Ropenia®

Filgrastim

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

Description

Ropenia® is a preparation of Filgrastim which is a Granulocyte Colony Stimulating

Factor (G-CSF), produced by recombinant DNA technology.

Mechanism of action

Ropenia® are glycoproteins that act on hematopoietic cells by binding to specific cellsurface receptors and stimulating proliferation, differentiation and some end cellfunctions. Endogenous G-CSF is a lineage specific colony stimulating factor that 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 functions including 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

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of **Ropenia® resulted** inmaximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours.

After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and cancer subjects. Clearance rates of **Ropenia® were** approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily intravenous doses, over a 14 day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration for subcutaneous administration. Continuous 24 hour intravenous infusions of 20 mcg/kg over an 11 to 20 day period produced steady state serum concentrations of **Ropenia®** with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of Ropenia® after subcutaneous administration is 60% to 70%.

Indication

Ropenia® is indicated for patients-

- With cancer receiving myelosuppressive chemotherapy to reduce the duration of neutropenia and the incidence of infection as manifested by febrile neutropenia.
- With acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy for reduction of time to neutrophil recovery and the duration of fever.

Recommended dosage adjustment during neutrophil recovery in patients with cancer following BMT

- With cancer undergoing bone marrow transplantation (BMT) for the reduction in the duration of neutropenia and neutropenia related sequelae.
- Undergoing autologous peripheral blood progenitor cell collection (PBPC) and therapy.
- With severe chronic neutropenia (SCN).
- Acutely exposed to myelosuppressive doses of radiation (Hematopoietic syndrome of acute radiation syndrome).
- Requiring treatment of persistent neutropenia (absolute neutrophil count, ANC < 1x109/L) in patients with advanced HIV infection.

Dose and administration

Route of administration:**Ropenia®** should be taken in subcutaneous (SC) andintravenous (IV) route.

Cancer patient on myelosuppressive chemotherapy

- The recommended dosage of Ropenia® is 5 mcg/kg/day, administered as a single daily injection by subcutaneous (SC) or intravenous infusion (IV) for 15-30 minutes or by continuous IV infusion.
- First dose should be administered at least 24 hours after chemotherapy.
- A dose escalation of 5 mcg/kg may be considered for each chemotherapeutic cycle taking into account the severity of the ANC nadir and duration of chemotherapy.
- The therapy should be stopped if absolute neutrophil count (ANC) increased beyond10000/mm3.
- To ensure sustained therapeutic response, administration of **Ropenia®**should be continued daily for upto 2 weeks or until the ANC has reached10,000/mm3 following the expected chemotherapy induced neutrophil nadir.

Cancer patients undergoing bone marrow transplantation (BMT)

The recommended dosage of **Ropenia® following** BMT is 10mcg/kg/day given as anintravenous infusion no longer than 24 hours. First dose of **Ropenia®** should beadministered at least 24 hours after cytotoxic chemotherapy and at least 24 hoursafter bonemarrow infusion. Complete blood count(CBC) and platelet counts monitoring should be carried out frequently following BMT.

Absolute neutrophil count	**Ropenia® dosage adjustment**
When ANC greater than 1000/mm3 for 3 consecutive days	Dose should be reduced to 5mcg/kg/day
Then, if ANC remains greater than 1000/mm3 for 3 more consecutive days	**Ropenia®** therapy should be discontinued
Then, if ANC decreases to less than 1000/mm3	Therapy with 5mcg/kg/day dose should be resumed

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

Patients undergoing autologous peripheral blood progenetor cell collection (PBPC)and therapy

The recommended dosage is 10 mcg/kg/day by subcutaneous injection for 5 to 7 days. The dose should be administered for atleast 4 days before the first leukapheresis and should continue until the last leukapheresis.

Administration of **Ropenia® for** 6 to 7 days with leukapharesis on days 5, 6 and 7 has been found to be safe and effective.

Neutrophil counts should be monitored after 4 days of **Ropenia® therapy**.

Ropenia® therapyshould be discontinued if the white blood cell (WBC) count rises to greater than 100,000/mm3.

Patients with severe chronic neutropenia (SCN)

Prior to starting treatment with **Ropenia®**, the diagnosis of severe neutropenia should beconfirmed. Incorrect diagnosis may impair or delay evaluation and treatment of otherunderlying causes of neutropenia other than SCN.

Starting dose

In congenital neutropenia, recommended starting dose is 6mcg/kg as a twice daily SCinjection.

In idiopathic or cyclic neutropenia, recommended starting dose is 5 mcg/kg as a single daily SC injection.

Dose adjustments

When the response has been obtained the minimal effective dose to maintain this level should be established. Long term daily administration is required to maintain an adequate neutrophil count.

- After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every1 to 2 weeks to maintain the average neutrophil count between 1.5 x 109/L and 10 x 109/L.
- A faster schedule of dose escalation may be considered in patients presenting with severe infections.

Patients with advanced HIV infection

- Recommended starting dose is 1 mcg/kg given daily by SC injection with up to a maximum of 4 mcg/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 109/L).
- Once the reversal has been achieved, minimal dose to maintain a normal ANC count should be established.
- Initial dose adjustment to alternate day dosing with 300 mcg/day by SC injection is recommended.
- Further dose adjustment should be individualized based on ANC count of the patient to maintain the neutrophil count greater than 2.0 x 109/L.
- **Patients with acute exposure to myelosuppressive dosed of radiation**
- 10 mcg/kg/day as a single daily SC injection for patients exposed to myelosuppressive doses of radiation.
- The dose should be administered as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

Use in elderly: Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with hepatic impairment: No dose adjustment is required

Patients with renal impairment: No dose adjustment is required

Contraindication

Filgrastim is contraindicated in patient with known hypersensitivity to filgrastim or any othercomponents of the product. It is also contraindicated in patient with E-coli derived proteins and human G-CSF's.

Warning and precaution

- Filgrastim should be used with caution in patients with allergic reactions, splenic rupture, alveolar hemorrhage hemoptysis, sickle cell disorders, capillary leak syndrome, leukocytosis, acute respiratory symptoms, cutaneous vasculitis, and secondary AML.
- Regular monitoring of complete blood count is recommended twice per week during the therapy.
- Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than six months.

- Caution should be taken when treating patients with high dose chemotherapy.
- Increased hematopoietic activity of the bonemarrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone imaging results.

Side effects

The most common side effect of filgrastim is large vessel vasculitis. Other side effectsinclude gastro-intestinal disturbances, headache, asthenia, musculoskeletal pain, bone pain, rash, alopecia, injection site reactions, thrombocytopenia, leukocytosis, chest pain, interstitial pneumonia, cutaneous vasculitis, acute febrile neutrophillicdermatosis.

Use in pregnancy and lactation

Pregnancy: Filgrastim is pregnancy category C drug.

Lactation: Unknown whether drug is excreted in breast milk, so it should be used with caution.

Use in children and adolescents

The dosage recommendations in pediatric patients are the same as those in adults receivingmyelosuppressive cytotoxic chemotherapy.

Drug interactions

Drug interaction with medication: Drug interactions between filgrastim and other drugshave not been fully evaluated. Drugs which may potentiate the release of neutrophils, suchas lithium, should be used with caution.

Drug interaction with food: Not applicable.

Drug interaction with others: Not applicable.

Overdose

The effect of filgrastim overdose has not been established.

Storage

Store at 2ºC to 8ºC (in a refrigerator), protected from light, do not shake and do not keep indeep freeze.

Packing

Ropenia® 30 MIU pre-filled syringe injection: Each box contains 1 pre-filled syringe with aneedle, needle cap and a needle safety guard attached to the syringe containing 0.5 mlsterile solution of Filgrastim BP 30 MIU (300mcg), a pair of hand gloves, a first aid bandage and an alcohol pad.

® Registered Trade Mark

Advanced Chemical

Industries Limited

7, Hajeegonj Road, Godnyl

Narayangonj, Bangladesh