8065811-9093

To be sold by retail on the prescription of
a Registered Medical Practitioner only

Pegfilgrastim Injection

Pegylated Recombinant Methionyl Human Granulocyte Colony Stimulating Factor (PEG-r-metHuG-CSF)

FILLIF-PEG

(For subcutaneous administration only)
Class: Biological Response Modifier/Hematopoietic Agents

INTRODUCTION

Pegfilgrastim is a covalent conjugate of Filgrastim (18.8 kDa) and monomethoxypolyethylene glycol (PEG) molecule (20 kDa). The average molecular weight of Pegfilgrastim is 39 kDa (approx). Pegfilgrastim is a longacting pegylated form of Filgrastim.

Filgrastim produced in E. coli is a recombinant form of human granulocyte colony stimulating factor.

COMPOSITION

Each prefilled syringe (0.6 mL) contains :

Active substance :

Pegfilgrastim or (Pegylated Recombinant Methionyl Human Granulocyte Colony Stimulating Factor) 6 mg

Excipients :

Acetate	0.59 mg / mL
D-Sorbitol (NF)	5% (w/v)
Polysorbate 20 (NF)	0.003% (w/v)
Sodium hydroxide (NF)	q.s.
Water for Injection (IP)	q.s.

INDICATIONS

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy.

FILLIF-PEG is used to decrease the risk of febrile neutropenia in patients with non-myeloid malignancies receiving myelo-suppressive antineoplastic cytotoxic chemotherapy that is associated with a clinically important risk of severe neutropenia with fever. Treatment with FILLIF-PEG leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia frequently observed in patients undergoing cytotoxic chemotherapy. Patients treated with FILLIF-PEG and cytotoxic Chemotherapy requires fewer and shorter hospitalization and decreased antibiotic usage compared to patients treated with cytotoxic chemotherapy alone; thus leading to a greater likelihood of patient compliance and decreased burden for both patients and healthcare professionals. In the absence of growth factor support, febrile neutropenia or severe neutropenia has been reported in patients receiving similar chemotherapy regimens.

DOSAGE AND ADMINISTRATION

FILLIF-PEG is supplied as a single dose pre-filled syringe of 0.6 mL for subcutaneous administration only. Each prefilled syringe of 0.6 mL contains 6 mg Pegfilgrastim.

For the treatment of chemotherapy-induced neutropenia, the recommended adult dosage of FILLIF-PEG is a single 6 mg injection administered subcutaneously once per chemotherapy cycle. Dosage of FILLIF-PEG does not need to be modified based on body weight. FILLIF-PEG should not be administered during the 14 days before or 24 hours after administration of cytotoxic chemotherapy.

Special Populations

No special population dosage recommendations at this time.

CONTRAINDICATIONS

In patients with known hypersensitivity to Pegfilgrastim or Filgrastim or any of the excipients in the formulation or proteins derived from *Escherichia coli.*

SPECIAL WARNINGS AND PRECAUTIONS

WARNINGS

Splenic Rupture : Rare cases of splenic rupture resulting in deaths, have been reported following administration of FILLIF-PEG for peripheral blood progenitor cell (PBPC) mobilization in both healthy donors and patients with cancer. A diagnosis of splenic rupture or splenomegaly should be considered in patients receiving FILLIF-PEG and experiencing left upper abdominal pain and/or shoulder tip pain.

Respiratory Effects :

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving FILLIF-PEG. It has been postulated that an influx of neutrophils into sites of inflammation in the lungs may have caused such disease.

The onset of pulmonary signs such as cough, fever and dyspnea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function manifesting as respiratory distress along with increased neutrophil count in neutropenic patients receiving FILLIF-PEG may warrant evaluation for the presence of ARDS.

In such circumstances FILLIF-PEG should be discontinued and /or withheld until ARDS has resolved, and the patients should receive appropriate treatment.

Sickle Cell Disease :

Severe sickle cell crisis, resulting in deaths has been reported in patients with sickle cell disease (specifically, homozygous sickle cell anemia, ickle cell-hemoglobin C disease, and sickle cell-β+-thalassemia disease) who received FILLIF-PEG.

Patients with sickle cell disease who receive FILLIF-PEG should be well hydrated and monitored for the occurrence of sickle cell crisis. If severe sickle cell crisis occurs, supportive care should be initiated, and interventions to ameliorate the underlying event (e.g., therapeutic red blood cell exchange transfusion) should be considered.

Allergic Reactions : Allergic reactions like skin rash, urticaria can occur in patients receiving FILLIF-PEG.

The majority of reported events occurred upon initial exposure. In some cases, symptoms recurred with a rechallenge, suggesting a casual relationship. Serious allergic reactions, including angioedema or anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue FILLIF-PEG in patients with serious allergic reactions. Do not administer FILLIF-PEG to patients with a history of serious allergic reactions to Pegfilgrastim or Filgrastim. Close follow up of the patients along with antihistamines should be the treatment of choice.

SENSITIVITY REACTIONS

FILLIF-PEG is contraindicated in patients with known hyper-sensitivity to Pegfilgrastim or Filgrastim.

GENERAL PRECAUTIONS

Administration : Because rapidly dividing myeloid cells may be particularly sensitive to cytotoxic chemotherapy, FILLIF-PEG should not be administered during the 14 days before or 24 hours after administration of cytotoxic chemotherapy. (See Dosage and Administration)

Potential Effect on Malignant Cells : The granulocyte colony stimulating factor (G-CSF) receptor through which Pegfilgrastim and Filgrastim act has been found on tumor cell lines like those of myeloid, T-lymphoid, lung, head and neck, and bladder tumor cells), the possibility that FILLIF-PEG could act as a growth factor for any tumor type cannot be excluded. Use of the drug in patients with myeloid malignancies or myelodysplastic syndrome (MDS) has not been studied.

Bone Pain : Bone pain was generally reported to be of mild-to-moderate severity. Among patients experiencing bone pain, most utilized non-narcotic analgesics and a few used narcotic analgesics. However no patient was withdrawn from the study due to bone pain.

Immunogenicity : As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Pegfilgrastim has been adequately determined using a BIAcore assay.

The approximate limit for detection of this assay is 500 ng/ml. While available data suggest that a small proportion of patients developed binding antibodies to Pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in patients who apparently developed binding antibodies.

Laboratory Monitoring : Leucocytosis (WBC counts > 100 x 109/L) was observed in less than 1% of 932 patients with non myeloid malignancies receiving FILLIF-PEG.

Leukocytosis was not associated with any adverse effects. Reversible elevations in LDH, alkaline phosphatase, and uric acid, not requiring treatment were seen in pegfilgrastim and placebo-treated patients in similar rates.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

Though there is a theoretical possibility that an antibody directed against FILLIF-PEG may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, this has not been observed in clinical studies.

SPECIFIC POPULATIONS

Pregnancy : There are no adequate data from the use of FILLIF-PEG in pregnant women. Studies in animal have shown reproductive toxicity. The potential risk for humans is unknown. FILLIF-PEG should not be used during pregnancy unless clearly necessary and only if the potential benefit to the mother justifies the potential risk to fetus.

Lactation : Not known whether FILLIF-PEG is excreted in milk. Caution is advised if the drug is administered in nursing women.

Pediatric Use : Safety and efficacy of FILLIF-PEG have not been established in pediatric patients. Hence the 6 mg fixed dose single-use syringe formulation should not be used in infants, children and adolescents weighing less than 45 kg.

Gediatric Use : No substantial differences in safety and efficacy between patients > 65 years and younger adults were noted.

Effects on ability to drive and use machines : No studies on the effects on the ability to drive and use machines have been performed.

SIDE EFFECTS

According to available literature and published papers, adverse effects reported ranged from 15-72 % of patients receiving Pegfilgrastim or Filgrastim include nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. These adverse effects generally were attributed to the underlying malignancy or to concomitant cytotoxic chemotherapy. The most common adverse effect attributed to Pegfilgrastim in clinical trials was mild-tomoderate medullary bone pain, which occurred in 26% of patients receiving Pegfilgrastim and in a comparable percentage of patients receiving Filgrastim and resulted in use of opiate or non-opiate analgesics in less than 6 or approximately 12 % of those who experienced this adverse effect, respectively.

OVERDOSE

The maximum amount of FILLIF-PEG that can be safely administered in single or multiple doses has not been determined. However leukocytosis was a common adverse event noted. Leukapheresis should be considered in the management of symptomatic individuals.

DRUG INTERACTIONS

No formal drug interaction studies have been performed.

Antineoplastic Agents : Concomitant use of Pegfilgrastim with fluorouracil or other antimetabolites has not been evaluated in patients.

Lithium : Potential pharmacologic interaction (potentiation of neutrophil release); more frequent monitoring of neutrophil counts is recommended. As a response to the growth factor therapy, increased hematopoietic activity of the marrow is manifested as transient positive bone imaging changes which should be considered while interpreting bone imaging results.

PRECLINICAL SAFETY DATA

Acute subcutaneous toxicity in Wistar Rats :
Single dose of 3.1, 6.2 and 12.4 mg/kg.
No clinical signs.
No mortality.
No statistical significant changes in body weight.
Spleen enlargement in mid and high dose groups of male and high dose groups of female.
Histopathological evaluation of spleen showed proliferation of megakaryocytes in red pulp.
These findings can be attributed to its pharmacological properties.

Acute subcutaneous toxicity in Swiss Albino Mice :
Single dose of 6.15, 12.3 and 24.6 mg/kg.
No clinical signs.
No mortality.
No statistical significant changes in body weight.
Spleen enlargement in mid and high dose groups of male and female. Histopathological evaluation of spleen showed proliferation of megakaryocytes in red pulp. These findings can be attributed to its pharmacological properties.

Acute intramuscular toxicity in Wistar Rats :
Single dose of 3.1, 6.2 and 12.4 mg/kg.

No clinical signs.
No mortality.
No statistical significant changes in body weight.
However, some degree of reduction in body weight gain was observed in treatment groups as compared to control.
Spleen enlargement in high dose group of male and female.
Histopathological evaluation of spleen showed proliferation of megakaryocytes in red pulp. These findings can be attributed to its pharmacological properties.

Acute intramuscular toxicity in Swiss Albino Mice :
Single dose of 6.15, 12.3 and 24.6 mg/kg.
No clinical signs.
No mortality.
No statistical significant changes in body weight.
Spleen enlargement in mid and high dose groups of female.
Histopathological evaluation of spleen showed proliferation of megakaryocytes in red pulp. These findings can be attributed to its pharmacological properties.

Repeated dose subcutaneous toxicity study in Wistar Rats :
Doses of 0, 1.55, 3.1, 6.2 mg/kg
Development of articular swelling and partial hind limb dysfunction in some high dose treated animals.
Hct., platelet count and reversible effect
Dose dependent increase in WBC and Absolute neutrophil count and decrease in RBC, hemoglobin, HcT and platelet count. Reversible effect.
Dose dependent increase in spleen size associated with proliferation of megakaryocytes in red pulp.
These findings can be attributed to its pharmacological properties.
Mild congestion of liver and kidney.

Repeated dose subcutaneous toxicity study in Rabbits (New Zealand White) :
Doses of 0.755, 1.55 and 3.1 mg/kg.
Increase in WBC and neutrophil count and dose dependent decrease in RBC, hemoglobin and Hct.

Reversible effect.
In males, marginal decrease in AST and urea level and in female increased triglyceride level.
Increasing trend was seen in Alp and decreasing trend in urea level.
Increase inn absolute organ weight of liver and spleen of low and mid dose of males as compared to control group.
Histopathologically; Proliferation of neutrophils in red pulp area of spleen.
Mild congestion in liver.
Focal area of minimal tubular swelling and degeneration in kidney.
One mortality in high dose female group. This occurred in the high dose group (3.1 mg/kg) whose equivalent dose in human is much higher than the therapeutic dose.

Skin sensitization test-Guinea Pig Maximization Test :
No clinical signs.
No mortality.
No skin reaction at 2.3 mg/mL at Challenge and Rechallenge exposure.
Therefore as per the Maximization sensitization classification system, Pegfilgrastim can be classified as Non-sensitizer.

Immunogenicity test in Wistar Rats and Rabbits (New Zealand White) :

In treated animals moderate levels of anti G-CSF antibody was found which were higher in rabbits than rats.
The anti-HCP titers of treated animals were not significantly different from their respective controls.
The low levels of anti-HCP titers confirm our direct observation of low HCP contamination in our product as tested by HCP- specific ELISA.

Reproductive toxicity :
No adverse effects observed in offspring from pregnant rats given Pegfilgrastim subcutaneously, but in rabbits Pegfilgrastim has been shown to cause embryo/fetal toxicity (embryo loss) at low subcutaneous doses. In rat studies, it was shown that Pegfilgrastim may cross the placenta. The relevance of these findings for humans is not known.

CLINICAL REPORT

The clinical trial Project No. PegfiL08.001.01 conducted by Zydus Cadila was an open label, multicentric trial, where the efficacy and safety of Pegylated Form of Recombinant Human Granulocyte Colony stimulating Factor (Pegfilgrastim) were assessed in 63 patients undergoing myelosuppressive chemotherapy.

Pegfil-grastim was given as single 6 mg subcutaneous injection per cycle.

The study showed the following results:

Reduction in the duration of grade 3 neutropenia from 4 days in documentation cycle to 2 days in cycle 1(p = 0.0078*) and 3 days in cycle 2 (p = 0.0219*).

Reduction in the time to neutrophil recovery from 15.5 days in documentation cycle to 12 days in cycle 1 (p=0.0005*) and 8 days in cycle 2 (p < 0.0001*).

Reduction in the incidence of febrile neutropenia from 4.92 % in the documentation cycle to 1.75% in cycle 2, while none of the subjects had febrile neutropenia in cycle 1.

Reduction in the incidence of parenteral antibiotics from 9.83% in documentation cycle to 6.56% in cycle 1 and 1.75% in cycle 2. There was no significant difference seen in the duration of parenteral antibiotics in all the cycles.

Pegfilgrastim was well tolerated among the patients with favorable safety profile. The results are also comparable to the published Filgrastim reports demonstrating that a single fixed dose of 6 mg of Pegfilgrastim provides support to patients with chemotherapy induced neutropenia in a manner similar to multiple daily doses of Filgrastim.

The results of Cycle 1 and Cycle 2 in which Pegfilgrastim was given were compared to the documentation cycle of chemo therapy where no Pegfilgrastim was administered.

As such, a fixed dose of Pegfilgrastim provides all the clinical benefits of Filgrastim but with the advantage of once-per-cycle dosing.

Once-per-cycle fixed dose Pegfilgrastim

Pegfilgrastim is expected to simplify the management of chemotherapy-induced neutropenia, and also provide significant quality-of-life benefits to oncology patients in the form of fewer injections.

PHARMACOLOGICAL PROPERTIES

Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20kD polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of Filgrastim due to decreased renal clearance. Pegfilgrastim and Filgrastim have been shown to have identical modes of action, causing marked increase in peripheral blood neutrophils counts within 24 hrs, with minor increases in monocytes and/or lymphocytes. Similarly to Filgrastim, neutrophils produced in response to Pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other hematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

PHARMACOKINETICS

After a single subcutaneous dose of Pegfilgrastim, the peak serum concentration of Pegfilgrastim occurs at 16 to 120 hrs after dosing and serum concentrations of Pegfilgrastim are maintained during the period of neutropenia after myelo suppressive chemotherapy.

The elimination of Pegfilgrastim is non-linear with respect to dose; serum clearance of Pegfilgrastim decreases with increasing dose.

Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of Pegfilgrastim declines rapidly at the onset of neutrophil recovery.

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of Pegfilgrastim is not expected to be affected by renal or hepatic impairment.

In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to Pegfilgrastim after receiving a dose normalized for body weight.

A large variability in the pharmacokinetics of Pegfilgrastim was observed in cancer patients. The half-life of Pegfilgrastim ranged from 15 to 80 hours after subcutaneous injection. Limited data indicate that the pharmacokinetics of Pegfilgrastim in elderly subjects > 65 years is similar to that in adults.

The pharmacokinetic profile in pediatric populations or in patients with hepatic insufficiency has not been assessed.

STORAGE

FILLIF-PEG should be stored between +2 °C to +8 °C (36 °F to 46 °F). Do not freeze. Keep the container in outer carton to protect from the direct sunlight.

INSTRUCTIONS FOR USE

Avoid shaking.
Excessive shaking may cause aggregation, rendering the product biologically inactive.
FILLIF-PEG is a sterile, preservative free solution.

Before administration, FILLIF-PEG solution should be inspected for visible particles. It should not be administered if any discoloration or particulates are observed.

Allow the pre-filled syringe to reach room temperature before injecting. It may be exposed to room temperature (not above 30 °C) for a maximum single period of up to 48 hours before injection. FILLIF-PEG left for more than 48 hours should be discarded.

HOW SUPPLIED

FILLIF-PEG is supplied as a single dose prefilled syringe containing 6 mg Pegfilgrastim with integrated 27 gauge, ½ inch needle.
Integrated needle is covered with a rigid needle guard.
FILLIF-PEG is available in single prefilled syringe.

EXPIRY

36 months from the date of manufacture

AVAILIBILITY

Route : Subcutaneous route only
Strength : 6 mg / 0.6 mL, pre-filled syringe

REFERENCES

1. Luxon B. Clinical considerations in pegylated protein therapy. From research to practice 2001; 3:1-7.
2. F. A.Holmes, S.E.Jones, J.O' Shaughnessy, S.Vukelja, T.George, M.Savin, D.Richards, J.Glaspy, L.Meza, G.Cohen, M.Dhami, D.R.Budman, J.Hackett, M.Brassard, B.B.Yang & B.C. Liang;
Comparable efficacy and safety profiles of once-per-cycle Pegfilgrastim and daily injection Filgrastim in chemotherapy induced neutropenia: a multicenter dose-finding study in women with breast cancer.
Annals of Oncology 2002; 13: 903-909.
3. M.D.Green, H.Koelbl, J.Baselga, A.Galid, V.Guillem, P.Gascon, S.Siena, R.I.Lalisang, H.Samonigg, M.R.Clemens, V.Zani, B.C.Liang, J.Renwick & M.J.Piccart; A randonized double-blind multicenter phase III study of fixed-dose single - administration.
Pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Annals of Oncology 2003; 14: 29-s35.
4. Common terminology Criteria for Adverse Events (CTCAE) 2003; v3.0.
5. Maher DW, Lieschke GJ, Green M, Bishop J, Harris RS, et al. Filgrastim in Patients with Chemotherapyinduced Febrile Neutropenia: A Double Blind, Placebo-Controlled Trial. *Annals of Internal Medicine*; October 1994/Volume 121 Issue 7; 492-501.

Torrent Pharma

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

Manufactured by :
Cadila Healthcare Limited
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H.No. 8A, Opp. Ramdev Masala, Village: Changodar, Tal. : Sanand, Dist.- Ahmedabad 382 213.