were able to continue recombinant Human G-CSF at a reduced dose.

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving recombinant Human G-CSF. Platelet counts should be monitored closely.

USE IN SPECIAL POPULATIONS

Pregnancy

Pregnancy Category C

Recombinant Human 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 the developing fetus of the reproductive capacity of the mother is unknown. There are no adequate and well-controlled studies in pregnant woman. However, the scientific literature describes transplacental passage of recombinant Human G-CSF when administered to pregnant rats during the latter part of gestation and apparent transplacental passage of recombinant Human G-CSF when administered to pregnant humans by < 30 hours prior to preterm delivery (< 30 weeks gestation). Recombinant Human G-CSF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether recombinant Human G-CSF is excreted in human milk. Caution should be exercised when administered to a nursing woman.

Pediatric Use

In a phase 3 study to assess the safety and efficacy of recombinant Human G-CSF was given in the treatment of SCN patients with a median age of 12 years were studied (1 month to 12 years of age). 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 recombinant Human G-CSF 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.
The safety and efficacy in neonates and patients with autoimmune neutropenia of infancy have not been established.

Geriatric Patients

No overall differences in safety or effectiveness are observed between elderly and younger patients.

DRUG INTERACTIONS

Drug interaction between recombinant Human G-CSF and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

UNDESIRABLE EFFECTS

In clinical trial patients receiving recombinant Human G-CSF following nonmyeloablative cytotoxicity 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 Human 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, diarrhea, neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnea, headache, cough, skin rash, chest pain, generalized weakness, sore throat, stomatitis, constipation, pain (unspecified).

Spontaneous reversible elevation in uric acid, lactate dehydrogenase and alkaline phophatase is seen in patients receiving recombinant Human G-CSF therapy following cytotoxic chemotherapy; increases were generally mild to moderate. There was no serious, life threatening or fatal adverse reaction attributed to recombinant Human G-CSF therapy.

OVERDOSE

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

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.

INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions. (Normal Saline 0.9% NaCl or half saline or 5% DNS-Dextrose Normal Saline)

SHELF LIFE: 36 Months

PACKING INFORMATION

NEUKINE is supplied in a 1.0 mL single use prefilled syringe containing 300 mcg filgrastim (G-CSF). Each prefilled syringe is placed in a plastic tray and packed in a carton along with a package insert.

STORAGE AND HANDLING INSTRUCTION

Store between 2 °C to 8 °C (36 °F to 46 °F). Protect from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

Manufactured by:
Intas Pharmaceuticals Ltd.
Plot No. 423/P/A, Sarkhej - Bavla Highway,
Village - Moraiya, Taluka - Sanand,
District - Ahmedabad-382 213, Gujarat, INDIA.

Marketing Authorization holder:
Accord Healthcare Ltd.
Saga House, 319, Pinner Road,
North Harrow, Middlesex, Ha1 4HF, UK.

AW-QA-1751-00

accord

For the use of Registered Medical Practitioner, Hospital or Laboratory only

NEUKINE

Recombinant Human Granulocyte Colony Stimulating Factor (rHu G-CSF)
Injection
(Filgrastim injection PFS 300 mcg)

DECSRIPTION AND COMPOSITION

Recombinant Human G-CSF (filgrastim), the active ingredient of **NEUKINE** PFS, is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia coli (*E. coli*) bacteria into which the human granulocyte colony stimulating factor gene has been inserted. Recombinant Human 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 N-terminal methionine necessary for expression in *E.coli*.

Each prefilled syringe of 1.0 mL contains: Recombinant Human G-CSF 30 MIU (300 mcg). The pH of the solution is 4.0

Contents	NEUKINE 300 mcg/1.0 mL
r-Hu G-CSF	300 mcg
Glacial Acetic Acid	0.60 mg
Sorbitol	50.0 mg
Ploysorbate 80	0.04 mg
Sodium Hydroxide	0.06 mg
Water for Injection q.s.	1.0 mL
pH	4.0

DOSAGE FORM

Solution for Injection (300 mcg per 1.0 mL in single use prefilled syringe)

PRECLINICAL PHARMACOLOGY

Biological activity of indigenously made recombinant Human G-CSF was assessed by in vitro assay using NFS-60 cell line (murine myeloblastic cell line) and compared with the reference standard from National Institute of Biological Standards and Controls (NIBSC). The biological activity of recombinant Human G-CSF is more than 1×10^9 IU/mg of protein and comparable to the specific activity of reference standard.
The relative potency of recombinant Human G-CSF was assessed in an in *vivo* assay using neutropenic mice and compared it with the reference standard. In this test, both the test and the reference drug were found comparable and equipotent.

ANIMAL TOXICITY

Acute toxicity studies were conducted in rats and mice by administering intravenous (i.v.) & subcutaneous (s.c.) single doses 250, 2500 and 5000 mcg/kg of recombinant Human G-CSF. The animals were observed for mortality, clinical signs and gross organ examinations. There was no death or any other adverse effects in the animals at all the dose levels. In repeat dose sub acute toxicity studies in rats and mice, doses of 50, 100, 250 mcg/kg was administered for a period of 28 days by s.c. and i.v. routes. The animals were examined for body weight changes, food consumption, blood chemistry and histopathological examination. Recombinant Human G-CSF was well tolerated in low, medium and high dose levels.

CLINICAL PHARMACOKINETIC PROPERTIES

Absorption and clearance of recombinant Human G-CSF follows first order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurs between the parenteral dose and both the serum concentration-time curves. Continuous i.v. infusion of 20 mcg/kg of recombinant Human G-CSF over 24 hours results in mean and median serum concentration of approximately 48 and 56 ng/mL respectively. Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg results in maximum serum concentration of 4 and 49 ng/mL respectively within 2 to 8 hours. The volume of distribution averages half life in both normal subject and cancer patients is approximately 3.5 hours. Clearance rates of recombinant Human G-CSF are approximately 0.5 to 0.7 mL/minute/kg. The half lives are similar for i.v. administration (210 minutes, following recombinant Human G-CSF doses of 3.45 mcg/kg). Pharmacokinetic data in generic patients (> 65 patients) are not available.

CLINICAL PHARMACODYANAMIC PROPERTIES

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

Pharmacologic Effects of Recombinant Human G-CSF

In patients with various nonmyeloid malignancies, recombinant Human G-CSF administered results in a dose-dependent increase in circulating neutrophils counts. With discontinuation of recombinant Human 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 under agarose using N-formyl-methionine-leucyl-phenylalanine) activity in vitro.

The absolute monocytes count is repeated to increase in a dose-dependent manner in most patients receiving recombinant Human G-CSF however, the 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 the normal range following administration of recombinant Human G-CSF. Increases in lymphocytes counts following recombinant Human G-CSF administration have been reported in some normal subjects and cancer patients.

White blood cell differentials obtained during clinical trials have demonstrated as shift towards earlier granulocyte progenitor cells (left shift) including the appearance of promyelocyytes and myelocytes, usually during neutrophil recovery following the chemotherapy induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as are transient and are not associated with clinical sequelae nor are they necessarily associated with infection.

CLINICAL EFFECTS

Cancer Patients Receiving Myelosuppressive Chemotherapy

Recombinant Human 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 III clinical trial, patients received s.c. administration of recombinant Human G-CSF (4 to 8 mcg/kg/day, days 4 to 17) or placebo. The benefits of Recombinant Human G-CSF therapy were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased i.v. antibiotic usage.

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

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
Treatment with Recombinant Human G-CSF significantly reduced the median time to ANC recovery and the median duration of the fever, antibiotic use, and hospitalization following induction chemotherapy. During consolidation chemotherapy, patients treated with Recombinant Human G-CSF also experienced significant reductions in the incidence of severe neutropenia, time to neutrophils recovery, the incidence and duration of fever, and in durations of i.v. antibiotic use and hospitalization. Patients treated with a further course of standard or high dose consolidation chemotherapy also experience 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 Human 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 20mcg/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 Recombinant Human G-CSF PFS in Indian Patients
The efficacy and safety of Recombinant Human G-CSF PFS 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 leukemia and Recombinant Human G-CSF PFS 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 Recombinant Human G-CSF PFS administration). In this study the median ANC in the index cycle was 480 cells/mm3 and in subsequent cycles were 1800 and 2552 cells/mm3. 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 the cycles with prophylactic Recombinant Human G-CSF PFS administration as compared to index cycle without Recombinant Human G-CSF PFS. There were more incidences of severe (ANC≤500 cells) and febrile (≤1000 with fever) neutropenia in-patients receiving cancer chemotherapy without Recombinant Human G-CSF PFS support than in cycles with prophylactic administration of Recombinant Human G-CSF PFS. The use of antibiotics was significantly reduced during cycles with Recombinant Human G-CSF PFS administration. The drug was well tolerated in all patients and no significant adverse effect was reported with Recombinant Human G-CSF PFS in this study.

INDICATIONS
Cancer patients receiving Myelosuppressive Chemotherapy
Recombinant Human G-CSF 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. A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy and twice per week during recombinant Human G-CSF therapy to avoid leukocytosis and to monitor the neutrophil count.

Patient with Acute Myeloid Leukemia (AML) Receiving Induction or Consolidation Chemotherapy
Recombinant Human 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 Patient Receiving Bone Marrow Transplant
Recombinant Human G-CSF is indicated to reduce the duration of neutropenia and neutropenia related clinical sequelae, e.g. febrile neutropenia, in patient with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation. It is recommended that CBC and platelet count be obtained at a minimum of 3 times per week following marrow infusion to monitor the recovery of marrow reconstitution.

Patient Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy
Recombinant Human G-CSF is indicated for the mobilization of haemopoietic 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.

DOSE AND METHOD OF ADMINISTRATION
Cancer Patient Receiving Myelosuppressive Chemotherapy
The recommended starting dose of recombinant Human G-CSF is 5 mcg/kg/day, administered either as a single daily injection by subcutaneous (s.c.) bolus injection, by short intravenous infusion (15 to 30 minutes), or by continuous s.c. or continuous i.v. infusion. A CBC and platelet count should be obtained before instituting recombinant Human 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 Human G-CSF should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Recombinant Human G-CSF should not be administered in the period 24 hours before the administration of the therapy.

Cancer Patient Receiving Bone Marrow Transplant (BMT)
The recommended dose of recombinant Human G-CSF following BMT is 10 mcg/kg/day given as an i.v. infusion of 4 or 24 hours, or as a continuous 24 hour s.c. infusion. For patients receiving BMT, the first dose of recombinant Human G-CSF should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Patient Undergoing Peripheral Blood Progenitor Cell Collection (PBPC) and Therapy
The recommended dose of recombinant Human G-CSF for the mobilization of PBPC is 10 mcg/kg/day either s.c. bolus or a continuous infusion. It is recommended that recombinant Human G-CSF be given for at least 4 days before the first leukapheresis

procedure and continued until the last leukapheresis.
Dilution
If required, recombinant Human G-CSF may be diluted in 5% dextrose. Recombinant Human G-CSF dilute to concentration between 5 and 15 mcg /mL should be protected from absorption to plastic material 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 Human G-CSF is compatible with glass bottles, PVC and polyolefin i.v. bags and polypropylene syringes.
Dilution of recombinant Human 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.

CONTRAINDICATIONS
Recombinant Human G-CSF is contraindicated in patients with known hypersensitivity to E. coli derived proteins, or any components 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 and dyspnea) and cardiovascular (hypotension and 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.

Acute Respiratory Distress Syndrome (ARDS)
Acute respiratory distress syndrome (ARDS) has been reported in patients receiving recombinant Human G-CSF, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving recombinant Human G-CSF who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, recombinant Human G-CSF should be withheld until resolution of ARDS or discontinued. Patients should receive appropriate medical management for this condition.

Alveolar Hemorrhage and Hemoptysis
Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing PBPC mobilization. Hemoptysis resolved with discontinuation of recombinant Human G-CSF.

Sickle Cell Disorders
Severe sickle cell crises, in some cases resulting in death, have been associated with the use of recombinant Human G-CSF in patients with sickle cell disorders. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe recombinant Human G-CSF for such patients, and only after careful consideration of the potential risks and benefits.

Patients With Severe Chronic Neutropenia (SCN)
The safety and efficacy of recombinant Human G-CSF 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 recombinant Human G-CSF therapy.
If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing recombinant Human G-CSF should be carefully considered.

PRECAUTIONS
General
Simultaneous Use with Chemotherapy and Radiation Therapy
The safety and efficacy of recombinant Human G-CSF 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 recombinant Human G-CSF in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.
The safety and efficacy of recombinant Human G-CSF have not been evaluated in-patients receiving concurrent radiation therapy. Simultaneous use of recombinant Human G-CSF with chemotherapy and radiation therapy should be avoided.
The safety of recombinant Human G-CSF in chronic myeloid leukemia (CML) and myelodysplasia has not been established.

Leukocytosis
White blood cell count of 100,000/mm3 or greater are observed in approximately 2% of patients receiving recombinant Human 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 the potential complication of excessive leukocytosis, a CBC is recommended twice per week during recombinant Human G-CSF therapy.

Cancer Patient Receiving Myelosuppressive Chemotherapy
A transient increase in neutrophils count is typically seen 1 to 2 days after initiation of recombinant Human G-CSF therapy. However for a sustained therapeutic response, recombinant Human G-CSF therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm^3. Increases are observed in serum uric acid, lactic dehydrogenase and serum alkaline phophatase.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving recombinant Human G-CSF 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 or in post-marketing experience. Patients who develop hypersensitivity to filgrastim may have allergic or hypersensitivity reactions to other E coli-derived proteins.

Cutaneous Vasculitis
Cutaneous vasculitis has been reported in patients treated with recombinant Human G-CSF. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term recombinant Human G-CSF therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients