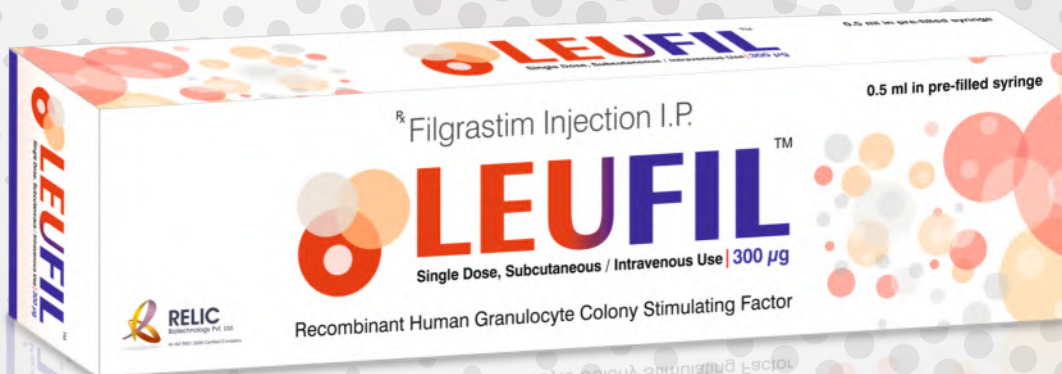


℞ Filgrastim Injection I.P.

 **LEUFIL**TM



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

^rFilgrastim Injection I.P.



Recombinant Human Granulocyte Colony Stimulating Factor

Prescribing Information

DESCRIPTION

Filgrastim (human granulocyte colony-stimulating factor, G-CSF) is a 175 amino acid protein manufactured by recombinant DNA technology by inserting human gene coding for G-CSF into *Escherichia coli* (*E. Coli*). The amino acid sequence in filgrastim is identical to human G-CSF except for the addition of an N-terminal methionine necessary for expression in *E. Coli* and is not glycosylated.

COMPOSITION

LEUFIL™ is a sterile, clear, colorless, preservative-free liquid containing Filgrastim for parenteral administration. It is available as single use Pre-Filled Syringe (PFS) of 0.5 mL containing 300 µg of Filgrastim concentrated solution I.P. in a sodium acetate aqueous buffer containing sorbitol and polysorbate 80.

Each 0.5 ml in Pre-filled syringe contains	
Filgrastim concentrated solution I.P.	600 µg/ml
Acetate	0.59 mg/ml
Sorbitol	50.0 mg/ml
Polysorbate 80	0.04 mg/ml
Sodium	0.035 mg/ml
Water for Injection	q.s.

PHARMACOLOGY

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors. Endogenous G-CSF is a lineage specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). G-CSF is not species specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage.

Pharmacokinetics:

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Peak serum concentrations following subcutaneous injection are generally attained within 4-5 hours. The volume of distribution averaged 150ml/kg. Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The mean serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg.

INDICATIONS AND USAGE

LEUFIL™ is indicated for use in:

- Cancer patients receiving myelosuppressive chemotherapy.
- Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy.
- Cancer patients receiving bone marrow transplant.
- Patients undergoing peripheral blood progenitor cell collection and therapy.
- Patients with severe chronic neutropenia.

CONTRAINDICATIONS

LEUFIL™ should not be administered to patients with known hypersensitivity to filgrastim or to any of the excipients in the preparation.

DOSAGE AND ADMINISTRATION

Cancer Patients Receiving Myelosuppressive Chemotherapy:

In these patients, to treat infections implicated as neutropenia, 5 mcg/kg/day, single daily SC bolus injection or short IV infusion (15 to 30 minutes) or by continuous SC or continuous IV infusion has to be used. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Hematological parameters (CBC, Platelet count) should be obtained before starting therapy & maintained twice weekly during therapy. **LEUFIL™** should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm³. **LEUFIL™** may be discontinued if the ANC increases beyond 10,000/mm³.

Acute Myeloid Leukemia, receiving induction or consolidation chemotherapy:

The dose of filgrastim for such patients is 5 µg/kg/day SC, from 24 hours after the last dose of chemotherapy until neutrophil recovery or for a maximum of 35 days.

Cancer patients receiving bone marrow transplant:

The recommended dose following BMT is 10 µg/kg/day given as an IV infusion for 4 or 24 hours or as a continuous 24-hour SC infusion after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

During the period of neutrophil recovery, the daily dose of filgrastim should be titrated against the neutrophil response as follows

Absolute Neutrophil Count	Dose Adjustment
When ANC > 1000/mm ³ for 3 consecutive days	Reduce to 5 mcg/kg/day ^a
then: If ANC remains > 1000/mm ³ for 3 more consecutive days	Discontinue
then: If ANC decreases to < 1000/mm ³	Resume at 5 mcg/kg/day

^a If ANC decreases to < 1000/mm³ at any time during the 5 mcg/kg/day administration, filgrastim should be increased to 10 mcg/kg/day, and the above steps should then be followed.

Patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy in cancer patients:

The recommended dose for the mobilization of PBPC is 10 µg/kg/day SC, either as a bolus or a continuous infusion. It is recommended that filgrastim be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of filgrastim administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukapheresis on days 5, 6, and 7 was found to be safe and effective.

Severe Chronic Neutropenia:

Filgrastim should be administered to those patients in whom a diagnosis of congenital, cyclic or idiopathic neutropenia has been definitively confirmed. Other diseases associated with neutropenia should be ruled out. Recommended starting dose for congenital neutropenia is 6 µg/kg, bid, SC every day. Recommended starting dose for cyclic or idiopathic neutropenia is 5 µg/kg, SC everyday. The dose may be further adjusted depending on the individual patients' clinical course and ANC.

Dilution:

LEUFIL™ should not be diluted with saline solution for IV administration as the product will precipitate. For infusion, **LEUFIL™** can be diluted with 5% dextrose solution to a final concentration of 5 to 15 µg/mL.

ADVERSE EFFECTS

Filgrastim generally is well tolerated, and very rarely produces adverse effects so severe that discontinuation is required. The adverse effect reported most frequently is mild to moderate (occasionally severe) medullary bone pain. The bone pain appears to be dependent on the dose and/or route of administration (lower incidence with subcutaneous injection, and higher with intravenous). The safety profile reveals **LEUFIL™** to be well tolerated with no significant adverse reactions observed. The most common adverse events were pyrexia, vomiting, diarrhea, asthenia, generalized pain, cough, abdominal pain, anemia, pain in extremity, nausea, anorexia, hypoaesthesia, paraesthesia, mucosal inflammation and dysuria, all of these being chemotherapy emergent and not treatment related. Most adverse events were of mild severity requiring no hospitalization or medication. The incidence of bone pain was also low, with only two patients complaining of severe bone pain.

PRECAUTIONS AND WARNINGS

Simultaneous use with Chemotherapy and Radiation Therapy:

Since the safety and efficacy of filgrastim given concomitantly with cytotoxic chemotherapy and radiation therapy has not been established, it is advisable that simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided. In patients receiving cytotoxic drugs, for 24 hrs prior to and 24 hrs after chemotherapy, filgrastim administration should be avoided, since the sensitivity of fast proliferating neutrophils to chemotherapy is not established.

Potential Effect on Malignant Cells:

Filgrastim is a growth factor that primarily stimulates neutrophils. However, the possibility that filgrastim can act as a growth factor for any tumor type cannot be excluded.

Pregnant women:

Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of filgrastim on the developing fetus or the reproductive capacity of the mother is unknown. Filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if filgrastim is administered to a nursing woman.

Pediatric Use:

The safety profile of filgrastim in pediatric patients appears similar to that reported in adults. The safety and efficacy in neonates and patients with autoimmune neutropenia of infancy have not been established. As rhG-CSF can cause increased uric acid levels, patients who have a history of gout or malignancies that are known to be associated with increased uric acid levels, should be monitored regularly.

OVERDOSAGE

Filgrastim therapy should be discontinued if the ANC surpasses 10,000/mm³ after the chemotherapy induced ANC nadir has occurred. Doses of filgrastim that increase the ANC beyond 10,000/mm³ may not result in any additional clinical benefit and should be avoided. The maximum tolerated dose of **LEUFIL™** has not been determined.

DRUG INTERACTIONS

Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Toxicology studies:

As with other therapeutic proteins, filgrastim also has a potential for immunogenicity. However the incidence and effect of this has not been adequately determined. The carcinogenic and mutagenic potential of filgrastim has not been studied. Single dose acute and chronic toxicity studies were conducted for **LEUFIL™** with intramuscular and subcutaneous dosing in Swiss Albino mice (1000 µg/kg body weight) and Sprague Dawley rats (500 µg/kg body weight). The studies revealed no apparent toxicity in the test animals. **LEUFIL™** did not cause any skin sensitization in test animals. It did not induce mutations in the mutagenicity model of Salmonella typhimurium.

PRESENTATION

LEUFIL™ is available as single use PFS containing 300 µg of filgrastim concentrated solution I.P.

STORAGE

Store between 2°C and 8°C. Do not freeze. Protect from light. Prior to injection, filgrastim may be allowed to attain room temperature. The shelf life of the single dose pre-filled syringe is two years from the date of manufacturing.