HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEUPOGEN safely and effectively. See full prescribing information for NEUPOGEN.

NEUPOGEN® (filgrastim) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 1991

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.6)	03/2015
Dosage and Administration (2.5)	03/2015
Warnings and Precautions: Glomerulonephritis (5.5)	07/2015

----------INDICATIONS AND USAGE----------

NEUPOGEN is a leukocyte growth factor indicated to

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.1)
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Patients acutely exposed to myelosuppressive doses of radiation
  - 10 mcg/kg/day subcutaneous injection (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Vial

- Injection: 300 mcg/mL in a single-use vial (3)
- Injection: 480 mcg/1.6 mL in a single-use vial (3)

Prefilled Syringe

- Injection: 300 mcg/0.5 mL in a single-use prefilled syringe (3)
- Injection: 480 mcg/0.8 mL in a single-use prefilled syringe (3)

----------CONTRAINDICATIONS----------

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim. (4)

----------WARNINGS AND PRECAUTIONS----------

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue NEUPOGEN in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of NEUPOGEN if causality is likely. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions in patients: (6.1)

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia and headache. (6.1)
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- NEUPOGEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- It is not known whether NEUPOGEN is excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [7/2015]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever *[see Clinical Studies (14.1)]*.

1.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

NEUPOGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) *[see Clinical Studies (14.2)]*.

1.3 Patients with Cancer Undergoing Bone Marrow Transplantation

NEUPOGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation *[see Clinical Studies (14.3)]*.

1.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

NEUPOGEN is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis *[see Clinical Studies (14.4)]*.

1.5 Patients with Severe Chronic Neutropenia

NEUPOGEN is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia *[see Clinical Studies (14.5)]*.

1.6 Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

NEUPOGEN is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation *[see Clinical Studies (14.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of NEUPOGEN is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting NEUPOGEN therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping NEUPOGEN if the ANC increases beyond 10,000/mm^3 *[see Warnings and Precautions (5.10)]*.

Administer NEUPOGEN at least 24 hours after cytotoxic chemotherapy. Do not administer NEUPOGEN within the 24-hour period prior to chemotherapy *[see Warnings and Precautions (5.12)]*. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of NEUPOGEN therapy. Therefore, to ensure a sustained therapeutic response, administer NEUPOGEN daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of NEUPOGEN therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

2.2 Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation

The recommended dosage of NEUPOGEN following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of

NEUPOGEN at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of NEUPOGEN against the neutrophil response (see Table 1).

Table 1. Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	NEUPOGEN Dosage Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days	Discontinue NEUPOGEN
Then, if ANC decreases to less than 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase NEUPOGEN to 10 mcg/kg/day, and then follow the above steps.

2.3 Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dosage of NEUPOGEN for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer NEUPOGEN for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of NEUPOGEN administration and leukapheresis schedule have not been established, administration of NEUPOGEN for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective *[see Clinical Studies (14.4)]*. Monitor neutrophil counts after 4 days of NEUPOGEN, and discontinue NEUPOGEN if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

2.4 Dosage in Patients with Severe Chronic Neutropenia

Prior to starting NEUPOGEN in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of NEUPOGEN prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

Dosage Adjustments in Patients with Severe Chronic Neutropenia

Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of NEUPOGEN were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of NEUPOGEN greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments

During the initial 4 weeks of NEUPOGEN therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

2.5 Dosage in Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

The recommended dose of NEUPOGEN is 10 mcg/kg as a single daily subcutaneous injection for patients exposed to myelosuppressive doses of radiation. Administer NEUPOGEN as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

Obtain a baseline CBC and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm^3 for 3 consecutive CBCs. Do not delay administration of NEUPOGEN if a CBC is not readily available.

Continue administration of NEUPOGEN until the ANC remains greater than 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir.

2.6 Important Administration Instructions

NEUPOGEN is supplied in single-dose vials (for subcutaneous use or intravenous infusion) and single-dose prefilled syringes (for subcutaneous use) *[see Dosage Forms and Strengths (3)]*. Prior to use, remove the vial or prefilled syringe from the refrigerator and allow NEUPOGEN to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any vial or prefilled syringe left at room temperature for greater than 24 hours. Visually inspect NEUPOGEN for particulate matter and discoloration prior to administration (the solution is clear and colorless). Do not administer NEUPOGEN if particulates or discoloration are observed.

Discard unused portion of NEUPOGEN in vials or prefilled syringes; do not re-enter the vial. Do not save unused drug for later administration.

Subcutaneous Injection

Inject NEUPOGEN subcutaneously in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. If patients or caregivers are to administer NEUPOGEN, instruct them in appropriate injection technique and ask them to follow the subcutaneous injection procedures in the *Patient Information*.

Administration Instructions for the Prefilled Syringe

Persons with latex allergies should not administer the NEUPOGEN prefilled syringe, because the needle cap contains dry natural rubber (derived from latex).

Administration Instructions for Dilution (Vial Only)

If required for intravenous administration, NEUPOGEN (vial only) may be diluted in 5% Dextrose Injection, USP from a concentration of 300 mcg/mL to 5 mcg/mL (do not dilute to a final concentration less than 5 mcg/mL). NEUPOGEN diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP or 5% Dextrose plus Albumin (Human), NEUPOGEN is compatible with glass bottles, polyvinyl chloride (PVC) and polyolefin intravenous bags, and polypropylene syringes. **Do not dilute with saline at any time because the product may precipitate.**

Diluted NEUPOGEN solution can be stored at room temperature for up to 24 hours. This 24 hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Vial:

- Injection: 300 mcg/mL in a single-use vial
- Injection: 480 mcg/1.6 mL in a single-use vial

Prefilled Syringe:

- Injection: 300 mcg/0.5 mL in a single-use prefilled syringe
- Injection: 480 mcg/0.8 mL in a single-use prefilled syringe

4 CONTRAINDICATIONS

NEUPOGEN is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, have been reported in patients receiving NEUPOGEN. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving NEUPOGEN can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue NEUPOGEN in patients with serious allergic reactions. NEUPOGEN is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim.

5.4 Sickle Cell Disorders

Sickle cell crisis, in some cases fatal, has been reported with the use of NEUPOGEN in patients with sickle cell trait or sickle cell disease.

5.5 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving NEUPOGEN. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of NEUPOGEN. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of NEUPOGEN.

5.6 Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in NEUPOGEN-treated healthy donors undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of NEUPOGEN. The use of NEUPOGEN for PBPC mobilization in healthy donors is not an approved indication.

5.7 Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after G-CSF administration, including NEUPOGEN, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.8 Patients with Severe Chronic Neutropenia

Confirm the diagnosis of SCN before initiating NEUPOGEN therapy.

Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with NEUPOGEN for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of

NEUPOGEN on the development of abnormal cytogenetics and the effect of continued NEUPOGEN administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing NEUPOGEN should be carefully considered.

5.9 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving NEUPOGEN. Monitor platelet counts.

5.10 Leukocytosis

Patients with Cancer Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving NEUPOGEN at dosages above 5 mcg/kg/day. In patients with cancer receiving NEUPOGEN as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that NEUPOGEN therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages of NEUPOGEN that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of NEUPOGEN therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell Collection and Therapy

During the period of administration of NEUPOGEN for PBPC mobilization in patients with cancer, discontinue NEUPOGEN if the leukocyte count rises to > 100,000/mm^3.

5.11 Cutaneous Vasculitis

Cutaneous vasculitis has been reported in patients treated with NEUPOGEN. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term NEUPOGEN therapy. Hold NEUPOGEN therapy in patients with cutaneous vasculitis. NEUPOGEN may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

5.12 Potential Effect on Malignant Cells

NEUPOGEN is a growth factor that primarily stimulates neutrophils. The granulocyte-colony-stimulating factor (G-CSF) receptor through which filgrastim acts has also been found on tumor cell lines. The possibility that filgrastim acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim in chronic myeloid leukemia (CML) and myelodysplasia has not been established.

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

5.13 Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of NEUPOGEN given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use NEUPOGEN in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy *[see Dosage and Administration (2.2)]*.

The safety and efficacy of NEUPOGEN have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of NEUPOGEN with chemotherapy and radiation therapy.

5.14 Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture *[see Warnings and Precautions (5.1)]*
- Acute Respiratory Distress Syndrome *[see Warnings and Precautions (5.2)]*
- Serious Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Sickle Cell Disorders *[see Warnings and Precautions (5.4)]*
- Glomerulonephritis *[See Warnings and Precautions (5.5)]*
- Alveolar Hemorrhage and Hemoptysis *[see Warnings and Precautions (5.6)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.7)]*
- Thrombocytopenia *[see Warnings and Precautions (5.9)]*
- Leukocytosis *[see Warnings and Precautions (5.10)]*
- Cutaneous Vasculitis *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy

The following adverse reaction data in Table 2 are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, methylprednisolone, and methotrexate ("VIM3") (Study 3).

A total of 451 patients were randomized to receive subcutaneous NEUPOGEN 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Table 2. Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in NEUPOGEN Compared to Placebo)

System Organ Class Preferred Term	NEUPOGEN (N = 294)	Placebo (N = 157)
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%
Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%

Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

*Percent difference (NEUPOGEN – Placebo) was 4%.

Adverse events with ≥ 5% higher incidence in NEUPOGEN patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day NEUPOGEN (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in NEUPOGEN patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in NEUPOGEN patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment controlled study in patients with Hodgkin's disease (HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4 hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24 hour infusion (Study 6) NEUPOGEN (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection

The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: NEUPOGEN was administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of NEUPOGEN ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Table 3. Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in NEUPOGEN Patients)

System Organ Class Preferred Term	Mobilization Phase (N = 166)
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving NEUPOGEN (Study 7). 123 patients were randomized to a 4 month observation period followed by subcutaneous NEUPOGEN treatment or immediate subcutaneous NEUPOGEN treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of NEUPOGEN was determined by the category of neutropenia. Initial dosage of NEUPOGEN:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

Adverse reactions with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory tract infection and urinary tract infection were higher in the NEUPOGEN arm, total infection related events were lower in NEUPOGEN treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving NEUPOGEN has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using NEUPOGEN, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including timing of sampling, sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to filgrastim with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NEUPOGEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- acute respiratory distress syndrome *[see Warnings and Precautions (5.2)]*
- anaphylaxis *[see Warnings and Precautions (5.3)]*
- sickle cell disorders *[see Warnings and Precautions (5.4)]*

- glomerulonephritis *[see Warnings and Precautions (5.5)]*
- alveolar hemorrhage and hemoptysis *[see Warnings and Precautions (5.6)]*
- capillary leak syndrome *[see Warnings and Precautions (5.7)]*
- leukocytosis *[see Warnings and Precautions (5.10)]*
- cutaneous vasculitis *[see Warnings and Precautions (5.11)]*
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- decreased bone density and osteoporosis in pediatric patients receiving chronic treatment with NEUPOGEN

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. The potential risk to the fetus is unknown. Reports in the scientific literature have described transplacental passage of NEUPOGEN in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). NEUPOGEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

8.3 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 women who are breastfeeding.

8.4 Pediatric Use

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 to 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous NEUPOGEN at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of NEUPOGEN in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of NEUPOGEN. In this population, NEUPOGEN was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly 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.

The safety and effectiveness of NEUPOGEN have been established in pediatric patients with SCN *[see Clinical Studies (14.5)]*. In a phase 3 study (Study 7) to assess the safety and efficacy of NEUPOGEN in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 to 17) *[see Indications and Usage (1.5), Dosage and Administration (2.6), and Clinical Studies (14.5)]*.

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of NEUPOGEN treatment. Limited data from

patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic NEUPOGEN treatment. The relationship of these events to NEUPOGEN administration is unknown *[see Warnings and Precautions (5.8) and Adverse Reactions (6)]*.

The use of NEUPOGEN to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on studies conducted in animals and clinical data supporting the use of NEUPOGEN in other approved indications *[see Dosage and Administration (2.1 to 2.4) and Clinical Studies (14.6)]*.

8.5 Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of NEUPOGEN-treated patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

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

10 OVERDOSAGE

The maximum tolerated dose of NEUPOGEN has not been determined. In NEUPOGEN clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

11 DESCRIPTION

NEUPOGEN (filgrastim) is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) 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 injection is a sterile, clear, colorless, preservative-free liquid containing filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single-use vials and prefilled syringes. The single-use vials contain either 300 mcg/mL or 480 mcg/1.6 mL of filgrastim. The single-use prefilled syringes contain either 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim. See table below for product composition of each single-use vial or prefilled syringe.

	300 mcg/mL Vial	**480 mcg/1.6 mL Vial**	**300 mcg/0.5 mL Syringe**	**480 mcg/0.8 mL Syringe**
filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
polysorbate 80	0.04 mg	0.064 mg	0.02 mg	0.032 mg
sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg
sorbitol	50 mg	80 mg	25 mg	40 mg
water for Injection USP q.s. ad*	1 mL	1.6 mL	0.5 mL	0.8 mL

*quantity sufficient to make

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

12.2 Pharmacodynamics

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

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving NEUPOGEN; however, the percentage of monocytes in the differential count remained within the normal range. 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 patients with cancer.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, and hypersegmented neutrophils have been observed. Such changes were transient and were not associated with clinical sequelae, nor were they necessarily associated with infection.

12.3 Pharmacokinetics

Filgrastim exhibits nonlinear pharmacokinetics. Clearance is dependent on filgrastim concentration and neutrophil count: G-CSF receptor-mediated clearance is saturated by high concentration of NEUPOGEN and is diminished by neutropenia. In addition, filgrastim is cleared by the kidney.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of filgrastim resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and cancer subjects. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/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 dosages of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of filgrastim after subcutaneous administration is 60% to 70%.

Specific Populations

Patients Acutely Exposed to Myelosuppressive Doses of Radiation
The pharmacokinetics of filgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetics data in irradiated non-human primates, the area under the time-concentration curve (AUC), reflecting the exposure to filgrastim in non-human primates at 10 mcg/kg dose of NEUPOGEN, appears to be similar to that in humans at 5 mcg/kg. Simulations conducted using the population pharmacokinetic model indicates that the exposures to filgrastim at a NEUPOGEN dose of 10 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation are expected to exceed the exposures at a dose of 10 mcg/kg in irradiated non-human primates.

Pediatric Patients
The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim *[see Use in Specific Populations (8.4)]*.

Renal Impairment
In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end-stage renal disease (n=4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment
Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, filgrastim dose adjustment for patients with hepatic impairment is not necessary.

13 NONCLINICAL TOXICOLOGY

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

13.2 Animal Toxicology and Pharmacology
Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a nonclinical toxicology program, which included studies up to 1 year duration.

In the repeated-dose studies, changes observed were attributable to the expected pharmacological actions of filgrastim (i.e., dose-dependent increases in white blood cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). Histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis, and dose-related increases in spleen weight were seen in all species. These changes all reversed after discontinuation of treatment.

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
The safety and efficacy of NEUPOGEN to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive NEUPOGEN (n=99) at a dose of 230 mcg/m^2 (4 to 8 mcg/kg/day) or placebo

(n=111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1000/mm^3 and temperature > 38.2°C. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for NEUPOGEN-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm^3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

14.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of NEUPOGEN to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, *de novo* AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous NEUPOGEN (n=259) at a dose of 5 mcg/kg/day or placebo (n=262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1000/mm^3 for 3 consecutive days or ≥ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, NEUPOGEN-treated patients 14 days, placebo-treated patients 19 days ($p = 0.0001$: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, NEUPOGEN-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, NEUPOGEN-treated patients: 20 days versus placebo-treated patients: 25 days.

There were no statistically significant differences between the NEUPOGEN and the placebo groups in complete remission rate (69% - NEUPOGEN, 68% - placebo), median time to progression of all randomized patients (165 days - NEUPOGEN, 186 days - placebo), or median overall survival (380 days - NEUPOGEN, 425 days - placebo).

14.3 Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo controlled trial (Study 10).

In Study 6 patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, NEUPOGEN 10 mcg/kg/day, and NEUPOGEN 30 mcg/kg/day as a 24 hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the NEUPOGEN-treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion NEUPOGEN 10 mcg/kg/day (n=19), NEUPOGEN 30 mcg/kg/day (n=10) and no treatment (n=14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) in the NEUPOGEN-treated groups versus the control group (21.5 days in the control group versus 10 days in the NEUPOGEN-treated groups, $p < 0.001$). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the NEUPOGEN-treated groups, $p < 0.0001$).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive NEUPOGEN 300 mcg/m^2/day (n=33) or placebo (n=37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, $p < 0.001$) and time to recovery of ANC to ≥ 500/mm^3 (21 days in the control group and 16 days in the treatment group, $p < 0.001$).

14.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of NEUPOGEN to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using NEUPOGEN mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: NEUPOGEN was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of NEUPOGEN ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using NEUPOGEN mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm^3 by day 28. In clinical trials of NEUPOGEN for the mobilization of hematopoietic progenitor cells, NEUPOGEN was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm^3) was reached. The rate of engraftment of these cells in the absence of NEUPOGEN post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received NEUPOGEN-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patients received daily NEUPOGEN 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to NEUPOGEN-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

14.5 Patients with Severe Chronic Neutropenia

The safety and efficacy of NEUPOGEN to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < $500/mm^3$ on three occasions during a 6 month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < $500/mm^3$ per cycle. In addition patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4 month observation period followed by NEUPOGEN treatment or immediate NEUPOGEN treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia.

NEUPOGEN was administered subcutaneously. The dose of NEUPOGEN was determined by the category of neutropenia. Initial dose of NEUPOGEN:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to NEUPOGEN treatment. ANC response from baseline (< $500/mm^3$) was defined as follows:

- Complete response: median ANC > $1500/mm^3$
- Partial response: median ANC ≥ $500/mm^3$ and ≤ $1500/mm^3$ with a minimum increase of 100%
- No response: median ANC < $500/mm^3$

There were 112 of 123 patients who demonstrated a complete or partial response to NEUPOGEN treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving NEUPOGEN of the following parameters:

- incidence of infection
- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

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

14.6 Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Efficacy studies of NEUPOGEN could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of NEUPOGEN for other approved indications *[see Dosage and Administration (2.1 to 2.4)]*.

Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of human dose for NEUPOGEN is aimed at providing exposures to filgrastim that exceed those observed in

animal efficacy studies. The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates *[see Pharmacokinetics (12.3)]*. The safety of NEUPOGEN at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in approved indications.

The efficacy of NEUPOGEN was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC $\geq$ 1,000/mm^3 for 3 consecutive days, or ANC $\geq$ 10,000/mm^3 for more than 2 consecutive days within study day 1 to 5, or ANC $\geq$ 10,000/mm^3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated non-human primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Prefilled Syringes (SingleJect®)
Single-dose, preservative-free, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe® Needle Guard, containing 300 mcg/0.5 mL of filgrastim.

- Pack of 1 prefilled syringe (NDC 55513-924-91).
- Pack of 10 prefilled syringes (NDC 55513-924-10).

Single-dose, preservative-free, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe® Needle Guard, containing 480 mcg/0.8 mL of filgrastim.

- Pack of 1 prefilled syringe (NDC 55513-209-91).
- Pack of 10 prefilled syringes (NDC 55513-209-10).

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex) *[see Dosage and Administration (2.6)]*.

Store NEUPOGEN at 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not leave NEUPOGEN in direct sunlight. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard NEUPOGEN if frozen more than once. Avoid shaking. Transport via a pneumatic tube has not been studied.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients of the following risks and potential risks with NEUPOGEN:

- Rupture or enlargement of the spleen may occur. Symptoms include left upper quadrant abdominal pain or left shoulder pain. Advise patients to report pain in these areas to their physician immediately *[see Warnings and Precautions (5.1)]*.
- Dyspnea, with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea to their physician immediately *[see Warnings and Precautions (5.2)]*.
- Serious allergic reactions may occur, which may be signaled by rash, facial edema, wheezing, dyspnea, hypotension, or tachycardia. Advise patients to seek immediate medical attention if signs or symptoms of hypersensitivity reaction occur *[see Warnings and Precautions (5.3)]*.
- In patients with sickle cell disease, sickle cell crisis and death have occurred. Discuss potential risks and benefits for patients with sickle cell disease prior to the administration of human granulocyte colony-stimulating factors *[see Warnings and Precautions (5.4)]*.
- Glomerulonephritis may occur. Symptoms include swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production. Advise patients to report signs or symptoms of glomerulonephritis to their physician immediately *[see Warnings and Precautions (5.5)]*.
- Cutaneous vasculitis may occur, which may be signaled by purpura or erythema. Advise patients to report signs or symptoms of vasculitis to their physician immediately *[see Warnings and Precautions (5.11)]*.
- Advise females of reproductive potential that NEUPOGEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.
- Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) that efficacy studies of NEUPOGEN for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals *[see Clinical Studies (14.6)]*.

AMGEN®

NEUPOGEN® (filgrastim)

Manufactured by:
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US License Number 1080

Patent: http://pat.amgen.com/neupogen/

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1xxxxxx
V2X

Patient Information

NEUPOGEN® (nu-po-jen)

(filgrastim)
injection

What is NEUPOGEN?

NEUPOGEN is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *Escherichia coli*. G-CSF is a substance produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection.

Who <u>should not take</u> NEUPOGEN?

Do not take NEUPOGEN if you have had an allergic reaction to human G-CSFs such as NEUPOGEN (filgrastim) or Neulasta® (pegfilgrastim) or other forms of filgrastim.

What should I tell my doctor before taking NEUPOGEN?

Before you take NEUPOGEN, tell your doctor if you:

- have a sickle cell disorder.
- have a problem with your kidneys, as you may need more frequent urine tests.
- are allergic to latex. The needle cap on the prefilled syringes contains dry natural rubber (derived from latex). You should not give NEUPOGEN if you have latex allergies.
- are pregnant or plan to become pregnant. It is not known if NEUPOGEN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if NEUPOGEN passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Why am I given NEUPOGEN if I was exposed to radiation?

Exposure to high levels of radiation damages bone marrow. Damage to the bone marrow can be deadly. NEUPOGEN increases your chance of survival.

Effectiveness of NEUPOGEN in increasing survival after radiation exposure was only studied in animals. NEUPOGEN given after deadly radiation levels could not be studied in people.

How will I receive NEUPOGEN?

- If you or your child is receiving NEUPOGEN because you or your child is also receiving chemotherapy, the last dose of NEUPOGEN should be injected at least 24 hours before your next dose of chemotherapy.
- If you or your child is receiving NEUPOGEN because you or your child has been exposed to harmful doses of radiation, your healthcare provider will monitor your response to NEUPOGEN. Your healthcare provider will advise you when to discontinue NEUPOGEN.

What are the possible serious side effects of NEUPOGEN?

NEUPOGEN may cause serious side effects, including:

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking NEUPOGEN. A ruptured spleen can cause death. Call your doctor right away if you or your child has pain in the left upper stomach (abdomen) area or your left shoulder.

- **A serious lung problem called acute respiratory distress syndrome (ARDS).** Call your doctor or get emergency medical help right away if you or your child has shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.

- **Serious Allergic Reactions.** NEUPOGEN can cause serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating. If you or your child starts to have any of these symptoms, stop using NEUPOGEN and call your doctor or get emergency help right away. If you or your child has an allergic reaction during the injection of NEUPOGEN, stop the injection right away.

- **Sickle Cell Crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and take NEUPOGEN. Serious and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim. Call your doctor right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.

- **Kidney injury (glomerulonephritis).** Kidney injury has been seen in patients who received NEUPOGEN. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown colored urine or you notice you urinate less than usual.

- **Capillary leak syndrome.** NEUPOGEN can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
    - swelling or puffiness and are urinating less often
    - trouble breathing

- swelling of your stomach-area (abdomen) and feeling of fullness
- dizziness or feeling faint
- a general feeling of tiredness

- **Decreased platelet count (thrombocytopenia).** Your doctor will check your blood during treatment with NEUPOGEN. Tell your doctor if you have unusual bleeding or bruising while taking NEUPOGEN. This could mean a decrease of platelets, which reduces the ability of blood to clot.
- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with NEUPOGEN.
- **Inflammation of your blood vessels (cutaneous vasculitis).** Tell your doctor if you develop purple spots or redness of your skin.

The most common side effects of NEUPOGEN include aching in the bones and muscles.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NEUPOGEN. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

HOW TO PREPARE AND GIVE A NEUPOGEN INJECTION

NEUPOGEN should be injected at the same time each day. If you miss a dose, contact your doctor or nurse.

Always use the correct dose of NEUPOGEN. Too little NEUPOGEN may not protect you against infections, and too much NEUPOGEN may cause too many neutrophils to be in your blood. Your doctor will determine your/your child's correct dose based on your/your child's body weight.

If you are giving someone else NEUPOGEN injections, it is important that you know how to inject NEUPOGEN, how much to inject, and how often to inject NEUPOGEN.

NEUPOGEN is available as a liquid in vials or in prefilled syringes. When you receive your NEUPOGEN, always check to see that:

- The name NEUPOGEN appears on the package and vial or prefilled syringe label.

- The expiration date on the vial or prefilled syringe label has not passed. **You should not use a vial or prefilled syringe after the date on the label.**

- The strength of the NEUPOGEN (number of micrograms in the colored dot on the package containing the vial or prefilled syringe) is the same as what your doctor prescribed.

- The NEUPOGEN liquid in the vial or in the prefilled syringe is clear and colorless. **Do not use NEUPOGEN** if the contents of the vial or prefilled syringe appear discolored or cloudy, or if the vial or prefilled syringe appears to contain lumps, flakes, or particles.

If you are using vials of NEUPOGEN, only use the syringe that your doctor prescribes.

Your doctor or nurse will give you instructions on how to measure the correct dose of NEUPOGEN. This dose will be measured in milliliters. You should only use a syringe that is marked in tenths of milliliters, or mL (for example, 0.2 mL). The doctor or nurse may refer to an mL as a cc (1 mL = 1 cc). If you do not use the correct syringe, you/your child could receive too much or too little NEUPOGEN.

Only use disposable syringes and needles. Use the syringes only once and dispose of them as instructed by your doctor or nurse.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

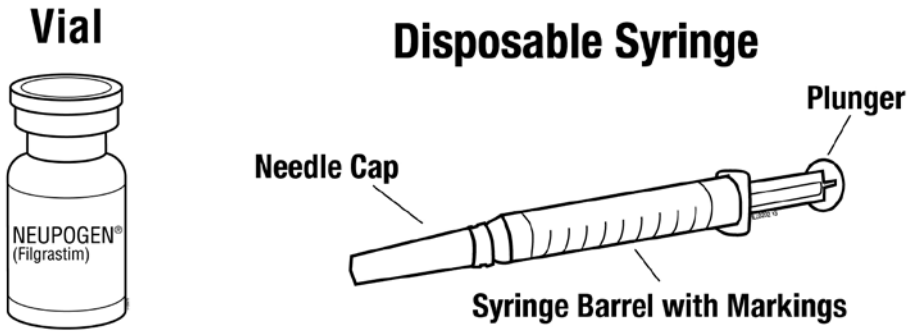
Note: The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

1. Find a clean flat working surface, such as a table.

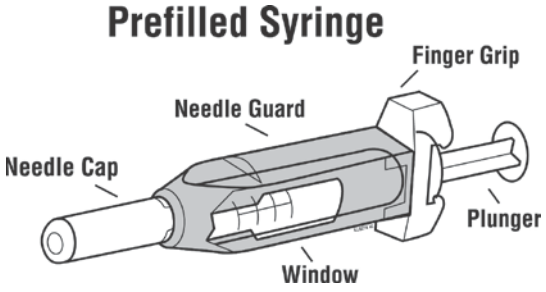
2. Remove the vial or prefilled syringe of NEUPOGEN from the refrigerator. Allow NEUPOGEN to reach room temperature (this takes about 30 minutes). Vials or prefilled syringes should be used only once. DO NOT SHAKE THE VIAL OR PREFILLED SYRINGE. Shaking may damage the NEUPOGEN. If the vial or prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

3. Assemble the supplies you will need for an injection:

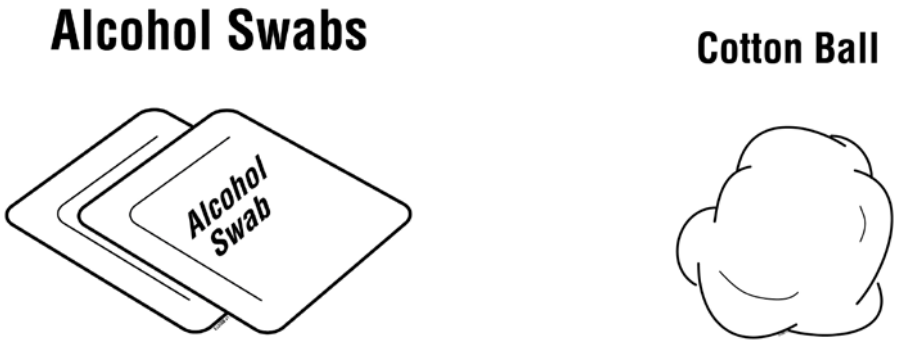
- NEUPOGEN vial <u>and</u> disposable syringe and needle



- <u>Or</u> NEUPOGEN prefilled syringe with transparent (clear) plastic orange needle guard attached



- Two alcohol swabs and one cotton ball or gauze pad



- Puncture-proof disposal container

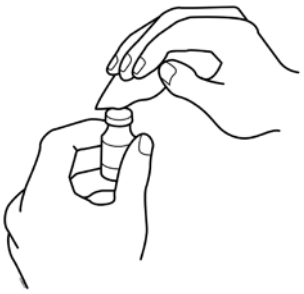
4. Wash your hands with soap and warm water.

HOW TO PREPARE THE DOSE OF NEUPOGEN IN VIALS OR PREFILLED SYRINGES

If you are using NEUPOGEN in a vial, follow the instructions in Section A. If you are using NEUPOGEN in a prefilled syringe, go to Section B.

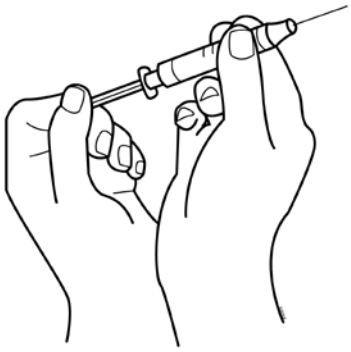
Section A. Preparing the dose using NEUPOGEN in a vial

1. Take the cap off the vial. Clean the rubber stopper with one alcohol swab.



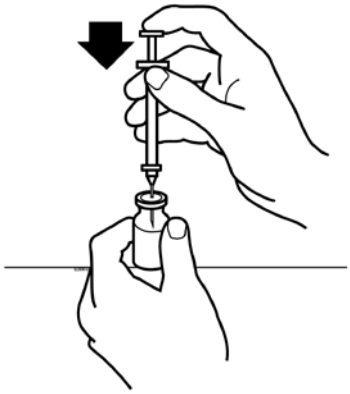
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.

3. Pull the needle cap straight off the syringe. Then, pull back the plunger and draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of NEUPOGEN that your doctor prescribed.

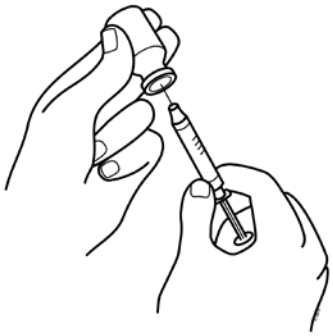


4. Keep the vial on the flat working surface and insert the needle straight down through the rubber stopper. Do not insert the needle through the rubber stopper more than once.

5. Push the plunger of the syringe down and inject the air from the syringe into the vial of NEUPOGEN.



6. Keeping the needle in the vial, turn the vial upside down. Make sure that the NEUPOGEN liquid is covering the tip of the needle.



7. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with NEUPOGEN liquid to the number (mL or cc) that matches the dose your doctor prescribed.

8. Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe.

9. Keeping the tip of the needle in the liquid, once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of NEUPOGEN. If there are still air bubbles, repeat the steps above to remove them.

10. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor. Remove the syringe from the vial but **do not lay it down** or let the needle touch anything. (Go to “Selecting and preparing the injection site”).

Section B. Preparing the dose using NEUPOGEN in a prefilled syringe

1. Remove the syringe from the package and the tray. Check to see that the plastic orange needle guard is covering the barrel of the glass syringe. **DO NOT push the orange needle guard over the needle cap before injection**. This may activate or lock the needle guard. If the orange needle guard is covering the needle that means it has been activated. DO NOT use that syringe. Dispose of that syringe in the puncture-proof disposal container. Use a new syringe from the package**.**

2. Hold the syringe barrel through the needle guard windows with the needle pointing up. Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cap straight off.

3. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.

4. Push the plunger up to the number (mL) on the syringe that matches the dose of NEUPOGEN that your doctor prescribed.

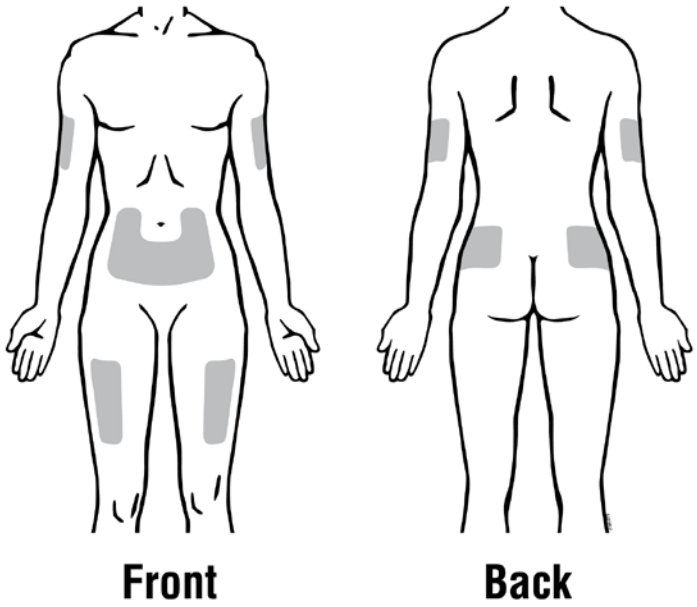
5. Check again to make sure the correct dose of NEUPOGEN is in the syringe.

6. Gently place the prefilled syringe with the window flat on your clean working surface so that the needle does not touch anything.

Selecting and preparing the injection site (for vials and prefilled syringes)

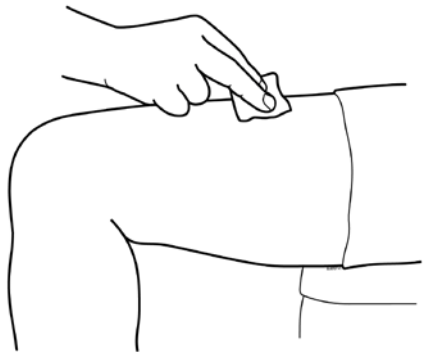
1. Choose an injection site. Four recommended injection sites for NEUPOGEN are:

    - The outer area of your upper arms
    - The abdomen, except for the two-inch area around your navel
    - The front of your middle thighs
    - The upper outer areas of your buttocks



Choose a new site each time you inject NEUPOGEN. Choosing a new site can help avoid soreness at any one site. Do not inject NEUPOGEN into an area that is tender, red, bruised, or hard or that has scars or stretch marks.

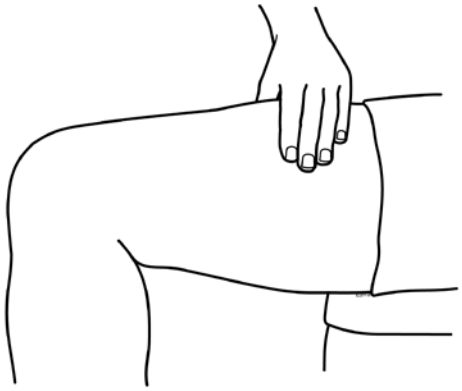
2. Clean the injection site with a new alcohol swab.



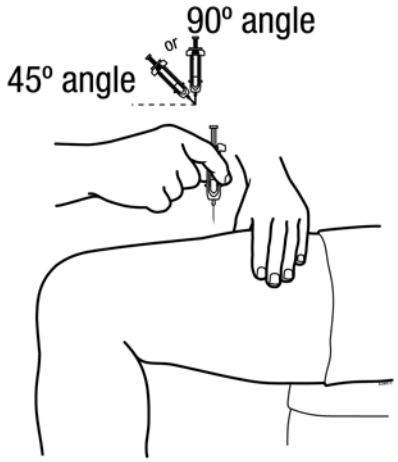
Injecting the dose of NEUPOGEN (for vials and prefilled syringes)

1. For injecting the dose of NEUPOGEN from a vial, remove the syringe and needle from the vial. For injecting the dose of NEUPOGEN from a prefilled syringe, pick up the prefilled syringe from the clean flat working surface by grabbing the sides of the needle guard with your thumb and forefinger.

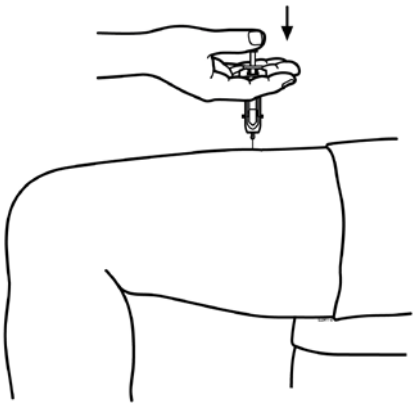
2. Hold the syringe in the hand you will use to inject NEUPOGEN. Use the other hand to pinch a fold of skin at the cleaned injection site. Note: If using a prefilled syringe with a needle guard, hold the syringe barrel through the needle guard windows when giving the injection.



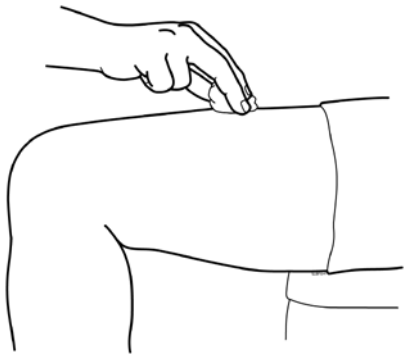
3. Holding the syringe like a pencil, use a quick “dart-like” motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



4. Inject the prescribed dose subcutaneously as directed by your doctor, nurse, or pharmacist.



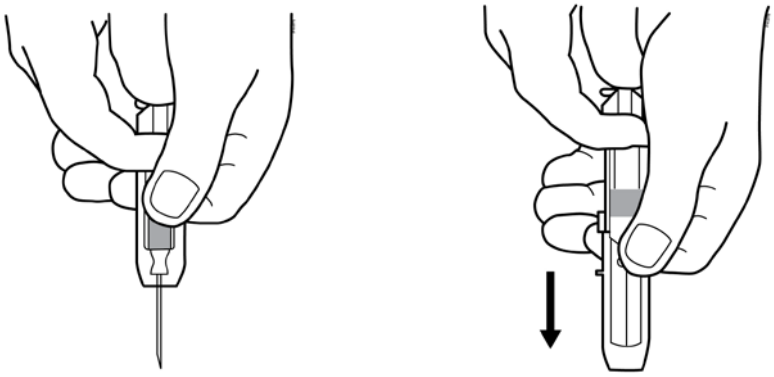
5. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



6. Use the prefilled syringe with the needle guard or a syringe and vial only once. If you are using a syringe, DO NOT put the needle cap back on the needle. Discard the vial with any remaining NEUPOGEN liquid.

Activating the Needle Guard for the prefilled syringe after the injection has been given

1. After injecting NEUPOGEN from the prefilled syringe, do not recap the needle. Keep your hands behind the needle at all times. While holding the clear plastic finger grip of the syringe with one hand, grasp the orange needle guard with your free hand and slide the orange needle guard over the needle until the needle is completely covered and the needle guard clicks into place. **NOTE: If an audible click is not heard, the needle guard may not be completely activated.**



2. Place the prefilled syringe with the activated needle guard into a puncture-proof container for proper disposal as described below.

How should I dispose of used syringes, needles, and vials

- Put your used syringes, needles, and vials in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes and vials in your household trash.**
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use, leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

How should I store NEUPOGEN?

- Store NEUPOGEN in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Avoid freezing NEUPOGEN. If frozen, thaw in the refrigerator before giving a dose. Throw away (dispose of) NEUPOGEN if it has been frozen more than 1 time.
- Store NEUPOGEN in the carton to protect from light until you are ready to use it.
- Do not leave NEUPOGEN in direct sunlight.
- Avoid shaking NEUPOGEN.
- NEUPOGEN can be left out at room temperature for up to 24 hours. Throw away (dispose of) NEUPOGEN that has been left at room temperature for longer than 24 hours.

What are the ingredients in NEUPOGEN?
Active ingredient: filgrastim
Inactive ingredients: acetate, polysorbate 80, sodium, and sorbitol

AMGEN®

NEUPOGEN® (filgrastim)
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799 U.S.A.
US License No. 1080
Revised: 7/2015

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