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

8028792-9093

FILLIF

[Filgrastim Injection I.P. PFS 300 mcg (Recombinant Human Granulocyte Colony Stimulating Factor Injection (G-CSF))]

COMPOSITION

Each prefilled syringe of 1.0 ml contains :

Filgrastim Concentrated Solution I.P. 30 MIU (300 mcg)

DESCRIPTION

Recombinant G-CSF (Filgrastim), the active ingredient of FILLIF, is a protein having the structure of the granulocyte colony-stimulating factor (G-CSF) produced and secreted by various human blood cell types. The protein stimulates the differentiation and proliferation of leucocyte stem cells into mature granulocytes. It is produced by a method based on rDNA technology, using bacteria *(E.Coli)* as host cells.Recombinant G-CSF has a molecular weight of 18799 daltones. 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 for *E.Coli*.

Empirical formula : $C_{846}H_{1339}N_{223}O_{243}S_9$

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, 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 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 the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the 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 modeling 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 rate of Recombinant G-CSF is 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 reported 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 reported to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased IV antibiotic usage. No difference in survival or disease progression was demonstrated.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 Leukemia 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. There were no statistically significant differences between Recombinant G-CSF and placebo groups in complete remission rate (69% Recombinant G-CSF (Filgrastim) vs 68% placebo, p = 0.77), disease-free survival (median 342 days Recombinant G-CSF (Filgrastim) [n = 178], 322 days placebo [n = 177], p = 0.99), time to progression of all randomized patients (median 165 days Recombinant G-CSF (Filgrastim), 186 days placebo, p = 0.87), or overall survival (median 380 days Recombinant G-CSF (Filgrastim), 425 days placebo, p = 0.83).

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) reported 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 reported 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 FILLIF in Indian population :

The efficacy and safety of Flilf was evaluated in an open label, phase III confirmatory trial conducted in 100 indian patients for prevention of neutropenia. This multicenter study enrolled adult patients with all types of cancers except leukemia and FILLIF was used for secondary prophylaxis in patients receiving chemotherapy.Patients were evaluated for magnitude of neutropenia (median ANC) and days to recovery from neutropenia in the index cycle (chemotherapy without FILLIF support) and subsequent two cycles (cycles with prophylactic FILLIF administration).In this study , the median ANC in the index cycle was 480 cell/mm^3 and in subsequent cycles were 1800 and 2552 cells/mm^3. The difference between the median ANC in the index cycle and subsequent cycles ware statistically significant (p < 0.0001). The recovery from neutropenia was faster in the cycles with prophylactic FILLIF administration as compared to index cycle without FILLIF . There were more incedences of severe (ANC <500 cells) and febrile (<1000 with fever) neutropenia in patients receiving cancer chemotherapy without FILLIF support than in cycles with prophylactic administration of FILLIF. The use of antibiotic was significantly reduced during cycles with FILLIF administration. The drug was well tolerated in all the patients and no significant adverse effect was reported with FILLIF in this study.

INDICATIONS

Cancer Patients Receiving Myelosuppressive Chemotherapy

Recombinant 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 G-CSF therapy to avoid leukocytosis and to monitor the neutrophil count.

Patients with Acute Myeloid Leukemia 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 the duration of neutropenia and neutropenia-related clinical sequelae, eg. 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 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.

CONTRAINDICATION

- Hypersensitivity to the active substance or to any of the excipients. FILLIF should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.
- FILLIF should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics.

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 most often skin (rash, urticaria, facial edema) , respiratory (wheezing, dyspnea) , 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 intravenously. 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

SPLENIC RUPTURE, INCLUDING FATAL CASES, HAS BEEN REPORTED FOLLOWING THE ADMINISTRATION OF RECOMBINANT G-CSF (FILGRASTIM). INDIVIDUALS RECEIVING RECOMBINANT G-CSF (FILGRASTIM) WHO REPORT LEFT UPPER ABDOMINAL AND/OR SHOULDER TIP PAIN SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving Recombinant G-CSF (Filgrastim), and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving Recombinant G-CSF (Filgrastim) who develop fever, lung infiltrates, interstitial pneumonia or respiratory distress should be evaluated for the possibility of ARDS. If ARDS occurs, Recombinant G-CSF (Filgrastim) 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 peripheral blood progenitor cell (PBPC) mobilization. Hemoptysis resolved with discontinuation of Recombinant G-CSF (Filgrastim). The use of Recombinant G-CSF (Filgrastim) for PBPC mobilization in healthy donors is not an approved indication.

Sickle Cell Disorders

Severe sickle cell crises, in some cases resulting in death, have been associated with the use of Recombinant G-CSF (Filgrastim) 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 G-CSF (Filgrastim) for such patients, and only after careful consideration of the potential risks and benefits.

Patients with Severe Chronic Neutropenia

The safety and efficacy of Recombinant G-CSF (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 Recombinant G-CSF (Filgrastim) therapy. It was reported that MDS and AML occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been reported in patients treated with Recombinant G-CSF (Filgrastim) for SCN. From the reported evidences, 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 Recombinant G-CSF (Filgrastim) on the development of abnormal cytogenetics and the effect of continued Recombinant G-CSF (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 Recombinant G-CSF (Filgrastim) should be carefully considered.

Precautions:

General

Simultaneous Use with Chemotherapy and Radiation Therapy

The safety and efficacy of Recombinant G-CSF (Filgrastim) 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 G-CSF (Filgrastim) in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. For Recombinant G-CSF (Filgrastim) and chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelo- suppressive doses of antimetabolites such as 5-fluorouracil evidences are lacking for efficacy. Similarly, there are lack of evidences for safety and efficacy of Recombinant G-CSF (Filgrastim) and patients receiving concurrent radiation therapy. Simultaneous use of Recombinant G-CSF (Filgrastim) with chemotherapy and radiation therapy should be avoided.

Potential Effect on Malignant Cells

Recombinant G-CSF (Filgrastim) is a growth factor that primarily stimulates neutrophils. However, the possibility that Recombinant G-CSF (Filgrastim) can act as a growth factor for any tumor type cannot be excluded. In a randomized study evaluating the effects of Recombinant G-CSF (Filgrastim) versus placebo in patients undergoing remission induction for AML it was reported that, there was no significant difference in remission rate, disease-free, or overall survival. The safety of Recombinant G-CSF (Filgrastim) in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When Recombinant G-CSF (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^3 or greater were reported in approximately 2% of patients receiving Recombinant G-CSF (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 Recombinant G-CSF (Filgrastim) therapy.

Risks associated with increased doses of chemotherapy

Special caution should be used when treating patients with high dose chemotherapy, because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used). Treatment with Recombinant G-CSF (Filgrastim) alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g., full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Premature Discontinuation of Recombinant G-CSF (Filgrastim) Therapy

Cancer Patients Receiving Myelosuppressive Chemotherapy

A transient increase in neutrophil counts is typically reported 1 to 2 days after initiation of Recombinant G-CSF (Filgrastim) therapy. However, for a sustained therapeutic response, Recombinant G-CSF (Filgrastim) therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm^3. Therefore, the premature discontinuation of Recombinant G-CSF (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. The incidence of antibody development in patients receiving Recombinant G-CSF (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 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, mild or moderate in severity, in patients treated with Recombinant G-CSF (Filgrastim). Most of the reports involved patients with SCN receiving long-term Recombinant G-CSF (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 Recombinant G-CSF (Filgrastim) at a reduced dose. Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with Recombinant G-CSF (Filgrastim) for more than 6 months. Recombinant G-CSF (Filgrastim) contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 Recombinant G-CSF (Filgrastim) therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when Recombinant G-CSF (Filgrastim) was administered, and WBC differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts.

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 Recombinant G-CSF (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 (i.e., 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.

During clinical trials, the following laboratory results were reported:

- Cyclic fluctuations in the neutrophil counts were frequently reported in patients with congenital or idiopathic neutropenia after initiation of Recombinant G-CSF (Filgrastim) therapy.
- Platelet counts were generally at the upper limits of normal prior to Recombinant G-CSF (Filgrastim) therapy. With Recombinant G-CSF (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 reported with Recombinant G-CSF (Filgrastim) therapy.

During other trials, increases in serum uric acid, lactic dehydrogenase, and serum alkaline phosphatase were reported.

DRUG INTERACTION

Drug interactions between Recombinant G-CSF (Filgrastim) and other drugs have not been fully evaluated. Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.Preliminary evidence from a small number of patients treated concomitantly with Recombinant G-CSF (Filgrastim) and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Since lithium promotes the release of neutrophils, lithium is likely to potentiate the effect of Recombinant G-CSF (Filgrastim).In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of Recombinant G-CSF (Filgrastim) is not recommended in the period from 24 hours before to 24 hours after chemotherapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

ADVERSE EVENTS

During clinical trial, the reported adverse reactions are categorised according to MedDRA system organ class and frequency as follows :

Very common: ≥1/10 Common: ≥ 1/100, <1/10 Uncommon: ≥ 1/1,000, < 1/100 Rare: ≥ 1/10,000, <1/1,000 Very rare: < 1/10,000

Not known: cannot be estimated from the available data

Most frequent adverse reaction reported was musculoskeletal pain and less frequently urinary abnormalities predominantly mild or moderate dysuria.

System organ class	Frequency	Undesirable effect
Blood and Lymphatic	Very Common	Anaemia, Splenomegaly System Disorder
	Common	Thrombocytopenia, Spleen disorder, Leukocytosis
Metabolism and Nutrition disorders	Very common	Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Aspartate aminotransferase increased, Blood uric acid increased, Blood glucose decreased, Hyperuricemia
	Common	Anorexia
Nervous system disorders	Common	Headache
Vascular disorders	Rare	Angiopathy
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
	Common	Cough, Pharyngolaryngeal pain
	Very rare	Lung infiltration
Gastrointestinal disorders	Very common	Nausea, Vomiting
	Common	Constipation, Diarrhoea
Hepatobiliary disorders	Very common	Gamma-glutamyl transferase increased
	Common	Hepatomegaly
Skin and subcutaneous tissue disorders	Common	Alopecia, Rash, Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain
	Common	Osteoporosis
Renal and urinary disorders	Very rare	Urine abnormality
	Uncommon	Haematuria, Proteinuria
General disorders and administration site conditions	Common	Fatigue, Asthenia, Mucosal inflammation, Chest pain, Injection site pain
	Uncommon	Pain

During Raandomized clinical trials, patients receiving cytotoxic chemotherapy and placebo or drug reported nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucosal inflammation, headache, cough, rash, chest pain, asthenia, pharyngolaryngeal pain, constipation and pain with equal frequency in both the group. There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation. Vascular disorders, including veno-oclusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. Other adverse reaction reported are aggravation of arthritic symptoms, bone pain, arthralgia, sweets syndrome (acute febrile dermatosis), pulmonary oedema, lung infiltrates, hypersensitivity reaction (anaphylaxis, rash, urticaria, angioedema, dyspnoea, hypotension), Isolated cases of sickle cell crises in patients with sickle cell disease, pseudogout, pulmonary haemorrhage, hypoxia, haemoptysis, neutropenic fever, stomatitis, generalised weakness, mucositis, sore throat, cardiac events (myocardial infarction, arrhythmia), petechiae, transfusion reaction, hypertension, peritonirtis, capillary leak syndrome were reported.

Post Marketing Experience:

Splenic rupture, acute respiratory distress syndrome, alveolar haemorrhage and hemoptysis, sickle cell crises, cutaneous vasculitis, Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported.

OVERDOSAGE

In cancer patients receiving Recombinant G-CSF (Filgrastim) as an adjunct to myelosuppressive chemotherapy, it is recommended, to avoid the potential risks of excessive leukocytosis, that Recombinant G-CSF (Filgrastim) therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Doses of Recombinant G-CSF (Filgrastim) that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. The maximum tolerated dose of Recombinant G-CSF (Filgrastim) has not been determined. 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. In cancer patients receiving myelosuppressive chemotherapy, discontinuation of Recombinant G-CSF (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.

DOSAGES AND ADMINISTRATION

Cancer Patients Receiving Myelosuppressive Chemotherapy

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

Cancer Patients Receivitg Bone Marrow Transplant

The recommended dose of FILLIF 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 FILLIF 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 FILLIF (Recombinant G-CSF (Filgrastim)) should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count	Recombinant G-CSF (Filgrastim) Dose Adjustment
When ANC > 1000/mm^3 for 3 consecutive days then :	Reduce to 5 mcg/kg/day*
If ANC remains > 1000/mm^3 for 3 more consecutive days then :	Discontinue Recombinant G-CSF (Filgrastim)
If ANC decreases to < 1000/mm^3	Resume at 5 mcg/kg/day

* If ANC decreases to < 1000/mm^3 at any time during the 5 mcg/kg/day administration, Recombinant G-CSF (Filgrastim) 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 Recombinant G-CSF (Filgrastim) 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 (Filgrastim) be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of Recombinant G-CSF (Filgrastim) administration and leukapheresis schedule have not been established, administration of Recombinant G-CSF (Filgrastim) for 6 to 7 days with leukaphereses on days 5, 6, and 7 was reported to be safe and effective. Neutrophil counts should be monitored after 4 days of Recombinant G-CSF (Filgrastim), and Recombinant G-CSF (Filgrastim) dose modification should be considered for those patients who develop a WBC count > 100,000/mm^3.

In all clinical trials of Recombinant G-CSF (Filgrastim) for the mobilization of PBPC, Recombinant G-CSF (Filgrastim) was also administered after reinfusion of the collected cells.

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.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Pregnancy Category C

Recombinant G-CSF (Filgrastim) 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 (Filgrastim) on the developing fetus or the reproductive capacity of the mother is unknown. However, the scientific literature describes transplacental passage of Recombinant G-CSF (Filgrastim) when administered to pregnant rats during the latter part of gestation and apparent transplacental passage of Recombinant G-CSF (Filgrastim) when administered to pregnant humans by ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). Recombinant G-CSF (Filgrastim) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rabbits, increased abortion and embryolethality were reported in animals treated with Filgrastim at 80 mcg/kg/day. Filgrastim administered to pregnant rabbits at doses of 80 mcg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, decreased body weight, live births, and food consumption. External abnormalities were not reported in the fetuses of dams treated at 80 mcg/kg/day. Reproductive studies in pregnant rats have reported that Filgrastim was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily IV injection during the period of organogenesis at dose levels up to 575 mcg/kg/day. In Segment III studies in rats, offspring of dams treated at > 20 mcg/kg/day exhibited a delay in external differentiation (detachment of auricles and descent of testes) and slight growth retardation, possibly due to lower body weight of females during rearing and nursing. Offspring of dams treated at 100 mcg/kg/day exhibited decreased body weights at birth, and a slightly reduced 4-day survival rate.

Nursing Mothers

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

Pediatric Use

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 Recombinant G-CSF (Filgrastim) treatment. The relationship of these events to Recombinant G-CSF (Filgrastim) administration is unknown. 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 G-CSF (Filgrastim) treatment. Limited data from patients who were followed 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. The palpable splenomegaly and musculoskeletal pain has been reported in paediatric patients who receive the Recombinant G-CSF (Filgrastim) with chemothrapy for neuroblastoma.

Geriatric Use

No overall differences in safety or effectiveness were reported between these subjects and younger subjects during clinical trials.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store between 2-8°C. Protect from light. Do not freeze or shake.

Keep out of reach of children. Do not use if particulate matter is present

PRESENTATION

FILLIF is available as 300 mcg/1.0 ml PFS for S.C./I.V. use

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
Intas Biopharmaceuticals Ltd.
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