Grafil
Filgrastim BP

DRUG INTERNATIONAL LTD.

COMPOSITION :

Grafil pre-filled syringe injection: Each pre-filled syringe contains 0.5 ml sterile solution of Filgrastim BP 300 mcg (30 MU).

CLINICAL PHARMACOLOGY

Mechanism of action: Filgrastim is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Filgrastim regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation and differentiation. It also causes the enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing and the increased expression of some cell surface antigens.

Pharmacokinetics: Filgrastim exhibits nonlinear pharmacokinetics. Clearance is dependent on Filgrastim concentration and neutrophil count. Filgrastim is cleared by kidney. It has a tmax of 2 to 8 hours. The absolute bioavailability of Filgrastim after subcutaneous administration is 60 - 70%.

INDICATIONS

Filgrastim is Indicatod for-

Cancer patients receiving myelosuppressive chemotherapy : The decrease of the incidence of infection, as manifested by febrile neutropenia, in patients with non myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.

Cancer patients undergoing Acute Myeloid Leukemia: The reduction of the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

Cancer Patients Receiving Bone Marrow Transplantation (BMT): The reduction of the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablatlve chemotherapy followed by bone marrow transplantation.

Patients with severe chronic neutropenia : The reduction of the incidence and duration of sequelae of neutropenia (e.g., fever, infection or opharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia.

Patients acutely exposed to myelosuppressive doses of radiation: The increase of the survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic syndrome of acute radiation syndrome).

Patients with HIV infection: The prevention and treatment of persistent neutropenia (ANC $\leq$ 1.0 x 10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections, when other options to manage neutropenia are inappropriate.

DOSAGE AND ADMINISTRATION

Cancer patients receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML: The recommended dose of Filgrastim is 0.5 MU (5 mcg)/kg/day, administered as a single daily subcutaneous injection or by intravenous infusion (over 30 minutes). The first dose shouldn't be administered in less than 24 hours following cytotoxic Chemotherapy. Continue until neutrophil count in normal range, usually for 14 days (up to 38 days in AML.)

Cancer patients undergoing bone marrow transplantation: The recommended dosage of Filgrastim following bone marrow transplantation (BMT) is 1.0 MU (10 mcg)/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of Filgrastim at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow transplantation. Dose adjustment should be accordingly to absolute neutrophil count (ANC).

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

Absolute Neutrophil Count	Filgrastim Dose Adjustment
When ANC greater than 1000/mm³ for consecutive 3 days	Reduce to 5 mcg/kg/day
If ANC remains greater than 1000/mm³ for 3 more consecutive days	Discontinue drug
If ANC decreases to less than 1000/mm³	Resume at 5 mcg/kg/day

Patients undergoing autologous peripheral blood progenitor cell (PBPC) collection and therapy: The recommended dosage of Filgrastim for the mobilization of autologous PBPC is 1.0 MU (10 mcg)/kg/day given by subcutaneous injection for 5-7 days. Administer Filgrastim for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Discontinue Filgrastim if the white blood cell (WBC) count rises to greater than 100,000/mm³.

Patients with severe chronic neutropenia: The recommended starting dosage in patients with congenital neutropenia is 0.6 MU (6 mcg)/kg as a twice daily subcutaneous injection and with idiopathic or cyclic neutropenia is 0.5 MU (5 mcg)/kg as a single daily subcutaneous injection. Dose adjustment should be accordingly to ANC and complete blood count (CBC).

Patients acutely exposed to myelosuppressive doses of radiation hematopoietic syndrome of acute radiation syndrome : The recommended dose of Filgrastim is 1.0 MU (10 mcg)/kg as a single daily subcutaneous injection for patients exposed to myelosuppressive doses of radiation.

Patients with HIV infection:

The recommended starting dose of Filgrastim is 0.1 MU (1.0 mcg)/kg/day is given daily by subcutaneous injection with titration up to a maximum of 0.4 MU (4 mcg) /kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 10^9/l), Or, as directed by the registered physicians.

SIDE EFFECTS

Most common side effects in patients -

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs are pyrexia, pain, rash, cough and dyspnea.
- With AML are pain, epistaxis and rash.
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT is rash.
- Undergoing peripheral blood progenitor cell mobilization and collection are bone pain, pyrexia and headache.
- With severe chronic neutropenia (SCN) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.

CONTRAINDICATIONS

Filgrastim is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as Filgrastim or peg-Filgrastim

- With severe congenltal neutropenia (Kostmann's syndrome)

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.

Precautions

- Filgrastim should not be administered within 24 hours before and afier chemotherapy
- The possibility of Filgrastim acting as a growth factor for any tumor type cannot be excluded
- To avoid -adverse effects of excessive neutrophils complete blood count is recommended twice per week

during treatment

- Filgrastim is given by subcutaneous or intravenous infusion as required
- Dilution of Filgrastim conc less than 5 mcg/ml is not recommended at any time
- Filgrastim may be diluted in 5% dextrose as required

Use in pregnancy and lactation: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Nursing Mother- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if it is administered to women who are breastfeeding.

OVERDOSE

The maximum tolerated dose of Filgrastim has not been determined. Patients in the BMT studies received up to 13.8 MU(138 mcg)/kg/day without toxic effects.

STORAGE

Store at 2°C to 8° C. Protect from light. Do not freeze & avoid shaking.

Packing:

Grafil pre-filled syringe injection: Each per-filled syringe contains 0.5 ml sterile solution which contains
Filgrastim BP 300 mcg (30 MU).