



**NEUKINE® – For use of registered medical practitioner, hospital or laboratory only**

Recombinant Human Granulocyte Colony Stimulating Factor (G-CSF) Injection  
(Filgrastim Injection)

Each 1-ml pre-filled syringe contains **Recombinant Human G-CSF –300 mcg**

**DESCRIPTION**

Recombinant G-CSF (Filgrastim), active ingredient of Neukine, is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia coli (E. coli) bacteria where the human granulocyte colony-stimulating factor gene is inserted. Recombinant G-CSF has a molecular weight of 18,800 Daltons. The protein has an amino acid sequence that is identical to the natural GCSF except for the addition of an N-terminal methionine necessary for expression in E.coli.

<b>Content</b>	<b>Neukine (1.0 ml Prefilled Syringe)</b>
<b>rHu G-CSF</b>	<b>300 mcg</b>
<b>Acetate</b>	<b>0.59 mg</b>
<b>Sorbitol</b>	<b>50.0 mg</b>
<b>Tween 80</b>	<b>0.004 %</b>
<b>Sodium</b>	<b>0.035 mg</b>
<b>Water</b>	<b>1.0 ml WFI</b>
<b>pH</b>	<b>4.0</b>

**Preclinical Pharmacology:** Biological activity of indigenously made recombinant human G-CSF (Neukine) was assessed by in-vitro assay using NFS-60 cell (murine myeloblastic cell lines) and compared with reference standard from National Institute of Biological Standards and Controls (NIBSC). The biological activity of Neukine is more than 1 x 10 IU/mg of protein and comparable to specific activity of reference standard. The relative potency of Neukine was assessed in an in-vivo assay using neutropenic mice, and comparing it with reference standard. In the test, both the test and reference drug were found comparable and equipotent.

Acute toxicity studies were conducted in rats and mice by administering I.V. and S.C. single doses of 250, 2500 and 5000 mcg/kg of Neukine. The animals were observed for mortality, clinical signs and gross organ examinations. There was no death or any other adverse effect in the animals at all the dose levels. In repeat dose, subacute toxicity studies in rats and mice a dose of 50, 100, 250 mcg/kg was administered for a period of 28 days by SC and IV routes. The animals were examined for body weight changes, food consumption, blood chemistry and histopathological examination of body organs. There was no abnormality detected in any of the parameters in both animals. Neukine was well tolerated in low, medium and high dose levels in these studies.



**Clinical Pharmacology:** Endogenous G-CSF is a lineage specific colony-stimulating factor, which is, produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates production of neutrophils within the bone marrow, affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of cellular metabolism associated with respiratory burst, antibody dependent killing and increased expression of some functions associated with cell surface antigens).

**Pharmacologic Effects of Recombinant G-CSF:** In patients with various nonmyeloid malignancies, Recombinant G-CSF administration results in a dose-dependent increase in circulating neutrophil counts. With discontinuation of Recombinant G-CSF therapy, neutrophil counts returns to baseline, in most cases within 4 days. Isolated neutrophils display 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 is reported to increase in a dose-dependent manner in most patients receiving Recombinant G-CSF, however, percentage of monocytes in the differential count remains within the normal range. Absolute counts of both eosinophils and basophils do not change and are within normal range following administration of Recombinant G-CSF. Increases in lymphocyte counts following Recombinant G-CSF administrations have been reported in some normal subjects and cancer patients.

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

**Pharmacokinetics:** Absorption and clearance of Recombinant G-CSF follows first-order pharmacokinetic modelling without apparent concentration dependence. A positive linear correlation occurs between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous IV infusion of 20 mcg/kg of Recombinant G-CSF over 24 hours results 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 result in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. The volume of distribution averages 150 mL/kg in both normal subjects and cancer patients. The elimination half- life, in both normal subjects and cancer patients, is approximately 3.5 hours. Clearance rates of Recombinant G-CSF are approximately 0.5 to 0.7 mL/ minute/kg. The half-lives are similar for IV administration (231 minutes, following doses of 34.5 mcg/kg) and for SC administration (210 minutes, following Recombinant G-CSF doses of 3.45 mcg/kg). Pharmacokinetic data in geriatric patients (> 65 years) are not available.



## CLINICAL EFFECTS

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** Recombinant G-CSF has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens. In a phase 3 clinical trial, patients received SC administration of Recombinant G-CSF (4 to 8 mcg/kg/day, days 4 to 17) or placebo. The benefits of Recombinant G-CSF therapy were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased IV antibiotic usage.

Several other studies, which did not directly measure the incidence of infection, but which did measure increases in neutrophils, support the efficacy of Recombinant G-CSF.

**Patients with Acute Myeloid Leukaemia Receiving Induction or Consolidation Chemotherapy:** Treatment with Recombinant G-CSF significantly reduced the median time to ANC recovery and the median duration of fever, antibiotic use, and hospitalization following induction chemotherapy. During consolidation therapy, patients treated with Recombinant G-CSF also experienced significant reductions in the incidence of severe neutropenia, time to neutrophil recovery, the incidence and duration of fever, and in the durations of IV antibiotic use and hospitalization. Patients treated with a further course of standard or high-dose consolidation chemotherapy also experienced significant reductions in the duration of neutropenia.

**Cancer Patients Receiving Bone Marrow Transplant:** In patients with Hodgkin's Disease (HD) and Non-Hodgkin's Lymphoma (NHL) treated with myeloablative chemotherapy and autologous bone marrow transplantation (ABMT), a statistically significant reduction in the median number of days of severe neutropenia ( $ANC < 500/mm^3$ ) occurred in the Recombinant G-CSF-treated group versus the control group. In another study, a statistically significant reduction in the median number of days of severe neutropenia occurred in the Recombinant G-CSF-treated group versus the control group (21.5 days in the control group and 10 days in both treatment groups,  $p < 0.001$ ). The number of days of febrile neutropenia was also reduced significantly (13.5 days in the control group, 5 days in the 10-mcg/kg/day group, and 5.5 days in the 20 mcg/kg/day group [5 days in the combined treatment groups,  $p < 0.0001$ ]). There were no effects on red blood cell or platelet levels.

**Efficacy of Neukine in Indian patients:** The efficacy and safety of Neukine was evaluated in an open label, phase III confirmatory trial conducted in Indian patients for prevention of neutropenia. This multicenter study enrolled 100 adult patients with all types of cancers except Leukaemia. Neukine was used for secondary prophylaxis in-patients receiving chemotherapy. Patients were evaluated for magnitude of neutropenia (median ANC) and days of recovery from neutropenia in the index cycle (chemotherapy without G-CSF support) and subsequent two cycles (cycles with prophylactic Neukine administration).

In this study, median ANC in index cycle was  $480 \text{ cell}/\text{mm}^3$  and in subsequent cycles were 1800 and  $2552 \text{ cells}/\text{mm}^3$ . The difference between the median ANC in the index cycle and subsequent cycles were statistically significant ( $p < 0.0001$ ). The recovery from neutropenia was faster in cycles with prophylactic Neukine administration as compared to index cycle



without Neukine. There were more incidences of severe (ANC <500 cells) and febrile (<1000 with fever) neutropenia in-patients receiving cancer chemotherapy without Neukine support than in cycles with prophylactic administration of Neukine. The use of antibiotics was significantly reduced during cycles with Neukine administration. The drug was well tolerated in all patients and no significant adverse effect was reported with Neukine in this study.

### **INDICATIONS AND USAGE**

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** Recombinant G-CSF is indicated to decrease 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. A Complete Blood Count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week during Recombinant G-CSF therapy to avoid leukocytosis and to monitor the neutrophil count.

**Patients with Acute Myeloid Leukaemia Receiving Induction or Consolidation Chemotherapy:** Recombinant G-CSF 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:** Recombinant G-CSF is indicated to reduce duration of neutropenia and neutropenia-related clinical sequelae, e.g. febrile neutropenia, in-patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation. It is recommended that CBCs and platelet counts be obtained at a minimum of 3 times per week following marrow infusion to monitor the recovery of marrow reconstitution.

**Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy:** Recombinant G-CSF is indicated for the mobilization of haematopoietic 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

### **CONTRAINDICATIONS**

Recombinant G-CSF is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, Recombinant G-CSF, or any component of the product.

### **WARNINGS**

Allergic-type reactions occurring on initial or subsequent treatment have been reported. These have generally been characterized by systemic symptoms involving, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia) system.

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.



Left upper abdominal pain or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored due to the rare but serious risk of splenic rupture.

### **PRECAUTIONS**

#### **General:**

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

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

The safety of Recombinant G-CSF in chronic myeloid leukaemia (CML) and myelodysplasia has not been established.

**Leukocytosis:** White blood cell counts of 100,000/mm<sup>3</sup> or greater are observed in approximately 2% of patients receiving Recombinant G-CSF at doses above 5 mcg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid potential complications of excessive leukocytosis, a CBC is recommended twice per week during Recombinant G-CSF.

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of Recombinant G-CSF therapy. However, for a sustained therapeutic response, Recombinant G-CSF therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm<sup>3</sup>. Increases are observed in serum uric acid, lactate dehydrogenase, and serum alkaline phosphatase.

**Drug Interaction:** Drug interactions between Recombinant G-CSF and other drugs have not been fully evaluated. Drugs, which may potentiate release of neutrophils, such as lithium, should be used with caution.

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

**Pregnancy Category C:** Recombinant G-CSF has been shown to have adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose. Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of Recombinant G-CSF on developing foetus or the reproductive capacity of the mother is unknown. However, scientific literature describes transplacental passage of Recombinant G-CSF when administered to pregnant rats during latter part of gestation and apparent transplacental passage of Recombinant G-CSF when administered to pregnant females by < 30 hours prior



to preterm delivery (< 30 weeks gestation). Recombinant G-CSF should be used during pregnancy only if the potential benefit justifies potential risk to the foetus.

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

**Geriatric Use:** No overall differences in safety or effectiveness are observed between elderly and younger subjects.

### **ADVERSE REACTIONS**

In clinical trials patients receiving Recombinant G-CSF following nonmyeloablative cytotoxic chemotherapy, most adverse experiences are the sequelae of the underlying malignancy or cytotoxic chemotherapy. Medullary bone pain is the only consistently observed adverse reaction attributed to Recombinant G-CSF therapy. This bone pain is generally reported to be of mild-to-moderate severity, and can be controlled in most patients with non-narcotic analgesics.

Other side effects include nausea/vomiting, skeletal pain, alopecia, diarrhoea, neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnea, headache, cough, skin rash, chest pain, generalized weakness, sore throat stomatitis, constipation, pain (unspecified).

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase is seen in patients receiving Recombinant G- CSF therapy following cytotoxic chemotherapy; increases were generally mild-to-moderate. There are no serious, life threatening, or fatal adverse reactions attributed to Recombinant G-CSF therapy.

### **OVERDOSAGE**

In cancer patients receiving Recombinant G-CSF as an adjunct to myelosuppressive chemotherapy, it is recommended, to avoid the potential risks of excessive leukocytosis that Recombinant G-CSF therapy be discontinued if the ANC surpasses 10,000/mm<sup>3</sup> after the chemotherapy- induced ANC nadir has occurred.

Patients in 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.

### **DOSAGE AND ADMINISTRATION**

**Cancer Patients Receiving Myelosuppressive Chemotherapy:** The recommended starting dose of Recombinant G-CSF 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 Recombinant G-CSF 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.



Recombinant G-CSF should be injected no earlier than 24 hours after administration of cytotoxic chemotherapy. Recombinant G-CSF should not be administered in the period 24 hours before the administration of chemotherapy.

**Cancer Patients Receiving Bone Marrow Transplant:** The recommended dose of Recombinant G-CSF 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 Recombinant G-CSF should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow transplant.

**Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients:** The recommended dose of Recombinant G-CSF for the mobilization of PBPC is 10 mcg/kg/day SC, either as a bolus or a continuous infusion. It is recommended that Recombinant G-CSF be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis.

**Dilution:** If required, Recombinant G-CSF may be diluted in 5% dextrose. Recombinant G-CSF 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), Recombinant G-CSF is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of Recombinant G-CSF 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.

**Storage:** Neukine should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, Neukine may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded.

### **HOW SUPPLIED**

Single-dose, prefilled syringe of 1 ml containing 300 mcg of rHu G-CSF.

### **MANUFACTURED & MARKETED BY**

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