15, 11.5, 115, 1150 | 4 weeks |
| Subacute | Monkey | 34 | iv | 11.5, 115, 1150 | 4 weeks |
| Subacute | Rat | 168 | iv | 1.15, 11.5, 115, 575 | 13 weeks |
| Subacute | Monkey | 38 | iv | 1.15, 11.5, 115 | 13 weeks |

† Number of animals

po=oral, iv=intravenous, ip=intraperitoneal, sc=subcutaneous

Acute Studies

Single dose administration of Filgrastim by the oral, intravenous or intraperitoneal route resulted in no significant toxicity in mice, rats, hamsters or monkeys. No deaths were observed in mice, rats, or monkeys at dose levels up to 3450 mcg/kg or in hamsters at doses of approximately 860 mcg/kg. No significant differences in body weights were seen, and histopathology of tissues and organs revealed no changes attributable to Filgrastim.

Subcutaneous inflammation and hemorrhage were observed at the injection sites of 2/20 hamsters, but reactions occurred with similar frequency and severity in both the control and 860 mcg/kg/day dose groups. These subcutaneous lesions were generally mild in severity and not unexpected at the injection site.

Leukocyte counts were elevated approximately two times the baseline values in the two highest dose monkey groups at day 7, but had returned to normal after 14 days. This finding is an expected pharmacological effect.

Consequently, the single-dose LD₅₀ of Filgrastim in these species is in excess of 3450 mcg/kg, which is more than fifty-fold greater than the highest anticipated human clinical dose.

Repeat Administration Studies

In subacute studies, changes observed were generally attributed to the anticipated pharmacological actions of the protein as evidenced by dose-dependent increases in white cell counts, increased proportion of segmented neutrophils in the circulation and increased myeloid:erythroid ratio in the bone marrow. The following observations were made in these studies.

- Body Weights

Body weights and food consumption were not affected in the hamster and dog, but average body weight was decreased in both 2-week (males, 1150 mcg/kg/day and control group) and 13-week (both sexes, 115 µg/kg/day) (including control) monkey studies. This finding was considered likely to be attributable to the stress of daily handling of the monkeys and the need for repeated sedation for sample collection.

- Hematopoiesis

In all species, increased granulopoiesis was evidenced by dose dependent increases in white blood cell counts and an increased proportion of segmented neutrophils in the circulation. Extramedullary hematopoiesis of the spleen (≥ 115 mcg/kg/day) and liver (2575 mcg/kg/day) of rats was observed. A similar observation was made in dogs in the spleen and mediastinal lymph nodes (≥ 11.5 mcg/kg/day) and liver (≥ 115 mcg/kg/day). The effects reversed upon cessation of treatment and are consistent with an exaggerated pharmacologic response. There was a reduction in platelet count in the 1150 mcg/kg/day dose monkey groups (2- and 4-week studies). In thirteen week intravenous administration studies in monkeys and rats, there was a dose related enlargement of the spleen in both species, and increased granulocytopenia in the bone marrow.

- Neurologic

In a four week subacute toxicology study performed with intravenous administration of Filgrastim to monkeys, all four high dose males and one of four females of the high dose group (1150 mcg/kg/day) died within 18 days after the start of Filgrastim administration. Death was preceded by signs of neurological toxicity including gait disturbances and paresis of both hind limbs. Leukocyte counts in these animals ranged from

112,000/mm³ to 260,000/mm³. Death was caused by cerebral hemorrhage precipitated by this exaggerated pharmacologic response. Platelet counts were normal in these animals. There were no deaths observed in the other monkey groups, nor in other species tested.

- Bones and Joints

In rats, osteoclasia and osteoanagenesis were found in the hind legs (where they were accompanied by synovitis), femur, humerus and coccyx after intravenous treatment for four weeks (115 to 1150 mcg/kg/day) and in the sternum after intravenous treatment for thirteen weeks (115 to 575 mcg/kg/day). These effects reversed to normal within four to five weeks following cessation of treatment. Similar symptoms were not detected in hamsters or dogs.

- Bone Marrow

In rats, dogs, and monkeys, bone marrow examinations conducted at the end of the r-metHuG-CSF administration period revealed a dose dependent increase in the myeloid:erythroid ratio. Increases were dose dependent up to 3 times controls in monkeys (115 mcg/kg/day x 13 weeks), 6 times controls in rats (575 mcg/kg/day x 13 weeks), and 17 times controls in dogs (345 mcg/kg/day x 2 weeks).

- Other

There was a dose dependent increase in serum alkaline phosphatase in the rat, but no other blood chemistry changes were observed in either species.

Reproductive Studies

- Segment I

Filgrastim had no effect on reproductive performance, fertility or fetal development when administered intravenously at doses of 23, 115 or 575 mcg/kg/day in a study in rats. Four groups of 44 rats (22/sex/group) were used to evaluate the effects of Filgrastim on fertility and reproductive performance at daily intravenous doses of 0, 23, 115, and 575 mcg/kg. Males were treated for 64 days prior to mating and then during and after mating for a further 27 days. Females were treated for 15 days prior to mating, then during mating until day 7 of gestation.

There were no deaths during the study period. No treatment related effect on the frequency of estrus (determined before mating) was observed, or on the copulation, insemination and fertility indices. There

was no significant effect on the following reproductive parameters: numbers of corpora lutea, implantations and live fetuses, pre-implantation loss, number of dead implantations, sex ratio of fetuses, and fetal body and placental weights. The incidences of external, visceral, and skeletal abnormalities were not significantly different between control and treated groups.

- Segment II

A dose ranging teratology study has been carried out in 20 rabbits at doses of 0 (vehicle), 0.92, 4.6, 23 or 115 mcg/kg/day intravenous. Filgrastim was administered from days 6 to 16 of gestation. There were no maternal deaths. Genitourinary bleeding (with vaginal bleeding at necropsy) was observed in 2 dams at 115 mcg/kg. An increase in the number of resorptions was seen in this group, with an increase in late resorptions. A decreased implantation rate was also noted, which was not dose related. No fetal external abnormalities were observed.

A second rabbit segment II study involving 60 rabbits was performed in which doses of 80 mcg/kg/day caused increased abortions, increased embryoletality, urogenital hemorrhage, reduced food consumption, increased fetal resorption, development abnormalities, and decreased body weight. At doses of ≥ 20 mcg/kg/day, reduced weight gain and increased spleen weights were observed.

Two studies were carried out in rats (40 and 151 animals, respectively) at doses of 0 (vehicle), 23, 115, and 575 mcg/kg Filgrastim intravenously at days 7 to 17 of gestation. Some dams were sacrificed after 20 days of gestation (all dams were sacrificed at this time point in the first study); the remainder was observed for 22 days after delivery, then sacrificed.

There were no maternal deaths or clinical signs of intolerance in any of the study groups. Increased spleen weights were observed in all treated dams at day 20 of gestation, reverting to normal at 22 days after delivery. There was no effect on the number of corpora lutea, implantations, live fetuses, pre-implantation losses, sex ratio, or body and placental weights when compared to controls. F1 generation animals were observed until 84 days after birth, and developed normally. There were no treatment related effects on the F2 fetuses. Based on these results, Filgrastim has no teratogenic or lethal effects on fetuses when administered intravenously to pregnant rats on days 7 to 17 of gestation, at doses of up to 575 mcg/kg/day.

- Segment III

A rat segment III study involving 100 dams was conducted to assess peri- and post-natal effects of Filgrastim. Dams treated at ≥ 20 mcg/kg/day had increased spleen weights. Offspring of these dams showed delays in external differentiation (detachment of auricles, descent of testes) and slight growth retardation due to lower body weight of females during the rearing and nursing period. Offspring of dams treated at 100/mcg/kg/day exhibited decreased body weights at birth and a slightly reduced 4-day survival rate.

G. Bacterial Mutagenicity Test

The effect of Filgrastim on bacterial mutation was investigated using E. coli and Salmonella typhimurium in the absence and presence of S-9, a drug-metabolizing enzyme system. Concentrations of Neupogen ranging from 9.71 to 155.3 ug/plate were used in the absence of S-9; a concentration range of 1.94 to 31.1 μ g/plate was used in the presence of S-9.

Negative results were obtained on all test plates containing Neupogen, regardless of the presence or absence of S-9 mixture. In contrast, plates containing known mutagens tested positive in the appropriate strain. These results indicate that Neupogen has no direct mutagenic potential.

Carcinogenic potential of Filgrastim has not been evaluated.

V. MEDICAL

Filgrastim has been evaluated clinically in approximately 350 cancer patients in efficacy and safety studies. The following data were obtained in support of its use to decrease the incidence of infections, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs which are associated with a significant incidence of severe neutropenia with fever. Although Filgrastim has been used with a variety of chemotherapeutic regimens, efficacy has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosourea), or with mitomycin C or with myelosuppressive doses of antimetabolites such as 5-flurouracil or cytosine arabinoside.

A. Summary of Clinical Studies

1. A Phase III, Placebo Controlled, Trial as an Adjunct to Combination Chemotherapy for Small Cell Lung Cancer

A Phase III multicenter (fourteen centers), randomized, double-blind, placebo-controlled parallel group study was designed to assess the effect of Filgrastim on the incidence and duration of infection (as manifested by febrile neutropenia) after cyclophosphamide, doxorubicin, and etoposide (CAE) chemotherapy. The chemotherapy regimen used in this study was CAE and the combination was administered in a 21 day cycle. Cyclophosphamide was administered at a dose of 1.0 gm/m^2 on day 1, doxorubicin at a dose of 50 mg/m^2 on day 1, and etoposide at a dose of 120 mg/m^2 on days 1 to 3.

In addition, this study was designed to determine the effect of treatment on the number of days of fever, occurrence of infections, antibiotic use and inpatient hospitalization; to assess the efficacy in the modulation of the hematopoietic toxicity (i.e. reducing the duration and severity of neutropenia) in small cell lung cancer patients who receive CAE.

Patients received daily subcutaneous injections starting on day 4, for up to 14 days of treatment, of either Filgrastim at a dose of 230 mcg/m^2 , or placebo, in a double-blind fashion, or open-label Filgrastim for each cycle for up to 6 cycles of chemotherapy. Febrile neutropenia was defined as both an $\text{ANC} < 1.0 \times 10^9$ and temperature $> 38.2 \text{ C}$. If a patient experienced an episode of febrile neutropenia, they were unblinded for the next cycle of chemotherapy and allowed to crossover to receive Filgrastim during subsequent cycles.

There were 207 patients evaluable for safety analysis and 210 evaluable for efficacy analysis. The results presented are based on an intent to treat analysis. Treatment with Filgrastim resulted in 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 Filgrastim-treated patients ($p < 0.001$). 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 one, versus 52% (51/99) for Filgrastim-treated patients ($p=0.032$). The incidence of intravenous antibiotic usage was 60% (67/111) for placebo-treated patients in cycle one versus 38% (38/99) for Filgrastim-treated patients ($p=0.003$). The incidence, severity, and duration of severe neutropenic ($ANC < 500/mm^3$) following chemotherapy were all significantly reduced. The incidence of severe neutropenia in cycle one was 84% (83/99) for patients receiving Filgrastim versus 96% (106/110) for patients receiving placebo ($p < 0.004$). The median duration of severe neutropenia in cycle one was reduced from 6 days for patients on placebo, to 2 days for patients receiving Filgrastim ($p < 0.001$). Over all cycles, the median duration of neutropenia was 3 days for patients receiving placebo versus 1 day for patients receiving Filgrastim. The severity of neutropenia (as measured by ANC nadir) was $0.072 \times 10^9/L$ for cycle one patients receiving Filgrastim versus $0.038 \times 10^9/L$ for placebo patients ($p=0.004$). Over all cycles, the ANC nadir for patients randomized to Filgrastim was $0.403 \times 10^9/L$, versus $0.161 \times 10^9/L$ for patients receiving placebo. Administration of Filgrastim was found to result in an earlier ANC nadir after chemotherapy than was experienced by patients receiving placebo (day 10 versus day 12). Filgrastim was well tolerated when given subcutaneously daily at doses of 4-8 mcg/kg for up to 14 consecutive days following each cycle of chemotherapy.

From this data, it is concluded that Filgrastim provided clinically and statistically significant reduction in the occurrence of infection as manifested by febrile neutropenia during combination cytotoxic chemotherapy.

The product was well tolerated at a dose of 230 mcg/m^2 subcutaneously for up to 14 consecutive days, (equivalent to a range of 4-7.7 mcg/kg). Adverse events included mild to moderate reversible musculoskeletal pain in approximately 22% of patients. Mild to moderate reversible elevations in serum uric acid, lactate dehydrogenase and alkaline phosphatase were noted in less than 5% of patients. No clinical sequelae were associated with these increases. There were no reports of flu-like symptoms, pleuritis, pericarditis or major systemic reactions. No patient developed antibodies to Filgrastim during the period of observation.

Most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy. Because many patients received higher doses of chemotherapy (full doses on the prescribed schedule), platelet count and hematocrit were affected more than in placebo treated patients. However, a direct effect of Filgrastim on platelets cannot be ruled out.

Tumor response, progression-free interval and survival were the same in patients treated with Filgrastim and placebo, and did not differ from those previously reported in the literature.

2. Other Controlled Comparative Studies

Information concerning Phase I and Phase II trials is for the purpose of providing a broader clinical experience of Filgrastim to the physician. There is no claim of safety or efficacy concerning such studies.

Two studies had similar Phase I-II designs. In both, patients were entered into an escalating dose Phase I study followed by a controlled study of Filgrastim given with cytotoxic chemotherapy. In the Phase II parts of these studies, patients acted as their own controls. Hematologic and clinical efficacy endpoints were measured in both studies.

In one study of 40 patients with advanced urothelial cancer, drug was administered intravenous daily for six days. The dose was escalated in groups of three to six patients from 1.15 to 115.0 mcg/kg/day. Patients who showed an elevation of ANC to a level at least two-fold greater than baseline were entered into the Phase II part of the study. In Phase II, patients received the same daily dose for eight days beginning on day 4 of one cycle of "M-VAC" chemotherapy. The M-VAC regimen comprised methotrexate, vincristine, doxorubicin and cisplatin given on day one followed by further methotrexate and vincristine given on days 14 and 21. Control data were obtained by treating the same patients with a second cycle of M-VAC given without Filgrastim.

Both the duration and severity of neutropenia were reduced during cycles of chemotherapy in which Filgrastim was administered, when compared to cycles of chemotherapy without drug. The accelerated recovery of neutrophil counts, during M-VAC cycles when Filgrastim was administered,

resulted in eligible to receive planned doses of methotrexate and vinblastine on schedule; on cycle day 14.

Filgrastim was generally well tolerated at all doses tested (up to 115 mcg/kg/day), when administered as a 15-30 minute intravenous infusion on days 4-11 of the 21 day M-VAC cycle. In addition, antibiotic use was decreased in cycles given with Filgrastim.

In the other study, 12 patients with Small Cell Lung Cancer received Filgrastim by continuous intravenous infusion daily for four days. The dose was escalated in groups of three to six patients from 1.15 to 46.0 mcg/kg/day. Patients from the Phase I group were then entered into the Phase II part of the study. In Phase II, patients received the same daily dose of Filgrastim as used in Phase I for up to 14 days from day four of alternate cycles of ifosfamide, doxorubicin, and etoposide (IAE) chemotherapy with mesna. The IAE regimen given on day one followed by further etoposide given on days 2 and 3. Control data were obtained by treating the same patients with alternate cycles of IAE given without Filgrastim. Patients were treated with up to six cycles of chemotherapy including three with Filgrastim.

Filgrastim therapy reduced the mean duration of chemotherapy-induced neutropenia by approximately one week per cycle. The duration of fever, febrile neutropenia, hospitalizations for infections, and antibiotic use were reduced in cycles which included Filgrastim administration. The drug was well tolerated at doses of 1-45 mcg/kg/day, given as a continuous infusion on days 4-17 of a 21 day chemotherapy cycle.

3. Safety Studies with High Dose Cytotoxic Chemotherapy

An open label, Phase II dose ranging study was performed in 18 patients with non-myeloid malignancy not amenable to standard treatment. Chemotherapy cycles given every 4 weeks comprised of cyclophosphamide (2.5 g/m² given intravenous on days 1 and 2), etoposide (500 mg/m² given intravenous on days 1 to 3) and cisplatin (50 mg/m² given intravenous on days 1 to 3); Filgrastim was given intravenous by 30 minute infusion daily from day 6 up to day 26 of each cycle at a dose of 23.0 to 69.0 mcg/kg/day.

There was a dose-related increase in ANC starting at day 14. Mean days of neutropenia (ANC < 100 x 10⁹/L) decreased from 10.3 to 7.5 to 5.4 days at dosage increments of 23, 46, and 69 mcg/kg/day. By day 16, mean ANC exceeded 20,000 x 10⁹/L, and by day 22 had reached 100,000 x 10⁹/L.

In this study, the most frequently reported adverse event that the investigator attributed as being related to Filgrastim was musculoskeletal pain which occurred in six patients (33%) and was judged as probably related in all cases.

Another uncontrolled study was performed in 22 patients with recurrent advanced breast or ovarian cancer. On day 1 patients received doxorubicin by slow intravenous infusion at one of four dose levels (75, 100, 125, or 150 mg/m²) according to their assigned treatment group. Four to six patients were entered at each dose level. Patients were enrolled in higher dose groups only if treatment was tolerated at the previous level. Filgrastim was administered at 10 mcg/kg/day for eight days (days 2-9) and 5 mcg/kg/day for the next three days (days 9-11). No Filgrastim was given on days 12 and 13. On Day 14 the treatment cycle was repeated. A total of three treatment cycles were specified by the protocol.

Filgrastim was well tolerated by patients with advanced breast or ovarian cancer who received high-dose doxorubicin and treatment did not negatively affect either the administration or efficacy of this high-dose therapy. No deaths attributed to Filgrastim were reported in the study. Filgrastim both hastened and abbreviated the neutropenia, allowing a redosing by week 2. The mean ANC nadir shifted from day 12 to day 7.

Reductions in platelet counts and red blood cell indices were reported, particularly in the highest doxorubicin dose groups. The investigator reported that Filgrastim probably contributed to one case of thrombocytopenia and to four cases of anemia in the nineteen patients studied. Mild or moderate increases in alkaline phosphates were reported in seven patients and mild increases in lactate dehydrogenase were reported in four.

4. Pediatric Use

Although efficacy has not been demonstrated in a pediatric population, safety data indicate that Filgrastim does not exhibit any greater toxicity in children than in adults. Interim data, from an

ongoing study of 12 pediatric patients with neuroblastoma receiving chemotherapy and Filgrastim, is similar to that observed in the adult chemotherapy patient population. During induction, the regimen of cyclophosphamide, cisplatin, and adriamycin is administered during cycles 1, 3, and 5 and the regimen of cyclophosphamide and VP-16 during cycles 2 and 6. Cycle 4 chemotherapy includes cisplatin and VP-16. During consolidation, cisplatin and VP-16 are administered during cycles 7, 8, and 10 and cyclophosphamide and adriamycin are administered during cycles 9 and 11.

To date, eight patients ages 1-9 have received up to six of eleven planned cycles of chemotherapy. Filgrastim was administered subcutaneously at doses of 5 to 15 mcg/kg/day. In cycles 1, 3, and 5 the incidence of neutropenia ($< 0.5 \times 10^9/L$) was reduced by 27-53% compared to historical controls. The incidence of neutropenia in cycles 2 and 6 and the incidence in cycle 4 was also lower by 5-14% and by 30%, respectively. Overall, during induction chemotherapy, the median duration of neutropenia was < 4 days. The median duration of neutropenia in study patients for cycles 1, 3, and 5 across all dose levels was 0-1 days. In cycles 2 and 6 the median duration was 3 and 4 days, respectively. In cycle 4 the median duration of neutropenia was 3.5 days. No adverse events were reported by the investigator to be related to Filgrastim. The pattern of adverse events observed in these children is similar to that observed in adults treated with chemotherapy, although bone pain does not appear to occur as frequently as has been reported in adults.

B. Safety Parameters

1. Laboratory Parameters

Changes in coagulation indices, red blood cell, and platelet counts reported during treatment with Filgrastim alone were minor and consistent with changes normally observed in a cancer population over a 1 to 4 week period. One patient with a near-normal platelet count at entry into a study was reported to have a WHO grade four downward shift of platelet count on day 8 of Filgrastim. The mechanism of this change was not determined. One or two-grade upward shifts in reticulocyte cell counts were reported in 56% of patients. It is not known whether this change was caused by Filgrastim. Earlier erythrocyte precursors were not reported.

There was no change in coagulation indices. Substantial and frequent clinically significant shifts in red blood cell indices and platelet counts were reported during treatment with cytotoxic chemotherapy and Filgrastim. These changes were consistent with those expected in a cancer population receiving cytotoxic chemotherapy. Approximately half of the patients were reported to experience downward shifts of three or four WHO grades in hemoglobin, hematocrit, red blood cell counts and platelet counts. Increased reticulocyte counts, consistent with a normal response to anemia in cancer patients, were reported in two-thirds of the patients.

There was no evidence that decreases in hemoglobin, hematocrit, red blood cell counts or platelet counts were dependent on the dose of Filgrastim. Red blood cell and platelet abnormalities were most frequent and most severe in the dose group 3.45 to 11.5 mcg/kg/day; this group included patients from the Phase III study who were treated with up to six cycles of CAE chemotherapy. In other dose groups, less myelosuppressive regimens and/or shorter periods of cytotoxic chemotherapy were given. These data, together with observations made in the Phase III study, support the view that cytotoxic chemotherapy was the major factor responsible for decreases in red blood cell and platelet counts. The observation of slightly decreased platelet counts in Phase I studies suggest that Filgrastim may exert contributory effects to cytotoxic chemotherapy-induced thrombocytopenia.

Increases in total WBC counts to levels greater than $100 \times 10^9/L$ were reported in 3 patients during treatment with Filgrastim alone. These elevations were reported at doses of > 11.5 mcg/kg/day. No patient's WBC exceeded $120 \times 10^9/L$ and there were no reported clinical sequelae associated with high counts. Precursor cells disappeared from the blood within 1 to 4 days of stopping drug. High WBC counts invariably normalized within 1 to 6 days. No clinical adverse events were reported in association with elevated WBCs or their precursors.

The pattern of WBC shifts reported during treatment with cytotoxic chemotherapy and Filgrastim was similar to that observed during treatment with Filgrastim alone. Increases in

total WBC counts to levels greater than $100 \times 10^9/L$ were reported at doses of ≥ 3.45 mcg/kg/day. Normalization after high counts was similar to that observed in Phase I studies.

Increases in white blood cell differential cell counts followed patterns which were consistent across all studies and in line with pharmacological actions of Filgrastim demonstrated in Phase I studies. There were no reported clinical adverse events associated with high WBC, differential or precursor cell counts.

A consistent pattern of biochemistry changes was reported in all Phase I studies and included Filgrastim dose-dependent increases in serum uric acid, lactate dehydrogenase and alkaline phosphatase but these changes did not require clinical treatment. Elevation of serum uric acid was the most frequently reported serum biochemistry abnormality and occurred in 40% of patients overall. Serum uric acid was reported to increase in 12%, 32%, and 68% of patients at doses of 0.345-3.45, 3.45-11.5 and 23.0-115.0 mcg/kg, respectively. Seven of 41 evaluable patients (17%) were reported to experience one to three grade increases in Gamma Glutamyl Transpeptidase (GGT). A number of other parameters were reported to show minor and infrequent increases. These included SGOT (one grade increase in 14% of patients) and SGPT (one or two grades increase in 8% of patients). Serum biochemistry abnormalities normalized within one week of discontinuing drug. No associated clinical sequelae were reported.

Changes in serum biochemistry values reported in patients treated with cytotoxic chemotherapy and Filgrastim were similar to those reported in Phase I investigations. Establishment of dose-dependency of biochemical abnormalities was less straightforward in these studies which were confounded by the biochemical effects of cytotoxic chemotherapy. Greater than WHO grade one increases in serum uric acid, alkaline phosphatase and lactate dehydrogenase were each reported in 13 to 17% of patients. All abnormalities associated with Filgrastim were reversible on stopping therapy. Other biochemical abnormalities were infrequent and/or mild. Elevations in uric acid were not associated with any adverse events.

There were no significant abnormalities of serum electrolytes which were associated with Filgrastim treatment in these studies.

2. Antibodies

None of the serum samples from 192 patients tested by radioimmunoassay demonstrated a significant increase in Filgrastim specific, post-treatment reactivity. There is no evidence for the generation of drug specific antibodies in any of the patient samples tested to date.

3. Adverse Reactions

The most commonly cited adverse event associated with Filgrastim was mild to moderate bone pain in 22% of patients given doses in the range of 3.45 to 11.5 $\mu\text{g}/\text{kg}$. In addition to causing dose-dependent, predictable and manageable musculoskeletal pain, Filgrastim causes dose-dependent, predictable and reversible elevations in serum uric acid, lactate dehydrogenase and alkaline phosphatase. No clinical sequelae have been reported in association with serum biochemistry abnormalities. Transient decreases in blood pressure ($<90/60$ mmHg), which did not require clinical treatment, were reported in 7 of 176 patients in phase III clinical studies.

In studies of Filgrastim 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 (i.e., full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and non-hematologic consequences of increased chemotherapy doses. Regular monitoring of the hematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of Filgrastim in conjunction with other drugs known to lower the platelet count. In septic patients receiving Filgrastim, the physician should be alert to the theoretical possibility of adult respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation. Cardiac events have been reported in 11 of 375 cancer patients receiving Filgrastim in clinical studies; the relationship to therapy is unknown. However, patients with pre-existing cardiac conditions should be monitored closely.

VI. ADVISORY COMMITTEE REVIEW

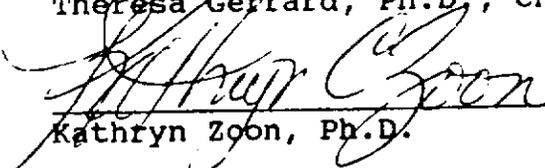
The data in support of this application for the use of Amgen's G-CSF for use in preventing infections following chemotherapy was reviewed by the members of the Biological Response Modifiers Advisory committee on December 14, 1990. The committee concurred with the efficacy of G-CSF in reducing infections, (as defined by febrile neutropenia), reducing days of hospitalization and reducing days of intravenous antibiotics; despite the lack of a proven survival benefit to treated patients. The committee suggested that the clinical use of G-CSF would be appropriate in settings where the intensity of chemotherapy and the period of neutropenia are similar to those used in studies that have demonstrated clinical benefit in patients with nonmyeloid malignancies. They further recommended that there is no reason to exclude children with nonmyeloid malignancies from receiving G-CSF therapy.

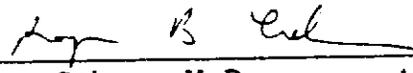
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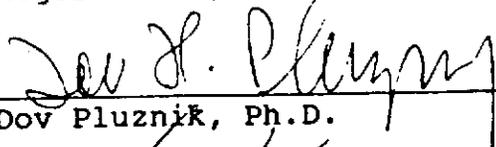
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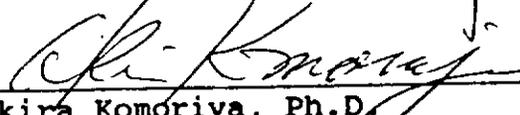
Filgrastim
Licensed: February 20, 1991
Licensing Committee Members

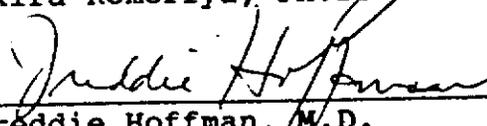

Theresa Gerrard, Ph.D., Chairperson

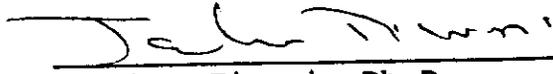

Kathryn Zoon, Ph.D.

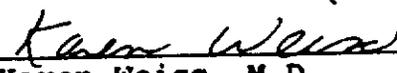

Roger Cohen, M.D.

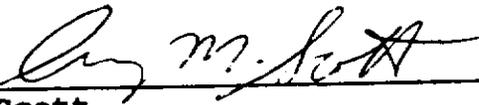

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Amy Scott

NEUPOGEN® (Filgrastim)

DESCRIPTION

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. G-CSF is a colony stimulating factor which has been shown to have minimal direct growth or survival effects on the production of other hematopoietic cell types. NEUPOGEN® is the Argen Inc. trademark for Filgrastim, which has been selected as the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

NEUPOGEN® (Filgrastim) is a 175 amino acid protein manufactured by recombinant DNA technology. 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 non-glycosylated 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 $1.0 \pm 0.1 \times 10^6$ U/mg (as measured by a cell matogenesis assay). The product is formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% mannitol and 0.004% Tween® 80. The quantitative composition (per mL) of NEUPOGEN® is:

| | |
|---------------------|----------|
| Filgrastim | 300 mcg |
| Acetate | 0.59 mg |
| Mannitol | 50.0 mg |
| Tween® 80 | 0.004% |
| Sodium | 0.035 mg |
| Water for Injection | |
| USP q.s. ad | 1.0 mL |

Manufacture is initiated at Argen Inc. from a master seed lot of E. coli containing the gene for r-metHuG-CSF. The E. coli are grown and the product is purified by conventional means. Prior to final purification, r-metHuG-CSF is allowed to oxidize to its native state and its final purity is achieved by sequential passage over a series of chromatography columns. The product is then formulated in an acetate buffer with mannitol and Tween® 80.

Filling and packaging operations for NEUPOGEN® are performed by an outside, FDA-approved contractor.

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 with selectivity for the neutrophil lineage. G-CSF is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

Pre-clinical Experience

Filgrastim 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 Filgrastim by the oral, intravenous, subcutaneous, or intraperitoneal 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 and 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 cerebellum and cerebellum. In contrast, no monkeys died following 13 weeks of daily intravenous administration of Filgrastim at a dose level of 115 mcg/kg.

In subacute, repeated-dose studies, changes observed were attributable to the expected pharmacological actions of Filgrastim (i.e., 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 four 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, osteoclasts and osteonogenesis were found in the femur, humerus, coccyx and hind legs (where they were accompanied by synovitis) after intravenous treatment for four weeks (115 to 1150 mcg/kg/day), and in the sternum after intravenous treatment for 13 weeks (115 to 575 mcg/kg/day). These effects reversed to normal within 4 to 5 weeks following cessation of treatment.

Pharmacologic Effects of NEUPOGEN®

In Phase I studies involving patients with a mean non-myeloid malignancy on NEUPOGEN® (Filgrastim) administration resulted in a dose-dependent increase in circulating neutrophil counts in the dose range of 1-70 mcg/kg/day. This increase in neutrophil counts was observed whether NEUPOGEN® was administered intravenously (1-70 mcg/kg twice daily) subcutaneously (1-1 mcg/kg once daily), or by continuous subcutaneous infusion (1-11 mcg/kg/day). With discontinuation of NEUPOGEN® therapy, neutrophil counts returned to baseline in most cases within two days. Mature 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 chemotactic activity) in vitro.

The absolute monocyte count was required 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 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 intravenous 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 0.5-0.7 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 doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following NEUPOGEN® doses of 3.45 mcg/kg). Continuous 24-hour intravenous infusions at 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.

INDICATIONS AND USAGE

NEUPOGEN® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (see CLINICAL EXPERIENCE). A complete blood count 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 III clinical studies, NEUPOGEN® therapy was discontinued when the absolute neutrophil count (ANC) was $210,000/mm^3$ after the expected chemotherapy-induced nadir.

Clinical Experience: Response to NEUPOGEN®

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 III clinical trial in small cell lung cancer, patients received subcutaneous administration of NEUPOGEN® 4 to 8 mcg/kg/day, days 1-12 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 intravenous antibiotic usage. No difference in survival or disease progression was demonstrated.

In the Phase III, 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 60% (60/99) 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 one, versus 53% (51/99) for NEUPOGEN®-treated patients (p<0.012). The incidence of intravenous antibiotic usage was 60% (67/111) for placebo-treated patients in cycle one, versus 38% (38/99) for NEUPOGEN®-treated patients (p<0.003). The incidence, severity, and duration of severe neutropenia (ANC< $500/mm^3$) following chemotherapy were all significantly reduced. The incidence of severe neutropenia in cycle one was 84% (81/99) 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) cycled rate of severe neutropenia versus 77% (416/543) cycles for patients randomized to placebo. The median duration of severe neutropenia in cycle one was reduced from 6 days (range 0-10 days) for patients receiving placebo to 2 days (range 0-9 days) for patients receiving NEUPOGEN® (p<0.001). The mean duration of neutropenia in cycle one was 5.6±2.27 for patients receiving placebo versus 2.4±1.90 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/mm³ (range 0/mm³-7912/mm³) in cycle one for patients receiving NEUPOGEN® versus 36/mm³ (range 0/mm³-9520/mm³) for patients receiving placebo (p<0.012). The mean severity of neutropenia in cycle one was 496/mm³±1382/mm³ for patients receiving NEUPOGEN® versus 204/mm³±953/mm³ for patients receiving placebo. Over all cycles, the ANC nadir for patients randomized to NEUPOGEN® was 403/mm³, versus 161/mm³ 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 versus day 12). NEUPOGEN® was well tolerated when given subcutaneously 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 III 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

data is reflective of the chemotherapy regimen it made. The effect of NEUPOGEN® (filgrastim) on tumor growth or on the antitumor activity of the chemotherapy were not assessed. The doses of NEUPOGEN® used in these studies are usually higher than those found to be effective in the Phase III study described above. Such Phase III studies are summarized in the following table.

| Type of Malignancy | Regimen | Chemotherapy Dose | Number of Pts. | Trial Phase | NEUPOGEN® Daily Dose* |
|------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------|-------------|------------------------------------------------------|
| Small Cell Lung Cancer | Cyclophosphamide Doxorubicin Etoposide | 1 g/m ² /day 50 mg/m ² /day 120 mg/m ² /day x3 q 21 days | 210 | III | 4.8 mcg/kg SC days 4-17 |
| Small Cell Lung Cancer† | Hexamethylmelamine Doxorubicin Etoposide Mesna | 5 g/m ² /day 50 mg/m ² /day 120 mg/m ² /day x3 8 g/m ² /day q 21 days | 12 | III | 5.75-46 mcg/kg IV days 4-17 |
| Urothelial Cancer‡ | Methotrexate Vincristine Doxorubicin Cisplatin | 30 mg/m ² /day x2 3 mg/m ² /day x2 30 mg/m ² /day 70 mg/m ² /day q 28 days | 40 | III | 3.45-69 mcg/kg IV days 4-11 |
| Various Non-Myeloid Malignancies†† | Cyclophosphamide Etoposide Cisplatin | 2.5 g/m ² /day x2 500 mg/m ² /day x3 50 mg/m ² /day x3 q 28 days | 18 | III | 23-69 mcg/kg IV days 8-28 |
| Breast/Ovarian‡‡ | Doxorubicin | 75 mg/m ² 100 mg/m ² 125 mg/m ² 150 mg/m ² q 14 days | 21 | III | 11.5 mcg/kg days 2-9 IV 5.75 mcg/kg days 10-12 IV |
| Neuroblastoma | Cyclophosphamide Doxorubicin Cisplatin | 150 mg/m ² x2 35 mg/m ² 90 mg/m ² q 28 days cycles 1,3,5††† | 12 | III | 5.45-17.25 mcg/kg SC days 8-19 |

* 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.

† Lowest dose(s) tested in the study.

†† Patients received doxorubicin at either 75, 100, 125 or 150 mg/m².

††† Cycles 2,6 = cyclophosphamide 150 mg/m² x 7 and etoposide 200 mg/m² x 3

Cycle 4 = cisplatin 90 mg/m² x 1 and etoposide 200 mg/m² x 3

CONTRAINDICATIONS

NEUPOGEN® is contraindicated in patients with known hypersensitivity to E. coli-derived proteins.

WARNINGS

In cancer patients who have received NEUPOGEN® to date, no serious adverse reactions that would limit the use of the product have been reported.

PRECAUTIONS

General

Simultaneous Use with Chemotherapy

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 to 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 (e.g., nitrosoureas) or with mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-fluorouracil or cytosine arabinoside.

Growth Factor Potential

NEUPOGEN® is a growth factor that primarily stimulates neutrophils. However, the possibility that NEUPOGEN® can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Therefore, because of the possibility of tumor growth, precaution should be exercised in using this drug in any malignancy with myeloid characteristics.

Leukocytosis

White blood cell counts of 100,000/mm³ 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 complete blood count (CBC) is recommended twice per week during NEUPOGEN® therapy (see LABORATORY MONITORING).

Premature Discontinuation of NEUPOGEN® Therapy

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 until the post nadir ANC reaches 10,000/mm³. 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).

Chronic Administration

The safety and efficacy of chronic administration of NEUPOGEN® (Filgrastim) have not been established. Preliminary investigational studies with NEUPOGEN® have been conducted in 224 patients with severe chronic neutropenia, 13 of whom have been treated for up to three years. In these patients, with clinical splenomegaly, doses led by CT or MRI scanning) was the most frequently observed adverse effect, occurring in approximately one third of patients receiving chronic administration of NEUPOGEN®. 1% of patients were noted to have clinical splenomegaly. Less frequently observed adverse events included exacerbation of some pre-existing skin disorders (e.g., pruritus), dyspepsia, hematuria, proteinuria, thrombocytopenia (platelets less than 50,000/mm³) and osteoporosis.

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 (i.e., full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and non-hematologic 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. In septic patients receiving NEUPOGEN®, the physician should be alert to the theoretical possibility of adult respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation. 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. However, patients with pre-existing cardiac conditions receiving NEUPOGEN® should be monitored closely.

Information for Patients

In those situations in which the physician determines that the patient can safely and effectively self-administer NEUPOGEN®, the patient should be instructed as to the proper dosage and administration. Patients should be referred to the full "Information for Patients" section attached; it is not a disclosure of all, or possible, intended effects. The most common adverse experience occurring with NEUPOGEN® therapy is bone pain. 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.

Laboratory Monitoring

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 white blood cell 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 white blood cell counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

Drug Interactions

No evidence of interaction of NEUPOGEN® with other drugs was observed in the course of clinical trials.

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. There are no adequate and well controlled studies in pregnant women. 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 100 mcg/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 100 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 intravenous 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 four 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

Although efficacy of NEUPOGEN® has not been demonstrated in a pediatric population, safety data indicate that NEUPOGEN® does not exhibit any greater toxicity in children than in adults. NEUPOGEN® has been used to treat 120 pediatric severe chronic neutropenia patients; such patients ranged in age from 3 months to 18 years and were treated with NEUPOGEN® at 0.5-120 mcg/kg/day for up to three years. Such doses were well tolerated, and the overall pattern of adverse events in children and adults appeared to be similar. While subclinical increases in spleen size detected by imaging studies (CT or MRI) were reported more often in children than in adults, the clinical significance of these radiographic findings relative to normal growth and development is not known. No hematologic abnormalities were noted which were unique to children treated with NEUPOGEN®. In addition, 17 pediatric patients with neuroblastoma have received up to six 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.

ADVERSE REACTIONS

In clinical trials involving over 150 patients receiving NEUPOGEN® (filgrastim) following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or of the chemotherapy. In all Phase II and III trials, medullary bone pain, reported in 24% of patients with only consistently observed adverse reaction attributed to NEUPOGEN® therapy. This bone pain was generally reported to be 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 (20-100 mcg/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of NEUPOGEN® (3-10 mcg/kg/day).

In the randomized, double-blind, placebo-controlled trial of NEUPOGEN® therapy following combination chemotherapy in patients in a 2071 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 three cycles versus one cycle for placebo.

| Event | % of Blinded Cycles with Events | |
|----------------------|----------------------------------------|--------------------------------------|
| | NEUPOGEN® N = 184 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 III clinical studies following administration of NEUPOGEN®.

No evidence of interaction of NEUPOGEN® with other drugs was observed in the course of clinical trials (see PRECAUTIONS — SIMULTANEOUS USE WITH CHEMOTHERAPY). To date, there have been no reported allergic reactions or anaphylaxis attributed to NEUPOGEN® administration in over 500 patients treated with NEUPOGEN® for a variety of conditions. In this group of patients, including 13 who have received NEUPOGEN® daily for almost two years, there has been no evidence of the development of antibodies to NEUPOGEN® or of a blunted or diminished response over time.

OVERDOSAGE

The maximum tolerated dose of NEUPOGEN® has not been determined. Twenty-seven patients have been treated at NEUPOGEN® doses of 2.69 mcg/kg/day. Of those, six patients have been treated at 113 mcg/kg/day with no toxic effects attributable to NEUPOGEN®. Efficacy has been demonstrated using much lower doses. (Doses of 4 to 8 mcg/kg/day showed efficacy in the Phase II study.) Doses of NEUPOGEN® which increase the ANC beyond 10,000/mm³ may not result in any additional clinical benefit.

In NEUPOGEN® clinical trials, white blood cell counts >100,000/mm³ have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leukocytosis, that NEUPOGEN® therapy should be discontinued if the ANC count surpasses 10,000/mm³ after the ANC nadir has occurred.

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 3 to 7 days.

DOSAGE AND ADMINISTRATION

The recommended starting dose of NEUPOGEN® is 5 mcg/kg/day, administered subcutaneously or intravenously as a single daily injection. No data are currently available regarding NEUPOGEN® stability or compatibility with infusion equipment or diluted in intravenous solutions. 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 two weeks, until the ANC has reached 10,000/mm³ following the expected chemotherapy-induced neutrophil nadir. The duration of NEUPOGEN® therapy needed to alternate 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/mm³ after the expected chemotherapy-induced neutrophil nadir (see PRECAUTIONS). In Phase III trials, efficacy was observed at doses of 4 to 8 mcg/kg/day.

Injectable solution: Each 1 mL of NEUPOGEN® (Filgrastim) contains 300 mcg of Filgrastim in a preservative-free solution containing 0.19 mg sodium, 50 mcg mannitol, 0.004% Tween® 80, 0.111% mg sodium, and 1 mL water for injection, USP, pH 4.0. Each 1.6 mL of NEUPOGEN® contains 480 mcg of Filgrastim in a preservative-free solution containing 0.94 mg sodium, 30 mg mannitol, 0.004% Tween® 80, 0.056 mg sodium, and 1.6 mL water for injection, USP, pH 4.0.

NEUPOGEN® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 6 hours. Any vial left at room temperature for greater than 6 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.

Single-dose, preservative-free vials containing 300 mcg (1 mL) of Filgrastim (300 mcg/mL). Boxes of 10 (NDC 55513-347-10).

Single-dose, preservative-free vials containing 480 mcg (1.6 mL) of Filgrastim (300 mcg/mL). Boxes of 10 (NDC 55513-348-10).

NEUPOGEN® should be stored at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking.

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Manufactured by:

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Amgen Inc.

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Issue Date 2/71/91

NEUPOGEN® (Filgrastim)

INFORMATION FOR PATIENTS

NEUPOGEN® AND CHEMOTHERAPY

Your doctor has advised you to receive chemotherapy. As your doctor has explained, chemotherapeutic drugs are used because they may help destroy rapidly growing cells like cancer cells. However, certain normal cells in the body are affected by some chemotherapeutic drugs as well. The cells in the blood that are responsible for helping the body fight off infections are especially sensitive to these types of cancer drugs. If these infection-fighting cells, called neutrophils, fall to low levels in your blood after receiving chemotherapy, you could be more likely to get a fever and/or a serious infection. As your doctor has indicated, you must take specific precautions to avoid getting infections while you are being treated with chemotherapy.

To help speed the recovery of the infection-fighting cells after chemotherapy, and to reduce the chances of a serious infection, your doctor has prescribed NEUPOGEN® (filgrastim). NEUPOGEN® helps to maintain adequate levels of infection-fighting cells, or neutrophils. These cells work by surrounding and destroying bacteria that may have entered the body. NEUPOGEN® works by increasing the number of neutrophils in the blood and by preventing them from falling to dangerously low levels for prolonged periods of time. You should not administer NEUPOGEN® in the 24 hour period just before or the 24 hour period just after administration of your chemotherapy. NEUPOGEN® therapy also requires that you have laboratory tests twice weekly so your doctor can monitor your white blood cell count.

In those situations where your doctor has determined that you can self-administer NEUPOGEN®, you will receive instruction on how much NEUPOGEN® to use, how to inject it, how often you should inject it, how you should dispose of unused portions of each vial, and for how many days your NEUPOGEN® therapy should continue. This schedule has been individualized for you. Proper treatment of your cancer requires close and constant cooperation with your doctor.

You have been instructed to be alert for fever, chills, or other signs of infection while you are at home between your chemotherapy cycles. If you experience any of these signs of infection, you must let your doctor know immediately. Although your doctor has discussed the expected side effects of your chemotherapy, a side effect attributed to NEUPOGEN® may be bone pain. If you experience bone pain, discuss its treatment with your doctor.

If your doctor has directed you to take NEUPOGEN®, when you receive your NEUPOGEN® from the physician or pharmacy, always check to see that:

1. The name NEUPOGEN® appears on the carton and vial label.
2. You will be able to use NEUPOGEN® before the expiration date stamped on the package.

NEUPOGEN®

NEUPOGEN® is produced in a non-disease-causing special laboratory strain of *Escherichia coli* bacteria which has been genetically altered by the addition of a gene for the natural substance granulocyte colony stimulating factor.

The NEUPOGEN® solution in the vial should always be clear and colorless. Do not use NEUPOGEN® if the contents of the vial appear discolored or cloudy, or if the vial appears to contain lumps, flakes, or particles. If the vial has been shaken vigorously, the solution may appear to be frothy or have bubbles at the top of the vial; this does not alter the effectiveness of NEUPOGEN®, but may decrease the amount of NEUPOGEN® that can be drawn into the syringe. Therefore, care should be taken not to shake the NEUPOGEN® vial before use. If the solution is frothy, allowing the vial to sit undisturbed for a few minutes should result in a decrease in froth or bubbles (see PREPARING THE DOSE). Vials of NEUPOGEN® are for single use. Any unused portion of a vial should be discarded.

Storage:

NEUPOGEN® should be stored in the refrigerator, but not in the freezing compartment. Do not let the vial freeze or leave it in direct sunlight. Do not use a vial of NEUPOGEN® that has frozen or after the expiration date that is stamped on the label.

USE THE CORRECT SYRINGE

Your doctor has instructed you on how to give yourself the correct dosage of NEUPOGEN®. This dosage will usually be measured in milliliters. It is important to use a syringe that is marked in terms of milliliters (for example, 0.1, 0.2, etc., mL). Failure to use the proper syringe can lead to a mistake in dosage, and you may receive too much or too little NEUPOGEN®. Too little NEUPOGEN® may not be effective in reducing your risk of infections, and too much NEUPOGEN® may lead to neutrophil levels that are too high.

You should only use disposable syringes and needles as they do not require sterilization; they should be used once and disposed of as instructed by your doctor.

IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

PREPARING THE DOSE

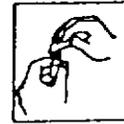
1. Wash your hands thoroughly with soap and water before preparing the medication.
2. Check the date on the NEUPOGEN® vial to be sure that the drug has not expired.



- Remove the vial of NEUPOGEN® (filgrastim) from the refrigerator and allow it to reach room temperature. Each NEUPOGEN® vial is designed to be used only once; do not re-enter the vial. **DO NOT SHAKE.** Assemble the other supplies you will need for your injection.



- Cleanse the skin where the injection is to be made with an alcohol swab.



- Flip off the protective cap but do not remove the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab.



- Using a syringe and needle designed for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your NEUPOGEN® dose.
- Carefully remove the needle cover. Put the needle through the rubber stopper of the NEUPOGEN® vial.



- Push the plunger in to discharge air into the vial. The air injected into the vial will allow NEUPOGEN® to be easily withdrawn into the syringe.

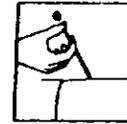


- Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the NEUPOGEN® solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of NEUPOGEN® into the syringe.

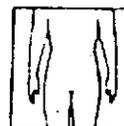
- 10 Check for air bubbles. The air is harmless, but too large an air bubble will reduce the NEUPOGEN® (filgrastim) dose. To remove air bubbles, gently push the solution back into the vial and re-measure your correct dose of NEUPOGEN®.
- 11 Double check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

INJECTING THE DOSE

1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.



2. Hold the syringe with the other hand, as you would a pencil. Double check that the correct amount of NEUPOGEN® is in the syringe. Insert the needle straight into the skin (90 degree angle). Pull the plunger back slightly. If blood comes into the syringe, do not inject NEUPOGEN®, as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the NEUPOGEN® by pushing the plunger all the way down.
3. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press the alcohol swab over the injection site for several seconds.
4. Use the disposable syringe only once to insure sterility of the syringe and needle and to insure accuracy of the dose. Dispose of syringes and needles as directed by your physician, by following these simple steps:
 - Place all used needles and syringes in a hard plastic container with a screw-on cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to contents. 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. When the container is full, tape around the cap or lid, and dispose of according to your doctor's instructions.
 - Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
 - Always store the container out of the reach of children.
 - Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.



5. Always change the site for each injection as directed by your doctor. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that doesn't go away, contact your physician.

USAGE IN PREGNANCY

If you are pregnant or nursing a baby, consult your physician before using NEUPOGEN® (Filgrastim).

ALLERGY TO NEUPOGEN®

Patients occasionally experience redness, swelling, or itching at the site of injection of NEUPOGEN®. This may indicate an allergy to the components of NEUPOGEN®, or it may indicate a local reaction. If you have a local reaction, consult your physician. A potentially more serious reaction, however, one never reported in clinical trials, would be a generalized allergy to NEUPOGEN®, which could cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. If you think you are having a generalized allergic reaction, stop taking NEUPOGEN® and notify a physician or emergency medical personnel immediately.

IMPORTANT NOTES

If your doctor allows you to self-administer NEUPOGEN®, please note the following:

1. Always follow the instructions of your doctor concerning the dosage and administration of NEUPOGEN®. Do not change the dose or instructions for administration of NEUPOGEN® without consulting your physician.
2. Your doctor will tell you what to do if you miss a dose of NEUPOGEN®. Always keep a spare syringe and needle on hand.
3. If you develop a fever or symptoms of infection, contact your doctor.
4. Consult your doctor if you notice anything unusual about your condition or your use of NEUPOGEN®.

Manufactured by:

AMGEN

Amgen Inc.
Amgen Center
Thousand Oaks, California 91320-1789

0347C200

Issue Date 2/21/91

Lot
EXP.

03476011
FILGRASTIM
NEUROGEN
1

ing Packs
(10 Vials)

U.S. License No. 1080

NDC 55513-347-10
4 - 10 Vial Dispensing Packs
(40 - 1 mL Single Use Vials)

NDC 55513-347-10

4 - 10 Vial Dispensing Packs
(40 - 1 mL Single Use Vials)

FILGRASTIM NEUPOGEN®

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

1 ml 300 mcg/mL (3×10^7 Units/mL) For
Subcutaneous or Intravenous Use Only
Sterile Solution - No Preservative

U.S. License No. 1080

AMGEN
Amgen Inc.
Thousand Oaks,
CA 91320 U.S.A.

Refrigerate
at 2° to 8°C
(36° to 46°F)
Do Not Freeze.
Avoid Shaking.

NDC 55513-347-10

4 - 10 Vial Dispensing Packs
(40 - 1 mL Single Use Vials)

1 mL FILGRASTIM NEUPOGEN®

Each 1 mL vial contains: 300 mcg (3×10^7 Units) of
FILGRASTIM in a sterile, preservative-free solution (pH 4.0)
containing acetate (0.59 mg), mannitol (50 mg), Tween® 80
(0.004%), sodium (0.035 mg) in Water for Injection, USP.

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Thousand Oaks,
CA 91320 U.S.A.

Refrigerate
at 2° to 8°C
(36° to 46°F)
Do Not Freeze.
Avoid Shaking.

0347C022

NDC 55513-347-10

4 - 10 Vial Dispensing Packs
(40 - 1 mL Single Use Vials)

1 mL
FILGRASTIM
NEUPOGEN[®]

300 mcg/mL (3 x 10⁷ Units/mL)

Refrigerate at 2° to 8°C (36° to 46°F)
Do Not Freeze. Avoid Shaking.

NDC 55513-347-10

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

1 mL

FILGRASTIM NEUPOGEN®

Each 1 mL vial contains: 300 mcg (3×10^7 Units) of
FILGRASTIM in a sterile, preservative-free solution (pH 4.0)
containing acetate (0.59 mg), mannitol (50 mg),
Tween® 80 (0.004%), sodium (0.035 mg)
in Water for Injection, USP.

5F)

1 mL

Steri

vative

Refrigerate at
2° to 8°C (36° to 46°F)
Do Not Freeze.

Avoid Shaking.

NDC 55513-347-10
1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)
1 mL
FILGRASTIM
NEUPOGEN®
300 mcg/mL (3×10^7 Units/mL)

U.S. License No. 1080

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

1 mL
FILGRASTIM
NEUPOGEN®

300 mcg/mL (3×10^7 Units/mL)



3 55513-347-10 5

NDC 55513-347-10

©Amgen Inc. 1991

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

1 mL **FILGRASTIM**
NEUPOGEN®

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Amgen Inc.
Thousand Oaks,
CA 91320 U.S.A.

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

300 mcg/mL (3 x 10⁷ Units/mL)

Refrigerate
at 2° to 8°C
(36° to 46°F)
Do Not Freeze.
Avoid Shaking.

0347C011

Caution: Federal Law
prohibits dispensing
without a prescription.

300 mcg/mL (3 x 10⁷ Units/mL)

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

FILGRASTIM NEUPOGEN®

1 mL

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

NDC 55513-347-10

NDC 55513-347-10

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

FILGRASTIM NEUPOGEN®

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

1 mL

300 mcg/mL (3 x 10⁷ Units/mL) For
Subcutaneous or Intravenous Use Only
Sterile Solution + No Preservative

U.S. License No. 1080

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Amgen Inc.
Thousand Oaks, CA 91320 U.S.A.

Refrigerate at
2° to 8°C (36° to 46°F)
Do Not Freeze.
Avoid Shaking.

U.S. License No. 1080

NDC 55513-347-10

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

1 mL FILGRASTIM NEUPOGEN®

300 mcg/mL (3 x 10⁷ Units/mL)



NDC 55513-347-10

1 - 10 Vial Dispensing Pack
(10 - 1 mL Single Use Vials)

1 mL
FILGRASTIM
NEUPOGEN®
300 mcg/mL (3 x 10⁷ Units/mL)

16
NDC 250-34-01 Filgrastim rF-P-FC
FILGRASTIM
NEUPOGEN
Net weight 0.175 (6.25 mg) Volume 1.0 mL
Injectable, Sterile Solution, 15.75 mg/mL All weights in mg

0348011

Lot
Exp.

Caution: Federal law
prohibits dispensing

300 mcg/mL (3 x 10⁷ Units/mL)

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

1.6^{ml} FILGRASTIM NEUPOGEN[®]

1 - 10 Vial Dispensing Pack
(10 - 1.6 mL Single Use Vials)

NDC 55513-348-10

NDC 55513-348-10

1 - 10 Vial Dispensing Pack
(10 - 1.6 mL Single Use Vials)

FILGRASTIM NEUPOGEN[®]

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

1.6^{ml} 300 mcg/mL (3 x 10⁷ Units/mL) For
Subcutaneous or Intravenous Use Only
Sterile Solution - No Preservative

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Thousand Oaks, CA 91320 U.S.A.

Refrigerate at
2° to 8°C (36° to 46°F)
Do Not Freeze.
Avoid Shaking.

NDC 55513-348-10 U.S. License No. 1080

1 - 10 Vial Dispensing Pack
(10 - 1.6 mL Single Use Vials)

1.6^{ml} FILGRASTIM NEUPOGEN[®]

300 mcg/mL (3 x 10⁷ Units/mL)



NDC 55513-348-10

1 - 10 Vial Dispensing Pack
(10 - 1.6 mL Single Use Vials)

1.6^{ml} FILGRASTIM NEUPOGEN[®]

1.6 mL Single Use Vial

NDC 55513-344-10

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1 - 10 Vial Dispensing Pack
(10 - 1.6 mL Single Use Vials)

**1.6^{mL} FILGRASTIM
NEUPOGEN[®]**

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Thousand Oaks,
CA 91320 U.S.A.

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

300 mcg/mL (3 x 10⁷ Units/mL)

Refrigerate
at 2° to 8°C
(36° to 46°F)
Do Not Freeze.
Avoid Shaking.

0348C011

4 - 10 Vial Dispensing Packs
(40 - 1.6 mL Single Use Vials)

NDC 55513-348-10

NDC 55513-348-10

4 - 10 Vial Dispensing Packs
(40 - 1.6 mL Single Use Vials)

FILGRASTIM NEUPOGEN®

A Recombinant Granulocyte Colony Stimulating Factor (rG-CSF)

1.6 mL 300 mcg/mL (3×10^7 Units/mL) For
Subcutaneous or Intravenous Use Only
Sterile Solution - No Preservative

U.S. License No. 1080

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Thousand Oaks,
CA 91320 U.S.A.

Refrigerate
at 2° to 8°C
(36° to 46°F)
Do Not Freeze.
Avoid Shaking.

NDC 55513-348-10

4 - 10 Vial Dispensing Packs
(40 - 1.6 mL Single Use Vials)

1.6 mL FILGRASTIM NEUPOGEN®

Each 1.6 mL vial contains: 480 mcg (4.8×10^7 Units) of
FILGRASTIM in a sterile, preservative-free solution (pH 4.0)
containing acetate (0.94 mg), mannitol (80 mg), Tween® 80
(0.004%), sodium (0.056 mg) in Water for Injection, USP.

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CA 91320 U.S.A.

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