Neograstim®

Filgrastim

FORMS AND PRESENTATION

Neograstim® 30: Box of 1 pre-filled syringe, SC/IV.
Neograstim® 48: Box of 1 pre-filled syringe, SC/IV.

COMPOSITION

Neograstim® 30: Each pre-filled syringe contains Filgrastim (rHuG-CSF): 30 MU (300 µg).
Neograstim® 48: Each pre-filled syringe contains Filgrastim (rHuG-CSF): 48 MU (480 µg).
Excipients: glacial acetic acid, sorbitol, polysorbate, sodium hydroxide, water for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Immunostimulants.
ATC code: L03AA02.
Filgrastim: Recombinant Human Granulocyte Colony Stimulating Factor (rHuG-CSF) is a highly purified non-glycosylated protein comprising 175 amino acids.
Human Granulocyte Colony Stimulating Factor is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Neograstim®, containing rHuG-CSF, causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some severe chronic neutropenia (SCN) patients, Filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced by the human body in response to Filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of Filgrastim therapy, circulating neutrophil counts decrease by 50% within 1-2 days, and to normal levels within 1-7 days.
Treatment with Filgrastim leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia frequently observed in patients undergoing cytotoxic chemotherapy or myeloablative therapy followed by bone marrow transplantation.
Treatment with Filgrastim significantly reduces the durations of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukemia. The incidence of fever and documented infections was not reduced in this setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.
Use of Filgrastim, either alone, or after chemotherapy, mobilizes hematopoietic progenitor cells into the peripheral blood. These autologous Peripheral Blood Progenitor Cells (PBPCs) may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates hematopoietic recovery reducing the duration of risk for hemorrhagic complications and the need for platelet transfusions.

Pharmacokinetic Properties

There is a positive linear correlation between the dose and the serum concentration of Filgrastim, whether administered intravenously or subcutaneously. Following SC administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8-16 hours. The volume of distribution in blood is approximately 150 ml/kg. Clearance of Filgrastim has been shown to follow first-order pharmacokinetics after both SC and IV 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. Continuous infusion with Filgrastim over a period of up to 28 days, in patients recovering from autologous bone marrow transplantation, resulted in no evidence of drug accumulation and comparable elimination half-lives.

INDICATIONS

Neograstim® is indicated for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation.
The safety and efficacy of Neograstim® are similar in adults and children receiving cytotoxic chemotherapy.
Neograstim® is indicated for the mobilization of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy in order to accelerate hematopoietic recovery by infusion of such cells, after myelosuppressive or myeloablative therapy.
In patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) of $\leq 0.5 \times 10^9$/l, and a history of severe or recurrent infections, long-term administration of Neograstim® is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.
Neograstim® is indicated for the treatment of persistent neutropenia ANC $\leq 1.0 \times 10^9$/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

CONTRAINDICATIONS

Known hypersensitivity to Filgrastim or to any of the excipients.
Patients with severe congenital neutropenia (Kostmann's syndrome) with abnormal cytogenetics.

PRECAUTIONS

Malignant cell growth: Granulocyte Colony Stimulating Factor can promote growth of myeloid cells in vitro, and similar effects may be seen on some non-myeloid cells in vitro. The safety and efficacy of Filgrastim administration in patients with myelodysplastic syndrome, or chronic myelogenous leukemia have not been established. Filgrastim is not indicated for these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukemia from acute myeloid leukemia.
Leukocytosis in patients receiving cytotoxic chemotherapy: white blood cell counts of 100×10^9/l or greater have been observed in < 5% of patients receiving Filgrastim at doses above 0.3 MU (3 µg)/kg/day. No adverse events directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during Filgrastim therapy. If leukocyte counts exceed 50×10^9/l after the expected nadir, Filgrastim should be discontinued immediately. However, during the period of administration of Filgrastim for PBPC mobilization, discontinuation of Filgrastim or dosage adjustment is appropriate if the leukocyte counts rise to > 70×10^9/l.
Risks of high doses of chemotherapy in patients receiving cytotoxic chemotherapy: special caution should be used when treating patients with high-dose chemotherapy, because improved tumour outcome has not been demonstrated, and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurological and dermatological effects. Treatment with Filgrastim alone does not preclude thrombocytopenia and anemia due to myelosuppressive chemotherapy. Regular monitoring of platelet count and hematocrit is recommended. The use of Filgrastim mobilized PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.
Transformation to leukemia or pre-leukemia in patients with SCN: special care should be taken in the diagnosis of SCN to distinguish from other hematologic disorders such as aplastic anemia, myelodysplasia and myeloid leukemia. Complete blood cell counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment. There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukemia in patients with SCN treated with Filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukemia are natural complications of the disease and are of uncertain relation to Filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities including monosomy 7, on routine repeat evaluation. If patients with SCN develop abnormal cytogenetics, the risks and benefits of continuing Filgrastim should be carefully weighed; Filgrastim should be discontinued if MDS or leukemia occur. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).
Blood cell counts in patients with SCN: platelet counts should be monitored closely, especially during the first few weeks of Filgrastim therapy. Consideration should be given to intermittent cessation or dose reduction in patients who develop thrombocytopenia, i.e. platelets consistently <100.000/mm^3. Other blood cell changes occur, including anemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.
Others precautions in patients with SCN: causes of transient neutropenia, such as viral infections, should be excluded. Splenic enlargement is a direct effect of treatment with Filgrastim. Dose reductions were noted to slow or stop the progression of splenic enlargement, and in 3% of patients a splenectomy was required.
Hematuria/proteinuria occurred in a small number of patients. Regular urinanalysis should be performed to monitor this event.
The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.
In Patients undergoing Peripheral Blood Progenitor Cell mobilization:
Mobilization: there are no prospectively randomized comparisons of the 2 recommended mobilization methods (Filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The choice of mobilization method should be considered in relation to the overall objectives of treatment for an individual patient.
Prior exposure to cytotoxic agents: patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilization of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ CD34$^+$ cells/kg) or acceleration of platelet recovery, to the same degree.
Some cytotoxic agents exhibit particular toxicities to the hematopoietic progenitor pool, and may adversely affect progenitor mobilization. Agents such as melphalan, carmustine (BCNU), and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilization may reduce progenitor yield. However, the administration of melphalan, carboplatin or BCNU together with Filgrastim, has been shown to be effective for progenitor mobilization.

PREGNANCY AND LACTATION

The safety of Filgrastim has not been established in pregnant women. There is no evidence from studies in rats and rabbits that Filgrastim is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen. In pregnancy, the possible risk of Filgrastim use to the foetus must be weighed against the expected therapeutic benefit. It is not known whether Filgrastim is excreted in human milk. Filgrastim is not recommended for use in nursing women.

DRUG INTERACTIONS

The safety and efficacy of Filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of Filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with Filgrastim and 5-fluorouracil indicates that the severity of neutropenia may be exacerbated. Possible interactions with other hematopoietic growth factors and cytokines have not yet been investigated in clinical trials.
Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.
Incompatibilities: Filgrastim should not be diluted with saline solutions.

ADVERSE EFFECTS

In patients receiving cytotoxic chemotherapy: administration of Filgrastim at the recommended dosage is frequently associated with musculoskeletal pain. This is usually mild or moderate (10%), but occasionally severe (3%), and is generally controlled with standard analgesics. Less frequent adverse events include urinary abnormalities (predominantly mild or moderate dysuria). Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.
Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase, alkaline phosphatase, serum uric acid and gamma-glutamyl transpeptidase may frequently occur.
Vascular disorders (e.g. veno-occlusive disease and fluid volume disturbances) have been reported occasionally in patients undergoing high-dose chemotherapy followed by autologous bone marrow transplantation. The causal association with Filgrastim has not been established.
Symptoms suggestive of allergic-type reactions have been reported in rare cases, approximately half of these were associated with the initial dose. Overall, reports were more common after IV administration. In some cases, rechallenge resulted in a recurrence of symptoms.
Rare and sometimes fatal cases of interstitial pneumonia have been described with the use of Filgrastim.
In patients with SCN: adverse reactions related to Filgrastim therapy in SCN patients have been reported and for some their frequency tends to decrease with time.
The most frequent clinical adverse events attributed to Filgrastim were bone pain and general musculoskeletal pain.
Other events seen include splenic enlargement, which may be progressive in a minority of cases, and thrombocytopenia. Headache and diarrhea have been reported shortly after starting Filgrastim therapy, typically in < 10% of patients. Anemia and epistaxis have also been reported.
Transient increases with no clinical symptoms were observed in serum uric acid, lactic dehydrogenase and alkaline phosphatase. Transient, moderate decreases in non-fasting blood glucose have also been seen.
Adverse events possibly related to Filgrastim therapy and typically occurring in < 2% of SCN patients were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis and rash.
During long-term use cutaneous vasculitis has been reported in 2% of SCN patients. There have been very few instances of proteinuria/hematuria.

DOSAGE AND ADMINISTRATION

Established cytotoxic chemotherapy: the recommended dose of Neograstim® is 0.5 MU (5 µg)/kg BW once daily. Neograstim® may be administered as a daily SC injection or as a daily IV infusion, diluted in 5% dextrose solution, given over 30 minutes.
The SC route is preferred in most cases. There is some evidence from a study of single-dose administration that IV dosing may shorten the duration of effect. The clinical relevance of this finding to multiple-dose administration is not clear. The choice of route should depend on the individual clinical circumstances.
The first dose of Neograstim® should not be administered < 24 hours following cytotoxic chemotherapy.
Daily dosing with Neograstim® should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukemias, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.
In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of Neograstim® therapy. However, for a sustained therapeutic response, Neograstim® therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of Neograstim® therapy, prior to the time of the expected neutrophil nadir, is not recommended.
In patients treated with myeloablative therapy followed by bone marrow transplantation: the recommended starting dose of Neograstim® is 1.0 MU (10 µg)/kg/day given as a 30 minutes or 24 hours IV infusion or 1.0 MU (10 µg)/kg/day given by continuous 24 hours SC infusion. Neograstim® should be diluted in 20 ml of 5% dextrose solution.
The first dose of Neograstim® should not be administered < 24 hours following cytotoxic chemotherapy but within 24 hours of bone marrow infusion.
Once the neutrophil nadir has been passed, the daily dose of Neograstim® should be titrated against the neutrophil response as follows:

Neutrophil Count	Neograstim® dose adjustment
> 1.0×10^9/l for 3 consecutive days	Reduce to 0.5 MU/kg/day
Then, if ANC remains > 1.0×10^9/l for 3 more consecutive days	Discontinue Neograstim®

If the ANC decreases to < 1.0×10^9/l during the treatment period, the dose of Neograstim® should be re-escalated according to the above steps.
For the mobilization of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation: the recommended dose of Neograstim® when used alone is 1.0 MU (10 µg)/kg/day as a 24-hour SC continuous infusion or a single daily SC injection for 5 to 7 consecutive days. For infusions Neograstim® should be diluted in 20 ml of 5% dextrose solution (see Instructions for dilution). Timing of leukapheresis: 1 or 2 leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Neograstim® dosing should be maintained until the last leukapheresis.
The recommended dose of Neograstim® for PBPC mobilization after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day given daily by SC injection from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from <0.5×10^9/l to >0.5×10^9/l. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.
In patients with SCN: congenital neutropenia: the recommended starting dose is 1.2 MU (12 µg)/kg/day subcutaneously as a single dose or in divided doses. Idiopathic or cyclic neutropenia: the recommended starting dose is 0.5 MU (5 µg)/kg/day subcutaneously as a single dose or in divided doses. Neograstim® should be administered daily by SC injection until the neutrophil count has reached and can be maintained at more than 1.5×10^9/l. 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 1-2 weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1-2 weeks to maintain the average neutrophil count between 1.5×10^9/l and 10×10^9/l. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses $\leq$ 24 µg/kg/day. The long-term safety of Neograstim® administration above 24 µg/kg/day in patients with SCN has not been established.
Pediatric use in the SCN and cancer settings: 65% of patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for pediatric patients treated for severe chronic neutropenia.
Data from clinical studies in pediatric patients indicate that the safety and efficacy of Neograstim® are similar in both adults and children receiving cytotoxic chemotherapy.
In patients with HIV infection:
For reversal of neutropenia: the recommended starting dose of Neograstim® is 0.1 MU (1µg)/kg/day given daily by subcutaneous injection with titration up to a maximum of 0.4 MU (4µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0×10^9/l). In a small number of patients (<10%), doses up to 1.0 MU (10µg)/kg/day were required to achieve reversal of neutropenia.
For maintaining normal neutrophil counts: when reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300µg)/day by SC injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0×10^9/l.
Instructions for dilution: If required, Neograstim® may be diluted in 5% dextrose solution. Diluted Neograstim® may be adsorbed to glass and plastic materials. However, when diluted correctly, Neograstim® is compatible with glass and a variety of plastic including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene. If Neograstim® is diluted to a concentration between 0.5 MU (5 µg)/ml and 1.5 MU (15µg)/ml, human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.
Dilution to a final concentration < 0.5 MU (5 µg)/ml is not recommended at any time.
Do not dilute with saline at any time; product may precipitate.

OVERDOSAGE

The effects of Filgrastim overdosage have not been established. Discontinuation of Filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1-2 days, with a return to normal levels in 1-7 days.

STORAGE CONDITIONS

Store between 2°C - 8°C. Do not freeze or shake. Protect from light.
Prior to injection, Neograstim® may be allowed to reach room temperature for a maximum of 24 hours. Any pre-filled syringe left at room temperature for greater than 24 hours should be discarded.

Date of revision: November 2012.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

PI044/4

Benta S.A.L.
Dbayeh - Lebanon