For the use of oncologists, hematologists or physicians and pediatricians experienced in treatment of cancer only

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# FILLIF-PEG®

## Pegfilgrastim Injection I.P. (6 mg/0.6 ml Pre-filled Syringe)

**GENERIC NAME:** Pegfilgrastim Injection

**DESCRIPTION**

FILLIF-PEG® (Pegfilgrastim Injection) is a chemically modified form of GCSF with 20 Kda polyethylene glycol molecule covalently bound to the N-terminal methionine residue resulting an approximate molecular weight of 39KDa. FILLIF-PEG® (Pegfilgrastim Injection) stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils and is indicated for similar indications as that of GCSF (neutropenia caused by chemotherapy in certain cancer patients). Pegfilgrastim due its chemical modification has extended blood serum half-life and is administered subcutaneously once per chemotherapy cycle.

**DOSAGE FORM AND STRENGTH:** Solution for injection in prefilled syringe (PFS) (6.0 mg).

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each single use Pre-filled Syringe contains:.

| Composition | Quantity per PFS |
|---|---|
| Pegfilgrastim (Peg-GCSF) I.P. | 6 mg |
| Sodium | 0.02 mg |
| Acetate | 0.35 mg |

| Composition | Quantity per PFS |
|---|---|
| Sorbitol I.P. | 30 mg |
| Polysorbate 20 I.P. | 0.02 mg |
| Water for Injection I.P. | (q.s. to 0.6 ml) |

**PHARMACOLOGICAL PROPERTIES**

**Mechanism of Action**

Pegfilgrastim is a colony-stimulating factor which increases the proliferation and differentiation of neutrophils from committed progenitor cells, induces maturation, and enhances the survival and function of mature neutrophils, resulting in dose-dependent increases in neutrophils.

A randomized, double-blind, two-treatment, single-period, parallel design study was conducted to compare the pharmacodynamics and pharmacokinetics of manufacturer's Pegfilgrastim Injection 6 mg/0.6 mL (test pegfilgrastim) with innovator product (reference pegfilgrastim) 6 mg/0.6 mL in healthy, adult, human subjects following subcutaneous administration under fasting condition.

Seventy subjects were enrolled in the study. i.e. 35 subjects in test arm and 35 subjects in the reference arm. Out of 35 subjects in test arm, 34 (97.14%) subjects completed the study.

**Pharmacodynamic properties**

For manufacturer's Pegfilgrastim Injection and Reference products, mean ANC_$C_{max}$ was 36.78 and 37.65 ($x10^3$/µL),ANC_$AUC_{0\text{-}t}$ was 8153.69 and 8682.19 ($x10^3$ X hr/µL) and ANC_$AUC_{0\text{-}\infty}$ was 10703.96 and 10703.61($x10^3$X hr/µL) respectively.

The median ANC_$t_{max}$ observed for manufacturer's Pegfilgrastim Injection and Reference product was 72 (range 48.00 - 144.00) hrs and 72.00 (range 48.00 - 168.00) hrs respectively. The ratios of the mean of the ln-transformed data (T/R ratio) for lnANC_$C_{max}$,lnANC_$AUC_{0\text{-}t}$ and lnANC_$AUC_{0\text{-}\infty}$ were 99.16, 97.43 and 96.70 respectively for pegfilgrastim.

**Pharmacokinetic properties**

For manufacturer's Pegfilgrastim Injection and Reference products, mean $C_{max}$ was 701.07 and 661.19 ng/mL, $AUC_{0t}$ was 40650.03 and 41510.46 (ng x hr/mL) and $AUC_{0\infty}$ was 43930.41 and 46506.67 (ng x hr/mL) respectively. The median $T_{max}$ observed for manufacturer's Pegfilgrastim Injection and Reference product was 24 (range 12.00- 48.00) hrs and 30.00 (range 18.00- 48.00) hrs respectively.

For manufacturer's Pegfilgrastim Injection and Reference products, mean $T_{1/2}$ was 103.19 and 108.73 hrs respectively. The ratios of the mean of the ln-transformed data (T/R ratio) for ln $C_{max}$ lnAUC$_{0\text{-}t}$ and lnAUC$_{0\text{-}\infty}$ were 107.70, 101.34 and 98.47 respectively for pegfilgrastim. Comparison of variability in the pharmacokinetic parameters of pegfilgrastim revealed that variability observed for ln$C_{max}$lnAUC$_{0\text{-}t}$ and lnAUC$_{0\text{-}\infty}$was 37.15, 49.22 and 51.56 respectively.

**CLINICAL PARTICULARS: Indications**

**1. Patients with Cancer Receiving Myelosuppressive Chemotherapy**

FILLIF-PEG® 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 clinically significant incidence of febrile neutropenia. FILLIF-PEG® is not indicated for the mobilization of peripheral blood progenitor cells forhematopoietic stem cell transplantation.

**2. Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome**

FILLIF-PEG® is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

**Posology and method of administration**

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of FILLIF-PEG® is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer FILLIF-PEG® between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2. Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome The recommended dose of FILLIF-PEG® is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose. Obtain a baseline complete blood count (CBC). Do not delay administration of FILLIF-PEG® if a CBC is not readily available. Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

**Administration**

FILLIF-PEG® is administered subcutaneously via a single prefilled syringe.

*Pediatric Patients weighing less than 45 kg*

The FILLIF-PEG® prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of manufacturer's Pegfilgrastim Injection less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors.

Table 1: FILLIF-PEG® (Pegfilgrastim Injection) to patients weighing less than 45 kg

| Body Weight | FILLIF-PEG® (Pegfilgrastim Injection) Dose | Volume to Administer |
|---|---|---|
| Less than 10 kg* | See below* | See below* |
| 10 -20 kg | 1.5 mg | 0.15 mL |
| 21 -30 kg | 2.5 mg | 0.25 mL |
| 31 -44 kg | 4 mg | 0.40 mL |

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of FILLIF-PEG® (Pegfilgrastim Injection).

**NONCLINICAL PROPERTIES**

**Animal toxicology or pharmacology**

The nonclinical studies comprised of single dose toxicity studies of 14-days duration by subcutaneous and intramuscular routes in rats and mice, and repeat dose subcutaneous toxicity studies of 4-weeks duration in the rats and rabbits and a guinea pig maximization test for the one batch of manufacturer's Pegfilgrastim Injection. A detailed comparative repeated dose toxicity with toxicokinetics of 8 weeks was also conducted. A limit test was conducted at a maximum dose of 10 mg/kg body weight. The selected dose level is 100 times that of the intended human dose.

In a single dose toxicity study, manufacturer's Pegfilgrastim Injection tested at 10 mg/kg did not reveal any adverse effects both in rats and mice by subcutaneous and intramuscular routes. The general repeat-dose toxicity studies of 28-day duration in rats and rabbits (dose administered once in three days) produced changes that reflected an exaggerated pharmacological response, or a reaction to the primary response (myeloid hyperplasia in bone marrow), such as extramedullary haematopoiesis in the spleen and liver up to a dose level of 5.58 mg/kg in rats or 2.79mg/kg in the rabbits. In the rat study, minimal antibodies were generated against manufacturer's Pegfilgrastim Injection The antibody response observed in rats was comparable between the innovator product and manufacturer's Pegfilgrastim Injection.

Carcinogenesis, Mutagenesis, Impairment of Fertility studies are not required for similar biologics as per the Review Committee on Genetic Manipulation (RCGM) guidelines of India.

**Clinical Study**

1. A Phase I study was conducted as a randomized, double-blind, two-treatment, single-period, parallel design study to compare the pharmacokinetics and pharmacodynamics of manufacturer's Pegfilgrastim Injection 6 mg/0.6 mL with innovator pegfilgrastim (reference pegfilgrastim) 6 mg/0.6 mL in healthy, adult, human subjects following subcutaneous administration under fasting condition.

Seventy healthy, adult, male subjects were enrolled in the study i.e. 35 subjects in manufacturer's Pegfilgrastim Injection arm and 35 subjects in the reference arm. A total of 66 subjects were considered for comparative pharmacokinetic and statistical analysis. All 70 subjects were considered for pharmacodynamic and safety analysis.

The pharmacokinetic and pharmacodynamic results are described under Pharmacology above.

Subjects who received at least a single dose of pegfilgrastim, either manufacturer's Pegfilgrastim Injection or reference product in the study were included in the safety analyses.

In this study, a total of 54 adverse events were reported. Out of 54 adverse events, 27 (77.14 %) were reported in the manufacturer's Pegfilgrastim Injection arm and 27 (77.14 %) were reported in Reference arm. Out of 27 AEs reported in the Test arm, 24 were probably related to pegfilgrastim and 3 were unrelated to the drug. Out of 27 AEs reported in the manufacturer's Pegfilgrastim Injection arm, 24 were moderate in severity and 3 were mild in severity. Out of 27 AEs reported in the Reference arm, 24 were probably related to pegfilgrastim and 3 were unrelated to pegfilgrastim. Out of 27 AEs reported in the Reference arm, 25 were moderate in severity and 2 were mild in severity. The majority of AEs reported in the study were from general disorders and administration site conditions SOC class. No serious adverse event was observed in the study.

The adverse events observed in this study were in line with the known safety profile of the product. No new significant safety concerns were noted during this study with manufacturer's Pegfilgrastim Injection or Reference formulation. Based on safety analysis, it can be concluded that both the formulations are safe and well-tolerated.

It was concluded that the PK and PD parameters of descriptive statistics for pegfilgrastim shows comparable profile for manufacturer's Pegfilgrastim Injection and Reference formulation. Both manufacturer's Pegfilgrastim Injection and Reference formulation were well tolerated in this study and no serious new observations for vital parameters, laboratory parameters and adverse event profile.

Hence, it was concluded that manufacturer's Pegfilgrastim Injection 6 mg/0.6 mL is bioequivalent with the innovator pegfilgrastim 6 mg/0.6 mL in normal, healthy, adult, human subjects under fasting conditions.

2. A prospective, multi-centric, open-label, two-arm, parallel-group, active-control, randomized comparative Phase III clinical study was carried out to evaluate the comparative efficacy and safety of manufacturer's Pegfilgrastim Injection Test pegfilgrastim) / innovator pegfilgrastim (Reference arm) in patients with chemotherapy-induced neutropenia.

A total of 105 patients were enrolled in the study across the centers in two arms [i.e. manufacturer's Pegfilgrastim Injection and innovator pegfilgrastim (Reference arm) in a 2:1 ratio]. After randomization, 70 patients were enrolled in manufacturer's Pegfilgrastim Injection arm and 35 patients in Reference arm.

As predefined in the protocol, all the subjects who were enrolled in the study, received at least one dose of manufacturer's Pegfilgrastim Injection / Reference arm in the first chemotherapy cycle, and have pre- and post-dose ANC data of at least the first cycle were considered as evaluable subjects for efficacy. Hence, a total of 104 subjects were included in safety population i.e. 69 subjects in manufacturer's Pegfilgrastim Injection arm and 35 subjects in Reference arm.

All subjects were assessed for Grade 4 neutropenia, incidence of febrile neutropenia and time to ANC recovery in the first 4 cycles of chemotherapy in the study. The primary and secondary efficacy analyses were based on severity, incidence and duration data linked to ANC count. The primary and secondary efficacy analyses are presented below for manufacturer's Pegfilgrastim Injection and Reference arms.

The primary endpoint of the study was to measure the duration of Grade 4 neutropenia (ANC<0.5x10 /L) in days in subjects receiving manufacturer's Pegfilgrastim Injection / Reference arm in the first cycle of chemotherapy during the study. In the evaluable population, the mean duration of Grade 4 neutropenia was 1.43 days in the manufacturer's Pegfilgrastim Injection and 2.00 days in the Reference arm. The observed results were comparable in both treatment arms in terms of duration of Grade 4 neutropenia.

In the secondary efficacy analysis, most cases of Grade 4 neutropenia occurred in the first cycle. No cases of Grade 4 neutropenia were noted during cycle 2 in either of the treatment arms. The incidence of Grade 4 neutropenia in the manufacturer's Pegfilgrastim Injection arm was 4.76% in cycle 3 and 1.11% in cycle 4. The incidence of Grade 4 neutropenia in the Reference arm was 6.25% in cycle 3. None of the subjects had Grade 4 neutropenia in cycle 4 in the Reference arm. The incidence of Grade 4 neutropenia was not statistically significantly different between the manufacturer's Pegfilgrastim Injection and Reference arm during cycle 3. (P= 0.759)

In the secondary efficacy analysis in evaluable population, 1 subject (1.45%) who received manufacturer's Pegfilgrastim Injection arm developed febrile neutropenia during cycle 1. The incidence of febrile neutropenia was very low. No subject in either arm developed febrile neutropenia in any of the cycles other than this sporadic case.

The depth of ANC nadir for each cycle was defined as the minimal ANC value for a patient in each respective cycle. The depth of ANC nadir in manufacturer's Pegfilgrastim Injection arm was lowest in cycle 1 ($2.914x10^9$ /L). In Reference arm, the depth of ANC nadir was lowest in cycle 4 ($3.23 x10^9$/L). The observed depth of ANC nadir in manufacturer's Pegfilgrastim Injection and Reference arm were comparable in both treatment arms and the observed difference between two arms in each cycle is statistically insignificant.

All the subjects with observed ANC nadir <2.0x$10^9$/L in both treatment arms were included for analysing the ANC recovery. The mean time to ANC recovery (≥2.0x$10^9$/L) in days after the ANC nadir was 2.22 days in manufacturer's Pegfilgrastim Injection and 1.86 days in Reference arm in cycle 1 (P=0.497). The mean time to ANC recovery (≥2.0x$10^9$/L) in days after the ANC nadir in manufacturer's Pegfilgrastim Injection and in Reference arm was comparable. The observed difference between the two arms in 2nd, 3rd and 4th cycle was statistically insignificant.

From a review of literature published on the innovator pegfilgrastim, it is clear that no clinical studies in hematopoietic subsyndrome of acute radiation syndrome were done. Efficacy studies of the innovator pegfilgrastim also could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting pegfilgrastim effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy.

The efficacy of innovator pegfilgrastim for the acute radiation syndrome setting was studied in a randomized, placebo-controlled non-human primate model of radiation injury. Rhesus macaques were randomized to either a control or treated cohort. On study day 0, animals were exposed to total body irradiation (TBI) in a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Animals were administered subcutaneous injections of a blinded treatment (control arm [5% dextrose in water] or innovator pegfilgrastim [300-319 mcg/kg/day]) on study day 1 and on study day 8. The primary endpoint was survival. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required. Innovator Pegfilgrastim significantly (at 0.0014 level of significance) increased 60-day survival in irradiated non-human primates: 91% survival (21/23) in the innovator pegfilgrastim group compared to 48% survival (11/23) in the control group.

**Undesirable effects**

General side effects associated with the administration of pegfilgrastim have included many effects that have been associated with the chemotherapy that was given concomitantly. These have included 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. Most of these effects have been attributed by the investigators to be the result of the underlying condition or the chemotherapy administered.

Respiratory side effects including adult respiratory distress syndrome (ARDS) has been reported with the use of filgrastim (the parent compound of pegfilgrastim). Because adult respiratory distress syndrome (ARDS) has been reported with the use of filgrastim, patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS.

In the clinical study, all the subjects received 6 mg single dose of manufacturer's Pegfilgrastim Injection / Reference drug subcutaneously, approximately 24 hours after the each chemotherapy cycle.

There were 69 subjects in manufacturer's Pegfilgrastim Injection arm and 35 subjects in Reference arm who received at least a single dose of study medication and were considered as a part of safety population while 57 subjects in manufacturer's Pegfilgrastim Injectionarm and 30 subjects in Reference arm received all 4 doses as planned in the study.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1. In all, 547 adverse events were reported. All the AEs reported in the study were treatment emergent adverse events.

There were 16 (23.19 %) subjects in the manufacturer's Pegfilgrastim Injection arm and 10 (28.57 %) subjects in the Reference arm with at least one treatment emergent adverse event (TEAE) related to study drug. There were 13 (18.84%) subjects in the manufacturer's Pegfilgrastim Injection arm and five (14.29%) subjects in the Reference arm with at least one TEAE in the study.

In the Phase III study, two (2.90%) serious adverse events (SAEs) [including one (1.45%) death] were reported in manufacturer's Pegfilgrastim Injection arm. As per MedDRA coding, these two SAEs were coded into Blood and lymphatic system disorders and vascular disorder system order class (SOC). One (1.45%) subject from manufacturer's Pegfilgrastim Injection arm and one (2.86%) subject from Reference arm discontinued the study due to an adverse event.

FILLIF-PEG®

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **PRODUCT NAME** | : | Fillif-Peg Inje. | **COUNTRY :** Domestic P2P | **LOCATION :** Reliance Life | | **Supercedes A/W No. :** | | |
| **ITEM / PACK** | : | Insert | **NO. OF COLORS :** 1 | **REMARK :** | | | | |
| **DESIGN STYLE** | : | Front Side | **PANTONE SHADE NOS.:** | **SUBSTRATE :** | | | | |
| **CODE** | : | 8098346-9093 | Black | **Activities** | **Department** | **Name** | **Signature** | **Date** |
| **DIMENSIONS (MM)** | : | 150 x 282 mm | | Prepared By | **Pkg.Dev** | | | |
| **ART WORK SIZE** | : | S/S | | Reviewed By | **Pkg.Dev** | | | |
| **DATE** | : | 13-11-2024 | | Reviewed By | **CR** | | | |
| | | | | Approved By | **Quality** | | | |
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**This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.**

Table 2 – Summary of Treatment Emergent Adverse Events by Treatment, Body System and Preferred Term [safety population (N= 69)

| Body System | Preferred Term | Manufacturer's Pegfilgrastim (Pegfilgrastim Injection) (N=69) n % E |
|---|---|---|
| Subjects with at least one Adverse Event | | 56 (81.16%) 320 |
| Blood and lymphatic system disorders | | 13 (18.84%) 34 |
| | Anaemia | 3 (4.35%) 3 |
| | Febrile neutropenia | 2 (2.90%) 3 |
| | Leukopenia | 1 (1.45%) 2 |
| | Neutropenia | 10 (14.49%) 25 |
| | Pancytopenia | 1 (1.45%) 1 |
| Ear and labyrinth disorders | | 1 (1.45%) 1 |
| | Vertigo | 1 (1.45%) 1 |
| Gastrointestinal disorders | | 30 (43.48%) 127 |
| | Abdominal pain | 2 (2.90%) 4 |
| | Ascites | 1 (1.45%) 1 |
| | Constipation | 6 (8.70%) 14 |
| | Diarrhoea | 2 (2.90%) 2 |
| | Enteritis | 1 (1.45%) 1 |
| | Hyperchlorhydria | 1 (1.45%) 1 |
| | Nausea | 21 (30.43%) 46 |
| | Painful defaecation | 1 (1.45%) 2 |
| | Salivary hypersecretion | 2 (2.90%) 3 |
| | Stomatitis | 5 (7.25%) 10 |
| | Vomiting | 14 (20.29%) 43 |
| General disorders and administration site conditions | | 26 (37.68%) 76 |
| | Asthenia | 15 (21.74%) 24 |
| | Disease progression | 1 (1.45%) 1 |
| | Injection site pain | 1 (1.45%) 1 |
| | Mucosal inflammation | 4 (5.80%) 6 |
| | Pain | 14 (20.29%) 25 |
| | Pyrexia | 7 (10.14%) 19 |
| Infections and infestations | | 2 (2.90%) 2 |
| | Cellulitis | 1 (1.45%) 1 |
| | Herpes zoster | 1 (1.45%) 1 |

| Body System | Preferred Term | Manufacturer's Pegfilgrastim (Pegfilgrastim Injection) (N=69) n % E |
|---|---|---|
| Investigations | | 6 (8.70%) 9 |
| | Neutrophil count decreased | 3 (4.35%) 3 |
| | Red blood cells urine positive | 1 (1.45%) 1 |
| | Urinary sediment abnormal | 1 (1.45%) 1 |
| | Weight decreased | 1 (1.45%) 2 |
| | White blood cell count increased | 1 (1.45%) 1 |
| | White blood cells urine positive | 1 (1.45%) 1 |
| Metabolism and nutrition disorders | | 4 (5.80%) 5 |
| | Decreased appetite | 4 (5.80%) 5 |
| Musculoskeletal and connective tissue disorders | | 9 (13.04%) 10 |
| | Back pain | 1 (1.45%) 1 |
| | Bone pain | 2 (2.90%) 2 |
| | Joint range of motion decreased | 6 (8.70%) 6 |
| | Musculoskeletal pain | 1 (1.45%) 1 |
| Nervous system disorders | | 10 (14.49%) 16 |
| | Dizziness | 3 (4.35%) 8 |
| | Headache | 2 (2.90%) 3 |
| | Neuropathy peripheral | 3 (4.35%) 3 |
| | Peripheral sensory neuropathy | 2 (2.90%) 2 |
| Renal and urinary disorders | | 1 (1.45%) 1 |
| | Pyuria | 1 (1.45%) 1 |
| Respiratory, thoracic and mediastinal disorders | | 2 (2.90%) 3 |
| | Cough | 2 (2.90%) 2 |
| | Pleural effusion | 1 (1.45%) 1 |
| Skin and subcutaneous tissue disorders | | 2 (2.90%) 3 |
| | Alopecia | 26 (37.68%) 29 |
| | Alopecia totalis | 2 (2.90%) 2 |
| | Skin discolouration | 2 (2.90%) 2 |
| | Skin hyperpigmentation | 2 (2.90%) 2 |
| Vascular disorders | | 1 (1.45%) 1 |
| | Haemorrhage | 1 (1.45%) 1 |

[N: Number of subjects in the safety population for each treatment; n: number of subjects; E: number of events. Percentages calculated using the number of subjects in the safety population for each treatment as the denominator (%=n/N*100)].

In the clinical studies of the innovator pegfilgrastim, the most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical 9 studies were bone pain and pain in extremity. Leukocytosis (WBC counts > 100 x 10 /L) was observed in less than 1% of patients with non-myeloid malignancies receiving innovator pegfilgrastim. No complications attributable to leukocytosis were reported in the innovator clinical studies.

In the phase III study, immunogenicity assessment was based on the resulting presence of antibodies at the end of 3rd cycle against baseline assessment. A total of 196 samples were analyzed in six sets. As per kit instructions, 14 serum samples were found to be putative positive for anti-peg-GCSF antibodies. Confirmatory ELISA was done for 14 putative positive samples. In confirmatory ELISA, samples were analyzed by spiking with drug (1 µg/well and 0.1 µg/well GCSF, PEG-GCSF) and without addition of drug. Samples were interpreted as positive only if there was more than or equal to 50% drop in OD values after spiking with the drug. Similar treatment was carried out for High Positive control and Low Positive control by spiking with drug. In the first set of confirmatory ELISA, no drop (=>50%) in OD values was observed for High and Low positive controls after spiking with the drug. This could be due to high levels of anti-drug antibodies in both High and Low positive controls. In the second set of confirmatory ELISA, Low positive control was further diluted and spiked with drug (1 µg/well GCSF or peg-GCSF). The controls were also incorporated without addition of drug. A drop of => 50% in OD values was observed. All positive samples, in confirmatory ELISA were negative after spiking with drug and analysis by ELISA. Thus, it was concluded that the above serum samples were negative for anti-drug antibodies (ADA).

**Reporting of side effects**

If you experience any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

**CONTRAINDICATIONS**

Known hypersensitivity to pegfilgrastim, filgrastim, any ingredient in the formulation or proteins derived from Escherichia coli.

**Overdose**

The maximum amount of FILLIF-PEG® (Pegfilgrastim Injection) that can be safely administered in single or multiple doses has not been determined. The effectiveness of leukapheresis in the management of symptomatic individuals with pegfilgrastim-induced leukocytosis has not been studied.

**Special warnings and precautions**

***Splenic Rupture***

Splenic rupture, including fatal cases, can occur following the administration of FILLIF-PEG® (Pegfilgrastim Injection). Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving FILLIF-PEG® (Pegfilgrastim Injection).

***Acute Respiratory Distress Syndrome***

Acute respiratory distress syndrome (ARDS) can occur in patients receiving FILLIF-PEG® (Pegfilgrastim Injection). Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving FILLIF-PEG® (Pegfilgrastim Injection), for ARDS. Discontinue FILLIF-PEG® (Pegfilgrastim Injection) in patients with ARDS.

***Serious Allergic Reactions***

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue FILLIF-PEG® (Pegfilgrastim Injection) in patients with serious allergic reactions. Do not administer FILLIF-PEG® (Pegfilgrastim Injection) to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

***Use in Patients with Sickle Cell Disorders***

Severe sickle cell crises can occur in patients with sickle cell disorders receiving FILLIF-PEG® (Pegfilgrastim Injection). Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

***Glomerulonephritis***

Glomerulonephritis has occurred in patients receiving pegfilgrastim. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of FILLIF-PEG® (Pegfilgrastim Injection).

***Leukocytosis***

White blood cell (WBC) counts of 100 x 10 /L or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

***Capillary Leak Syndrome***

Capillary leak syndrome has been reported after G-CSF administration and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

***Potential for Tumor Growth Stimulatory Effects on Malignant Cells***

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

***Aortitis***

Aortitis has been reported in patients receiving pegfilgrastim. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue pegfilgrastim if aortitis is suspected.

***Nuclear Imaging***

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.

**Drug interactions**

Table 3 below shows the possible drug interactions of pegfilgrastim

Table 3 – Drug interactions of pegfilgrastim

| Drug | Interaction | Comments |
|---|---|---|
| Antineoplastic agents | Sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy may be increased Concomitant use of pegfilgrastim and fluorouracil or other antimetabolites has not been evaluated; increased mortality in mice reported when pegfilgrastim was administered 0, 1, and 3 days prior to fluorouracil | Administration of pegfilgrastim during the 14 days before or 24 hours after administration of cytotoxic chemotherapy is not recommended |
| Lithium | Possible potentiation of neutrophil release | More frequent monitoring of neutrophil counts is recommended |

No formal drug interaction studies between FILLIF-PEG® (Pegfilgrastim Injection) and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes.

**Use in special population**

***Pregnancy Category C***

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area) according to the innovator literature. Signs of maternal toxicity occurred at these doses. Pegfilgrastim should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

***Nursing Mothers***

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

***Pediatric Use***

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on post-marketing surveillance and review of the scientific literature of the innovator product.

Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma.

***Geriatric Use***

No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients in the innovator product studies.

**Effect on ability to drive and use machines**

No studies done.

**PHAMACEUTICAL PARTICULARS**

**Incompatibilities**

No data available.

**Packaging information**

FILLIF-PEG® (Pegfilgrastim Injection) is supplied as preservative free solution (0.6ml) containing 6 mg of Pegfilgrastim (10mg/ml) as a single dose prefilled syringe in a dispensing pack containing one syringe.

Storage, shelf-life and handling instructions FILLIF-PEG® (Pegfilgrastim Injection) should be refrigerated at 2°C–8°C. Prior to administration, FILLIF-PEG® (pegfilgrastim) syringes may be allowed to reach room temperature for up to 48 hours before use. During the period of storage, the prefilled syringe should be kept in the outer container to protect from light. Discard the syringe if stored beyond 48 hours at room temperature. Pegfilgrastim should not be shaken vigorously. For details of product's shelf life, please refer to Expiry Date mentioned on the label & carton.

**PATIENT COUNSELLING INFORMATION**

Advise the patient about the medication and usage.

Advise patients of the following risks and potential risks with FILLIF-PEG® (pegfilgrastim):

- Splenic rupture and splenomegaly
- Glomerulonephritis
- Acute Respiratory Distress Syndrome
- Capillary Leak Syndrome
- Serious allergic reactions
- Aortitis
- Sickle cell crisis

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) that efficacy studies of pegfilgrastim for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals.

Instruct patients who self-administer FILLIF-PEG® (pegfilgrastim Injection) using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

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

Manufactured by : Reliance Life Sciences Pvt. Ltd.
Plant 2 & 7, R-282,TTC Area of MIDC,
Rabale, Thane Belapur Road, Navi Mumbai,
Maharashtra, India - 400 701, INDIA.

**DETAILS OF PERMISSION AND/OR LICENCE NUMBER WITH DATE**

MF-73/2016 dated 13 May 2016
License # KD/7

**DATE OF REVISION:** October 2024

®= Registered Trade Mark

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|---|---|---|---|---|---|---|---|
| **PRODUCT NAME :** | Fillif-Peg Inje. | **COUNTRY :** Domestic P2P | **LOCATION :** Reliance Life | **Supercedes A/W No. :** | | | |
| **ITEM / PACK :** | Insert | **NO. OF COLORS :** 1 | **REMARK :** | | | | |
| **DESIGN STYLE :** | Back Side | **PANTONE SHADE NOS.:** | **SUBSTRATE :** | | | | |
| **CODE :** | 8098346-9093 | Black | **Activities** | **Department** | **Name** | **Signature** | **Date** |
| **DIMENSIONS (MM) :** | 150 x 282 mm | | Prepared By | **Pkg.Dev** | | | |
| **ART WORK SIZE :** | S/S | | Reviewed By | **Pkg.Dev** | | | |
| **DATE :** | 13-11-2024 | | Reviewed By | **CR** | | | |
| | | | Approved By | **Quality** | | | |
| | | | Approved By | **Quality** | | | |

**This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.**