For the use only of an Oncologist or Hospital or a Laboratory only.

Biocon

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rh-GCSF (FILGRASTIM) INJECTION

NUFIL Sf™

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0.5mL

Hematopoietic growth factor
For s.c., i.v. infusion
1 single-dose pre-filled syringe

Composition:

Each 0.5 mL Pre-filled syringe contains	
rh-GCSF	300 µg
(rh-Granulocyte Colony Stimulating Factor / Filgrastim)	
Sorbitol	25 mg
Polysorbate 20	0.02 mg
Sodium	0.018 mg
Acetate	0.295 mg
Water for injection	0.5 mL

Description

Filgrastim is a recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF). NUFIL Sf™ is Biocon's trade name for formulated Filgrastim. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology using Escherichia coli as an expression host. Filgrastim has a molecular weight of 18,800 daltons. The protein has an amino acid sequence similar to the natural sequence predicted from the human DNA sequence analysis, except for the addition of an N-terminal methionine. NUFIL Sf™ is a sterile, clear, colorless liquid for parenteral administration containing Filgrastim at a specific gravity of 1.0 (±0.3) x 10^8 U/mg (as measured by cell proliferative assay). The product is available in single prefilled syringes containing 300 µg Filgrastim at a fill volume of 0.5 mL.

Clinical Pharmacology

Pharmacodynamics -
Filgrastim is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Filgrastim causes marked increases in peripheral blood neutrophil counts within twenty-four hours, with minor increases in monocytes. Elevations of neutrophil counts are dose-dependent at recommended doses. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days. Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into peripheral blood. These autologous peripheral blood progenitor cells (PBPCs) may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Pharmacokinetic
Absorption and clearance of filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation was observed 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 of (r-metHuG-CSF). Filgrastim 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 in Indian patients. 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 345 mcg/kg). Continuous 24-hour IV infusions of 20 mcg/kg over 11- to 20-days produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. Pharmacokinetic data in geriatric patients (> 65 years) are not available.

Clinical trials

BIOCON rh-GSCF has been shown to be safe and effective in accelerating the recovery of neutrophil counts following myelosuppressive chemotherapy regimens. In a trial conducted in patients receiving myelosuppressive chemotherapy for mainly advanced stage carcinomas, filgrastim was administered a day , after receiving the last dose of chemotherapy. Out of 46 patients enrolled in this study, 36 patients were evaluated for efficacy and 44 patients were evaluated for safety [1 patient refused to participate and another lost to follow-up after screening]. The incidence, severity and duration of severe neutropenia (absolute neutrophil count [ANC] <500/mm^3) following chemotherapy were all significantly reduced after administration of Biocon's GCSF The incidence of severe neutropenia in control cycle was 100% (36/36) while for patients receiving Biocon's GCSF in treatment cycle 1 it was 61.11% (22/36).

In all the treatment cycles , patients who received Biocon's GCSF had 46% (54/117 cycles) rate of severe neutropenia versus 100% (36/36 cycles) for the same patients in control cycle when they received only best standard of care. Severe neutropenia was markedly reduced in cycles when patients received Biocon's GCSF as compared to when the same patients received best standard of care (46 % (54/117) vs 100% (36/36)).

The median duration of severe neutropenia reduced from 2 days (range 1 to 6 days) in control cycle to 1 day (range 0 to 3 days) in treatment cycle 1. In treatment cycle 2, the median was 0.50 (range 0 to 5). In the subsequent treatment cycles the median duration of severe neutropenia was 0 days (range 0 to 4 days). The mean duration of severe neutropenia in control cycle was 2.23 ± 1.64 days versus 0.88 ± 0.82 days ($p < 0.0001$) for patients receiving Biocon GCSF. Over all the chemotherapy cycles , the median duration of neutropenia was 2 days in the control cycle versus <1 day for the same patients when they received filgrastim in the treatment cycles.

The median severity of neutropenia (as measured by ANC nadir) was 164/mm^3 (range 0/mm^3 to 500/mm^3) in the control cycle versus 475/mm^3 (range 16/mm^3 to 10500/mm^3) for the same patients in the treatment cycle 1 when they received filgrastim ($p < 0.0001$). The mean severity of neutropenia in control cycle was 194/mm^3 ± 156/mm^3 versus 1120/mm^3 ± 1959/mm^3 for patients receiving filgrastim in the treatment cycle 1. Over all cycles , the median ANC nadir for patients in the treatment cycles was 422/mm^3 (range 95/mm^3 to 6900/mm^3) versus 164/mm^3 (range 0/mm^3 to 500/mm^3) for same patients in control cycle.

Treatment with Biocon GCSF resulted in significant reduction in the incidence of infection , as manifested by febrile neutropenia and by IV antibiotics use (the secondary efficacy parameter). The incidence of febrile neutropenia was 6/44 control cycles versus 2/120 treatment cycles.

The incidence of i.v. antibiotic usage was 58% (21/36) in control cycle while in the treatment cycle 1 it was 8% (3/36).

Overall incidence of i.v. antibiotic usage in all the treatment cycles was only 13 % (15/117). The median duration of i.v. antibiotic administration was 4 days per patient (range 0 to 17 days) in the control cycle while the same patients nearly required only 0 days (range 0 to 3.5 days) when they received filgrastim in the treatment cycles.

Safety

A total of 71 adverse events were reported in the study. AEs that occurred with > 10 % frequency were Neutropenia (45.45 %), Vomiting (45.45 %), Leukopenia (40.91 %), Anaemia (38.64 %), Thrombocytopenia (29.55 %), Pyrexia (27.27 %), Back pain (22.73 %),Abdominal pain (20.45 %), Diarrhoea (20.45 %), Cough (20.45 %), Pain (18.18 %), Nausea (15.91 %), Pain in extremity (15.91 %), Headache (15.91 %), Constipation (13.64%), Stomatitis (11.36 %), Asthenia (15.91 %), Mucosal inflammation (13.64 %) Alopecia (11.36 %).

The remaining AEs were reported in less than 10 % patients, and were mostly the expected toxicities of chemotherapeutic agents that these trial patients received. 16 AEs were reported as causally related to the study drug and most of were mild to moderate in severity and every event resolved with complete recovery. Thrombocytopenia was most common study drug related adverse event while the next most common adverse event was body pain.

Indications and usage

a. Cancer patients receiving myelosuppressive chemotherapy; rh-GCSF 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.

b. Patients with Acute Myeloid Leukemia, receiving Induction or consolidation chemotherapy; rh-GCSF is indicated for reducing the time to neutrophilecovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

c. Cancer patients receiving bone marrow transplant; rh-GCSF is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g. febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloab lative chemotherapy followed by marrow transplantation.

d. Patients undergoing peripheral blood Progenitor cell collection and therapy; rh-GCSF 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 with collection by leukapheresis without mobilization or bone marrow harvest.

e. Patients with severe chronic neutropenia; rh-GCSF 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.

Dosage and administration

Administration
Filgrastim should not be administered within 24 hours before or after chemotherapy, since antineoplastic agents target rapidly proliferating cells thus attenuating the effect of filgrastim.

Filgrastim is administered by subcutaneous injection or i.v. infusion. When administered by i.v. infusion in patients with chemotherapy-induced neutropenia, filgrastim is usually infused over 15–30 minutes, although infusion periods extending up to 24 hours may be used. In patients who have undergone bone marrow transplantation (BMT), filgrastim is infused i.v. over 30 min. When administered by subcutaneous infusion for either use, filgrastim usually is infused over 24 hours. For direct, rapid subcutaneous injection, filgrastim injection is administered undiluted.

Dosage

a. Chemotherapy induced neutropenia (CIN); The optimum recommended dose of filgrastim in CIN is 5 µg/kg daily administered by subcutaneous injection continued f o r up to 2 weeks or until the absolute neutrophil count (ANC) reaches 10,000/mm^3 following the expected chemotherapy-induced ANC nadir. If the time to neutrophil response is inadequate after 5–7 days of filgrastim therapy, dosage may be increased in increments of 5 µg/kg with each chemotherapy cycle; dosage increases should be based on the duration and severity of the ANC nadir associated with the chemo therapy.

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b. Bone marrow transplant (BMT); 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 BMT, the recommended initial dosage of filgrastim is 10 µg/kg daily given by by i.v. infusion of 4 or 24 hours or by subcutaneous infusion over 24 hours. This initial dosage is continued until the ANC has remained at greater than 1000/mm^3 for 3 consecutive days, at which time dosage should be reduced to 5 µg/kg daily.

c. Peripheral blood progenitor cell collection and therapy to mobilize hematopoietic progenitor cells into peripheral blood for collection by leukapheresis; the recommended dosage of Filgrastim is 10 µg/kg daily given by subcutaneous injection or continuous subcutaneous infusion once daily for at least 4 days prior to the first leukapheresis to collect peripheral blood progenitor cells (PBPC) and continued until the last leukapheresis is performed.

d. Severe chronic neutropenia The recommended dose filgrastim for the treatment of cyclic/idiopathic/chronic neutropenia is 5 µg/kg administered once daily by subcutane ous injection. Dosage in patients with congenital neutropenia is 6 µg/kg BID daily by subcutaneous injection. ANC should be observed periodically to evaluate duration of therapy

Contraindications

Filgrastim is contraindicated in patients hypersensitive to the drug, any ingredient in the formulation, or proteins derived from Escherichia coli.

Precautions

a. Complete blood cell counts (CBCs) and platelet counts should be performed prior to initiation of filgrastim therapy and routinely during therapy to monitor myeloid recovery and avoid the potential complications of excessive leukocytosis and/or thrombo-cytopenia. It is recommended that these hematologic tests be performed twice weekly in patients receiving the drug for chemotherapy-induced neutropenia and 3 times weekly in patients receiving the drug following bone marrow transplantation

b. In patients with congenital, cyclic or idiopathic neutropenia, CBCs and platelet counts should be performed twice weekly during the initial 4 weeks of filgrastim therapy, twice weekly during the first 2 weeks following any dosage adjustment and once monthly after the patient is clinically stable.

c. Regular monitoring of leukocyte counts (especially at the time of recovery from the A N C nadir) is recommended to avoid excessive leukocytosis. It is recommended that filgrastim be discontinued if the ANC exceeds 10,000/mm^3 after the ANC nadir has occurred; dosages that increase the ANC to such levels may not result in any additional clinical benefit but might be associated with an increased risk of toxicity (e.g., bone pain).

d. Patients receiving filgrastim and experiencing pain in left upper abdominal and/or shoulder tip should be evaluated for the presence of splenomegaly or splenic rupture.

e. Neutropenic patients receiving the drug who develop fever, lung infiltrates, or respiratory distress should be evaluated for the presence of Acute Respiratory Distress Syndrome (ARDS). If ARDS occurs, filgrastim should be discontinued and/or withheld until ARDS has resolved, and patients should receive appropriate treatment for this condition.

f. Because some malignant myeloid cells have receptors for G-CSF and because the clinical importance of these receptors has not been fully determined to date, extreme caution regarding the use of filgrastim in patients with any malignancy having myeloid characteristics (e.g., acute myeloid leukemia [AML]) is advised. However, the drug currently is used in patients with AML receiving induction or consolidation chemotherapy without evidence of a negative effect on the disease (e.g., proliferation of the leukemic clone).

g. Effect of filgrastim on the development of abnormal cytogenetics and the effect of continued therapy with drug in patients with abnormal cytogenetics are unknown, the risks and benefits of continuing filgrastim therapy should be carefully considered if a patient with severe chronic neutropenia develops abnormal cytogenetics during filgrastim therapy.

h. When filgrastim is used for mobilization of hematopoietic progenitor cells, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells administered concomitantly with radiation therapy. has not been well studied and the limited data available to date are inconclusive.

i. Because rapidly dividing myeloid cells may be particularly sensitive to cytotoxic chemotherapy, filgrastim should not be administered during the 24 hours before or after administration of cytotoxic chemotherapy. Filgrastim should not be administered concomitantly with radiation therapy.

Pediatric precautions

a. Filgrastim has been used in children 3 months to 18 years of age without unusual adverse effect. However, safety and efficacy of the drug in neonates or patients with autoimmune neutropenia of infancy have not been established

b. Cytogenetic abnormalities and transformation to myelodysplastic syndrome and acute myeloid leukemia (AML) have occurred during filgrastim therapy in pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocy to sis, Schwachman-Diamond syndrome). The relationship between these events and filgrastim therapy is unknown.

Pregnancy and lactation

a. Although there are no adequate and controlled studies to date in humans, filgrastim has been shown to adversely affect pregnancy and the fetus in animals. Filgrastim should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

b. It is not known whether filgrastim is distributed into milk. Because many drugs are distributed into milk, filgrastim should be used with caution in nursing women.

Drug Interactions

a. The safety and efficacy of concomitant administration of doses of filgrastim with doses of myelosuppressive antineoplastic agents have not been established. Because filgrastim stimulates proliferation of neutrophil precursors and because many antineo plastic agents target rapidly proliferating cells, filgrastim doses should not be administered within 24 hours before or after a dose of one of these agents

b. Because transient decreases in platelet counts have been reported in some patients receiving filgrastim, it is recommended that the drug should be used with caution in patients receiving other drugs known to decrease the platelet count

Acute toxicity

Limited information is available on the acute toxicity of filgrastim in humans. Overdosage of the drug would be expected to produce manifestations that are principally extensions of the pharmacologic and common adverse effects of the drug. The maximum tolerated dosage of the drug in humans has not been determined

Storage

NUFIL Sf™ should be store between 2°C and 8°C in a refrigerator. Do not freeze.
Keep out of reach of children.

Shelf Life

Please refer to expiry date on label / carton.

Presentation

NUFIL Sf™ is available as 0.5 mL single use prefilled syringe containing 300 µg of Filgrastim.

Manufactured by: Biocon Limited
Biocon Special Economic Zone,Plot No. 2-4, Phase IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bangalore - 560 099.

Marketed by: Biocon Limited
20th KM, Hosur Road, Electronics City, Bangalore - 560 100.

For further details, please contact:
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To report adverse events and/or product complaints visit our website www.biocon.com or call toll free No: 1800 102 9465 or e mail us at drugsafety@biocon.com

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