

# Filgrastim



## 1. GENERIC NAME

Filgrastim

## 2. DESCRIPTION

Filgrastim is human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Filgrastim is produced by *Escherichia coli* (*E.coli*) bacteria into which has been inserted the human granulocyte-colony stimulating factor gene. The protein comprising 175 amino acids has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of a methionine at the N-terminus. Because filgrastim is produced in *E. coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

**Nugraf™** (Filgrastim) is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing G-CSF. The product is available as pre-filled syringes.

## 3. COMPOSITION

Each Nugraf™ pre-filled syringe (0.5 ml) contains 30 Million International Units (MIU) equivalent to 300 micrograms of filgrastim at pH 4.0. See table below for quantitative composition of each single use pre-filled syringe.

	<b>Each Nugraf™ pre-filled syringe contains</b>
<b>Filgrastim</b>	300 mcg
<b>Sodium acetate</b>	10 mM
<b>D-Sorbitol</b>	25 mg
<b>Polysorbate 80</b>	0.004%
<b>Water for injection q.s. ad</b>	0.5 ml

## 4. INDICATIONS

### **Cancer Patients Receiving Myelosuppressive Chemotherapy**

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.

### **Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy**

Filgrastim is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

### **Cancer Patients Receiving Bone Marrow Transplant**

Filgrastim is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae eg. febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.

**Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy** Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care.

### **Patients with Severe Chronic Neutropenia**

Filgrastim is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg. fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia.

## 5. DOSE AND METHOD OF ADMINISTRATION

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** The recommended starting dose of filgrastim is 5 mcg/kg/day, administered as a single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. A CBC and platelet count should be obtained before instituting filgrastim 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.

Filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Filgrastim should not be administered in the period 24 hours before the administration of chemotherapy. Filgrastim should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm<sup>3</sup> following the expected chemotherapy-induced neutrophil nadir. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Filgrastim therapy should be discontinued if the ANC surpasses 10,000/mm<sup>3</sup> after the expected chemotherapy-induced neutrophil nadir.

### Patients with Acute Myeloid Leukemia Receiving Induction Chemotherapy

Filgrastim is indicated for reducing the time to neutrophil recovery and the duration of fever. Filgrastim at a dose of 5mcg/kg/day after last dose of chemotherapy until neutropenia recovery or for a maximum of 35 days significantly reduced the median time to ANC recovery and the median duration of fever, antibiotic use and hospitalization following induction chemotherapy

**Cancer Patients Receiving Bone Marrow Transplant:** The recommended dose of filgrastim following BMT is 10 mcg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion. For patients receiving BMT, the first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. During the period of neutrophil recovery, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count	Nugraf™ Dose Adjustment
When ANC > 1000/mm <sup>3</sup> for 3 consecutive days	
then:	Reduce to 5 mcg/kg/day
IF ANC remains > 1000/mm <sup>3</sup> for more consecutive days	
then:	Discontinue Nugraf™
If ANC decreases to < 1000/mm <sup>3</sup>	Resume at 5 mcg/kg/day
If ANC decreases to < 1000/mm <sup>3</sup> at any time during the 5 mcg/kg/day administration, Nugraf™ should be increased to 10 mcg/kg/day, and the above steps should then be followed.	

**Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients:** The recommended dose of filgrastim for the mobilization of PBPC is 10 mcg/kg/day SC, either as a bolus or a continuous infusion. It is recommended that filgrastim be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of filgrastim administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Neutrophil counts should be monitored after 4 days of filgrastim and filgrastim dose modification should be considered for those patients who develop a WBC count > 100,000/mm<sup>3</sup>.

**Patients with Severe Chronic Neutropenia:** Filgrastim should be administered to those patients in whom a diagnosis of congenital, cyclic, or idiopathic neutropenia has been definitively confirmed. Other diseases associated with neutropenia should be ruled out.

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

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

Dose Adjustments: Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patients' clinical course as well as ANC. In rare instances, patients with congenital neutropenia have required doses of filgrastim ≥ 100 mcg/kg/day.

## 6. DILUTION

If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 mcg/ml should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 mcg/mL is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

## 7. USE IN SPECIAL POPULATIONS

**Pregnancy:** Pregnancy Category C. Filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

**Nursing Mothers:** It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if filgrastim is administered to a nursing woman.

**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 filgrastim treatment. The relationship of these events to filgrastim administration is unknown. The safety and efficacy in neonates and patients with autoimmune neutropenia of infancy have not been established.

**Geriatric Use:** No overall differences in safety or effectiveness were observed between the elderly subjects and younger subjects, and other clinical experience has not identified differences in the responses between elderly and younger patients.

## 8. CONTRAINDICATIONS

Filgrastim is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, filgrastim, or any component of the product.

## 9. WARNINGS

**Allergic Reactions:** Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnoea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim IV. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged.

**SPLENIC RUPTURE:** RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF COLONY STIMULATING FACTORS INCLUDING FILGRASTIM, FOR PERIPHERAL BLOOD PROGENITOR CELL (PBPC) MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. INDIVIDUALS RECEIVING FILGRASTIM WHO REPORT ABDOMINAL OR SHOULDER TIP PAIN, SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.

**Adult Respiratory Distress Syndrome (ARDS):** Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

**Sickle Cell Disease:** Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease and sickle/b+ thalassemia) who received filgrastim for PBPC mobilization or following chemotherapy. Filgrastim should be used with caution in patients with sickle cell disease and only after careful consideration of the potential risks and benefits. Patients with sickle cell disease who receive filgrastim should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crises, supportive care should be administered and interventions to ameliorate the underlying event, such as therapeutic red blood cell exchange transfusion, should be considered.

**Patients with Severe Chronic Neutropenia:** The safety and efficacy of filgrastim in the treatment of neutropenia due to other hematopoietic disorders (eg, myelodysplastic syndrome [MDS]) have not been established. Care should be taken to confirm the diagnosis of SCN before initiating filgrastim therapy.

MDS and 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 filgrastim for SCN. Based on available data, 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 filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim 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 filgrastim should be carefully considered.

## 10. PRECAUTIONS

### General

**Simultaneous Use with Chemotherapy and Radiation Therapy:** The safety and efficacy of filgrastim given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, filgrastim should not be used in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.

The efficacy of filgrastim has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelosuppressive doses of antimetabolites such as 5-fluorouracil.

The safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided.

**Potential Effect on Malignant Cells:** Filgrastim is a growth factor that primarily stimulates neutrophils. However, the possibility that filgrastim can act 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 filgrastim 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.

### Leukocytosis

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** White blood cell counts of 100,000/mm<sup>3</sup> or greater were observed in approximately 2% of patients receiving filgrastim 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 CBC is recommended twice per week during filgrastim therapy.

### Premature discontinuation of filgrastim therapy

**Cancer Patients Receiving Myelosuppressive Chemotherapy :** A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm<sup>3</sup>. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended.

**Immunogenicity:** As with all therapeutic proteins, there is a potential for immunogenicity with filgrastim. The incidence of antibody development in patients receiving filgrastim 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. Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against filgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia; however, this has not been reported in clinical studies. Patients who develop hypersensitivity to filgrastim may have allergic or hypersensitivity reactions to other *E. coli*-derived proteins.

## Others

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy. 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 filgrastim in conjunction with other drugs known to lower the platelet count.

There have been rare reports (< 1 in 7000 patients) of cutaneous vasculitis in patients treated with filgrastim. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue filgrastim at a reduced dose.

## 11. DRUG INTERACTIONS

Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

### **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, or on gestation at doses up to 500 mcg/kg.

## 12. UNDESIRABLE EFFECTS

### **Cancer Patients Receiving Myelosuppressive Chemotherapy**

In clinical trials patients receiving filgrastim following non-myeloablative cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. The only consistently observed adverse reaction attributed to filgrastim is medullary bone pain, which is reported to be of mild to moderate severity and could be controlled in most patients with non narcotic analgesics: infrequently bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 mcg/kg/day) administered IV, and less frequently in patients treated with lower SC doses of filgrastim (3 to 10 mcg/kg/day).

In a randomized, double-blind, placebo-controlled trial of filgrastim therapy following combination chemotherapy in patients with small cell lung cancer, nausea, vomiting, skeletal pain, alopecia, diarrhea, neurotropic fever, mucositis, fever, fatigue, anorexia, dyspnoea, headache, cough, skin rash, chest pain, generalized weakness, sore throat, stomatitis, constipation and unspecified pain reported during blinded cycles of study medication (placebo or filgrastim at 4 to 8 mcg/kg/day). Events are reported as exposure-adjusted since patients remained on double-blind filgrastim a median of 3 cycles versus 1 cycle for placebo. In this study there were no serious life threatening or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like syndromes, pleuritis, pericarditis, or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase occurred in patients receiving filgrastim therapy following cytotoxic chemotherapy; increases were generally mild-to-moderate. Transient decreases in blood pressure, which did not require clinical treatment, were also reported following administration of filgrastim. Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11 of 375 cancer patients receiving filgrastim in clinical studies; the relationship to filgrastim therapy is unknown. No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials.

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

**Patients with Acute Myeloid Leukemia:** Overall, the frequency of all reported adverse events was similar in both the filgrastim and placebo groups (83% vs 82% in Induction 1; 61% vs 64% in Consolidation 1). Adverse events reported more frequently in the filgrastim-treated group included: petechiae (17% vs 14%), epistaxis (9% vs 5%), and transfusion reactions (10% vs 5%). There were no significant differences in the frequency of these events.

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

**Cancer Patients Receiving Bone Marrow Transplant:** In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplant (BMT). The most common events reported in both control and treatment groups included stomatitis, nausea, and vomiting, generally of mild-to-moderate severity and were considered unrelated to filgrastim.

Generally, adverse events observed in nonrandomized studies were similar to those seen in randomized studies, occurred in a minority of patients, and were of mild-to-moderate severity. The relationship of these events to filgrastim remains unclear since they occurred in patients with culture-proven infection with clinical sepsis who were receiving potentially nephrotoxic antibacterial and antifungal therapy.

**Cancer Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy:** In clinical trials, where filgrastim was given for PBPC mobilization it was generally well-tolerated. Adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms. These symptoms were predominantly events of medullary bone pain. Headache was reported related to filgrastim. Transient increases in alkaline phosphatase related to filgrastim were reported in patients who had serum chemistries measured; most were mild-to-moderate.

All patients had increases in neutrophil counts during mobilization, consistent with the biological effects of filgrastim. Two patients had a WBC count  $> 100,000/\text{mm}^3$ . No sequelae were associated with any grade of leukocytosis. Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts. Anemia and thrombocytopenia have been reported to be related to leukapheresis; however, the possibility that filgrastim mobilization may contribute to anemia or thrombocytopenia has not been ruled out.

**Patients with Severe Chronic Neutropenia:** Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with non-narcotic analgesics. Generalized musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently, and thrombocytopenia ( $< 50,000/\text{mm}^3$ ) was noted in 12% of patients with palpable spleens. Fewer than 3% of all patients underwent splenectomy, and most of these had a pre-study history of splenomegaly. Fewer than 6% of patients had thrombocytopenia ( $< 50,000/\text{mm}^3$ ) during filgrastim therapy, most of whom had a pre-existing history of thrombocytopenia. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. An additional 5% of patients had platelet counts between 50,000 to  $100,000/\text{mm}^3$ . There were no associated serious hemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness, or concomitant medications. Other adverse events infrequently observed and possibly related to filgrastim therapy were: injection site reaction, rash, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of some pre-existing skin disorders (eg, psoriasis). Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with filgrastim for SCN.

### 13. OVERDOSE

In cancer patients receiving filgrastim as an adjunct to myelosuppressive chemotherapy, it is recommended, to avoid the potential risks of excessive leukocytosis, filgrastim therapy should be discontinued if the ANC surpasses  $10,000/\text{mm}^3$  after the chemotherapy-induced ANC nadir has occurred. Doses of filgrastim that increase the ANC beyond  $10,000/\text{mm}^3$  may not result in any additional clinical benefit. In filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts  $> 100,000/\text{mm}^3$  have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

### 14. CLINICAL PHARMACOLOGY

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Endogenous G-CSF is a lineage specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, 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). G-CSF is not species specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage.

**Pharmacokinetics:** Absorption and clearance of filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous IV infusion of 20 mcg/kg of 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, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of filgrastim were approximately 0.5 to 0.7 ml/minute/kg. Single parenteral doses or daily IV doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for IV administration (231 minutes, following doses of 34.5 mcg/kg) and for SC administration (210 minutes, following filgrastim doses of 3.45 mcg/kg). Continuous 24-hour IV infusions of 20 mcg/kg over an 11- to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. Pharmacokinetic data in geriatric patients ( $\geq 65$  years) are not available.

### 15. LABORATORY MONITORING

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** A CBC and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during filgrastim therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurs earlier during cycles when filgrastim is administered, and WBC differentials demonstrate a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia is reduced, and is followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

**Cancer Patients Receiving Bone Marrow Transplant:** Frequent CBCs and platelet counts are recommended (at least 3 times per week) following marrow transplantation.

#### **Patients with Severe Chronic Neutropenia**

During the initial 4 weeks of filgrastim therapy and during the 2 weeks following any dose adjustment, a CBC with differential and platelet count should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet count should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular CBCs (ie, as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment.

In clinical trials, the following laboratory results were observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.
- Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but usually remained within normal limits.
- Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients.
- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.
- As in other trials, increases were observed in serum uric acid, lactic dehydrogenase and serum alkaline phosphatase.

## 16. INCOMPATIBILITIES

**Nugraf™** (Filgrastim) should not be diluted with 0.9% sodium chloride (saline) solution. **Nugraf™** (Filgrastim) is a clear and colorless solution. Do not use if particulate matter or discoloration is observed. Unused portion of the product should be discarded.

## 17. SHELF-LIFE

**Nugraf™** (Filgrastim) can be kept until the expiry date indicated on the package, provided it is stored under the prescribed conditions.

## 18. PACKAGING INFORMATION

One pre-filled syringe containing 0.5 ml (30 million IU) of injection solution packed in a carton. The syringe has a 27 gauge, ½ inch long, embedded needle covered with a rigid needle shield.

## 19. STORAGE AND HANDLING INSTRUCTIONS

**Nugraf™** (Filgrastim) should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Avoid shaking prior to injection. **Nugraf™** (Filgrastim) may be allowed to reach room temperature for a maximum of 24 hours. A prefilled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration; if particulates or discoloration is observed, the product should not be used.

## 20. REFERENCE

US Prescribing Information of NEUPOGEN, AMGEN, USA, May 2002.

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Survey Nos. 250, 251 & 252,

Turkapally (V),

Shameerpet (M),

Hyderabad – 533 378,

R.R. Dist., A.P.

India

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