Neulastim®

Pegfilgrastim

Composition

Active ingredient: pegfilgrastim 6 mg.

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections.

Pharmaceutical Form and Quantity of Active Substance per Unit

Solution for injection

6 mg pegfilgrastim in 0.6 ml (10 mg/ml*) solution for injection.

* based on protein only. The concentration is 20 mg/ml if the PEG moeity is included.

Indications and Potential Uses

To shorten the duration of neutropenia and reduce the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for a malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndrome).

Dosage and Administration

Adults

One 6 mg dose of Neulastim (a single pre-filled syringe) is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy. Neulastim should not be administered over the period between 14 days before and 24 hours after the administration of cytotoxic chemotherapy.

Neulastim therapy should be initiated and supervised by physicians experienced in oncology and/or hematology.

Children and adolescents

There are insufficient data to recommend the use of Neulastim in infants, children and small adolescents under 45 kg.

Renal impairment

No dose change is recommended in patients with renal impairment, including those with end-stage renal disease.

Contraindications

Hypersensitivity to the active substance pegfilgrastim, filgrastim, proteins produced in *E. coli*, or any constituent excipient.

Warnings and Precautions

In patients with *de novo* acute myeloid leukemia, limited clinical data from 83 treated patients from a study prematurely discontinued in error suggest that pegfilgrastim and filgrastim have a similar effect on time to recovery from severe neutropenia (see "Properties and Effects"). However, the long-term effects of Neulastim have not been adequately investigated in acute myeloid leukemia; Neulastim should therefore be used with caution in this patient population.

Granulocyte-colony stimulating factors 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 Neulastim have not been investigated in patients with myelodysplastic syndrome, chronic myeloid leukemia, or in patients with secondary AML; Neulastim should therefore not be used in such patients. Particular care is required in the differential diagnosis between blast transformation in chronic myeloid leukemia and acute myeloid leukemia.

The safety and efficacy of Neulastim have not been investigated in patients receiving high-dose chemotherapy.

In rare cases (>0.01% and <0.1%), pulmonary adverse effects, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

The onset of pulmonary signs, such as cough, fever and dyspnea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function associated with an increased neutrophil count, may herald adult respiratory distress syndrome (ARDS). In such cases, Neulastim should be discontinued at the discretion of the physician and an appropriate treatment initiated.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. Spleen size should therefore be monitored clinically (by ultrasound). The diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder pain.

Treatment with Neulastim alone does not preclude the occurrence of thrombocytopenia and anemia because full-dose myelosuppressive chemotherapy is maintained on the prescribed dosage schedule. Regular monitoring of the platelet count and hematocrit is recommended.

Neulastim should not be used to increase the dose of cytotoxic chemotherapy beyond the recommended dosage schedule.

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Physicians should therefore perform careful supervision when using Neulastim in patients with sickle cell anemia, monitoring appropriate clinical parameters and laboratory values, and being alert to a possible association between Neulastim and splenomegaly and vasoocclusive crises.

During Neulastim therapy, white blood cell counts of 100×10^9/l or more have been observed in fewer than 1% of patients. No undesirable effects directly attributable to this degree of leukocytosis have been reported. Such elevation of the white blood cell count is transient, typically occurring 24 to 48 hours after administration, and is consistent with the pharmacodynamic effects of Neulastim.

The safety and efficacy of Neulastim for the mobilisation of hematopoietic progenitor cells in patients or healthy donors have not been adequately investigated.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging findings. This should be considered when interpreting bone imaging results.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. No adequate data are available on the occurrence of antibodies in patients treated with Neulastim. While available data suggest that a small proportion of patients developed antibodies binding to filgrastim or pegfilgrastim, the nature and specificity of these antibodies have not been investigated in depth. No neutralising antibodies were detected using a cell-based bioassay in 46 patients who had apparently developed binding antibodies.

The detection of antibody formation is highly dependent on assay sensitivity and specificity and the observed incidence of such antibodies in the assay may be influenced by various factors, including sample handling, comedication, and underlying disease. Comparison of the incidence of antibodies to Neulastim with that of antibodies to other drugs may therefore be misleading.

Rare cases of cytopenia have been reported resulting from an antibody response to exogenous growth factors in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim could react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

Interactions

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neulastim should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical studies, Neulastim has been safely administered 14 days before chemotherapy. Neulastim coadministration with a chemotherapy agent has not been investigated in patients. In animal models, coadministration of Neulastim and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

Possible interactions with other hematopoietic growth factors and cytokines have not been specifically investigated in clinical studies.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such interaction would

be harmful. The safety and efficacy of Neulastim have not been investigated in patients receiving chemotherapy associated with delayed myelosuppression, e.g. nitrosoureas.

Specific interaction or metabolism studies have not been performed. However, clinical studies have shown no evidence of interaction between Neulastim and other medicinal products.

Pregnancy and Lactation

No adequate data are available on the use of pegfilgrastim in pregnant women. Animal studies have shown reproductive toxicity (see "Preclinical Data"). The potential risk for humans is unknown.

Neulastim should not be used in pregnancy unless clearly necessary.

There is no clinical experience with lactating women: Neulastim should therefore not be used during lactation.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive or use machines have been performed.

Undesirable Effects

In randomised clinical studies in cancer patients receiving Neulastim after cytotoxic chemotherapy, most undesirable effects were caused by the underlying cancer or cytotoxic chemotherapy.

The most frequently reported undesirable effect related to the study drug was bone pain (26%). Bone pain was generally of mild to moderate severity, transient, and controllable in most patients with a standard analgesic.

Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnea, hypotension, injection site reactions, erythema and flushing, have been reported on initial or subsequent treatment with Neulastim. In some cases, these symptoms have recurred on rechallenge, suggesting a causal relationship. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Reversible, mild to moderate elevations in uric acid, alkaline phosphatase and lactate dehydrogenase – without associated clinical effects – occurred in 7%, 10% and 20% of patients receiving Neulastim after cytotoxic chemotherapy. Nausea was observed in healthy volunteers (11%) and in fewer than 1% of patients receiving chemotherapy.

In rare cases, pulmonary undesirable effects have been reported, such as interstitial pneumonia, pulmonary edema, pulmonary infiltrates and pulmonary fibrosis. Some of these reported cases resulted in respiratory failure or adult respiratory distress syndrome (ARDS), which may be fatal.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see "Warnings and Precautions").

Rare cases of thrombocytopenia and leukocytosis have been reported.

Rare cases of Sweet's syndrome (acute febrile dermatosis) have been reported, although in some cases an underlying hematological condition may have played a role.

Very rare events of cutaneous vasculitis have been reported in patients treated with Neulastim. The mechanism of development for vasculitis in patients receiving Neulastim is unknown.

There have been isolated reports of sickle cell crises in patients with sickle cell disease (see "Warnings and Precautions").

Elevations in liver function tests (LFTs) have been observed in patients receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

Very common (>10%) and common (>1%, <10%) undesirable effects in clinical studies were:

Musculoskeletal system:

Very common: bone pain (26%)

Common: arthralgia, myalgia, and back, limb, muscle, skeletal and neck pain

Body as a whole and application site reactions:

Common: (non-cardiac) chest pain, pain, pain at the injection site

Nervous system:

Common: headache

Overdosage

There is no experience of Neulastim overdose in humans and the maximum amount of Neulastim that can be safely administered in single or multiple doses has not been determined. Single 300 µg/kg doses were administered subcutaneously to eight healthy volunteers and three patients with non-small cell lung cancer without serious undesirable effects. These subjects displayed a mean maximum absolute neutrophil count (ANC) of 55×10^9/l, with a corresponding mean maximum leukocyte count of 67×10^9/l. The maximum ANC observed was 96×10^9/l, with a corresponding absolute maximum leukocyte count of 120×10^9/l. The duration of leukocytosis ranged from 6 to 13 days. Leukopheresis should be considered in the management of symptomatic persons.

Properties and Effects

ATC code: L03AA13

Pegfilgrastim is produced by recombinant DNA technology in *E. coli* (K12).

Mechanism of action

Human granulocyte colony-stimulating factor (G-CSF) is a glycoprotein which regulates the production of neutrophils and their release from the bone marrow.

Pharmacodynamics

Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kDa polyethylene glycol (PEG) molecule. Pegfilgrastim is a form of filgrastim with sustained duration due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical mechanisms of action, causing a marked increase in the peripheral blood neutrophil count within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim therapy display normal or enhanced functionality as shown by tests of chemotactic and phagocytic function. As with other hematopoietic growth factors, G-CSF has shown stimulating properties on human endothelial cells *in vitro*. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro*; similar effects may be observed on some non-myeloid cells *in vitro*.

Clinical efficacy

In two randomised double-blind clinical studies in patients receiving myelosuppressive chemotherapy with doxorubicin and docetaxel and a single dose per cycle of pegfilgrastim every 21 days for up to four cycles for the treatment of metastatic breast cancer, pegfilgrastim once per cycle reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to daily filgrastim administration (a median of 11 once-daily administrations). In the absence of growth factor administration, this treatment schedule resulted in a mean duration of grade 4 neutropenia of 5–7 days and a 30–40% incidence of febrile neutropenia. In the first study (n=157), which used a 6 mg fixed dose of pegfilgrastim, the mean duration of grade 4 neutropenia in the pegfilgrastim group was 1.8 days compared to 1.6 days in the filgrastim group (difference: 0.23 days, 95% CI -0.15, 0.63). Over the whole study, the rate of febrile neutropenia in patients treated with pegfilgrastim was 13% compared to 20% in the patients treated with filgrastim (difference: 7%, 95% CI -19%, 5%). In a second study (n=310), which used a weight-adjusted dose (100 µg/kg), the mean duration of grade 4 neutropenia was 1.7 days in the pegfilgrastim group compared to 1.8 days in the filgrastim group (difference: 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% in patients treated with pegfilgrastim and 18% in patients treated with filgrastim (difference: 9%, 95% CI -16.8%, -1.1%).

A placebo-controlled study investigated the effect of pegfilgrastim on the incidence of febrile neutropenia after a chemotherapy regimen (docetaxel 100 mg/m^2 every 3 weeks for four cycles) for which the reported frequency of febrile neutropenia was 10–20%. 928 patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was significantly lower in the patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p \leq 0.001$). The incidence of

hospitalisations and intravenous antimicrobial therapy associated with a clinical diagnosis of febrile neutropenia was significantly lower in the pegfilgrastim group than with placebo (1% versus 14%, p<0.001 and 2% versus 10%, p<0.001).

A small (n=83), double-blind, randomised phase II study that was terminated prematurely in error compared pegfilgrastim (single 6 mg dose) with filgrastim during induction chemotherapy in patients with *de novo* AML receiving chemotherapy. (Median) time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long-term treatment outcome was not investigated (see "Warnings and Precautions"). Supplementary supporting studies in male and female cancer patients were terminated.

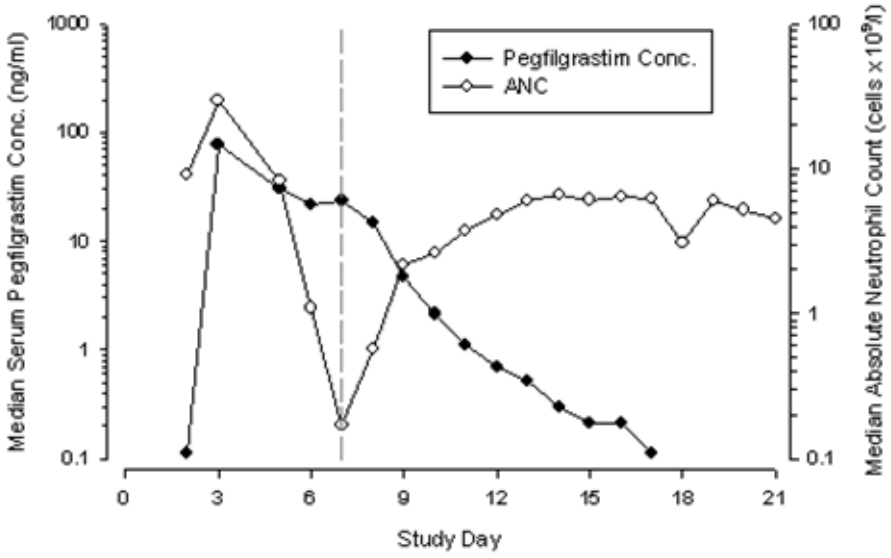
Pharmacokinetics

Absorption

After administration of a single subcutaneous dose of pegfilgrastim, peak serum pegfilgrastim concentrations are reached in 16 to 120 hours; serum pegfilgrastim concentrations are maintained after myelosuppressive chemotherapy for the duration of neutropenia.

The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil-mediated clearance, which reaches saturation at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgastrim rapidly declines at the onset of neutrophil recovery (see Figure 1).

Figure 1. Profile of median pegfilgrastim serum concentration and absolute neutrophil granulocyte count (ANC) after injection of a single 6 mg dose in patients treated with chemotherapy



Pharmacokinetics in Special Patient Groups

Patients with hepatic or renal impairment:

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open-label, single-dose study (n=31), various degrees of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Elderly patients

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly patients (>65 years) is similar to that in adult patients.

Preclinical Data

Preclinical data from conventional studies of repeated-dose toxicity showed the expected pharmacological effects. These include increases in the leukocyte count, myeloid hyperplasia in bone marrow, extramedullary hematopoiesis and splenomegaly.

No adverse effects were observed in offspring from pregnant rats given pegfilgrastim subcutaneously. However, in rabbits pegfilgrastim was shown to cause embryo/fetal toxicity (embryo loss) at low subcutaneous doses. In rat studies it was shown that pegfilgrastim may cross the placenta. The relevance of these findings for humans is not known.

Additional Information

Incompatibilities

Neulastim is incompatible with sodium chloride solutions.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Store in a refrigerator (at 2 °C – 8 °C).

Neulastim may be kept at room temperature (not above 30 °C) for a single period of up to 72 hours. Neulastim left at room temperature for more than 72 hours should be discarded.

Do not freeze. Accidental exposure of Neulastim to temperatures below freezing for a single period of less than 24 hours does not impair the stability of Neulastim.

Store the container in the original pack to protect the contents from light.

Instructions for use and handling

Neulastim is a sterile but unpreserved solution. Before use, Neulastim solution should be inspected for visible particles. Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

Unused medicinal product or waste material should be disposed of in accordance with local requirements.

Packs

Pre-filled syringe of 0.6 ml 1

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.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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