SCHEDULING STATUS
S4

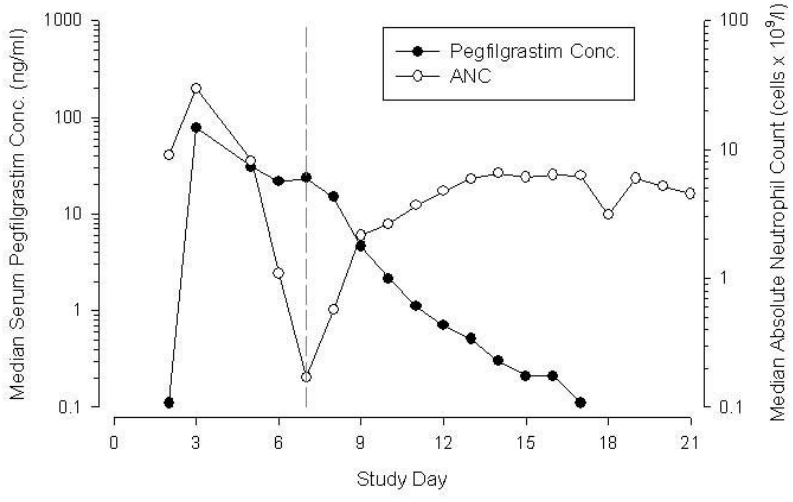
PROPRIETARY NAME AND DOSAGE FORM
NEULASTIM® Injection

COMPOSITION
Each pre-filled syringe contains 6 mg of pegfilgrastim in 0,6 ml (10 mg/ ml) in solution for injection. Pegfilgrastim is composed of filgrastim (recombinant methionyl human granulocyte colony stimulating factor (G-CSF)) with a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is produced in Escherichia coli cells by recombinant DNA technology.
Excipients: Sodium acetate, sorbitol, polysorbate 20, water for injections.

PHARMACOLOGICAL CLASSIFICATION
A 8.5 Medicines acting on blood and haemopoietic system - others

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. 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 sustained duration form of filgrastim due to decreased renal clearance. A transient increase in the white cell count is the expected consequence of pegfilgrastim administration. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells *in vitro,* and similar effects may be seen on some non-myeloid cells *in vitro*.
Pharmacokinetic properties
Absorption
After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing.
Distribution
Serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The distribution of pegfilgrastim was limited to the plasma compartment.
Elimination
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 (> 99 %), which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see Figure 1). **Figure 1:** Profile of median pegfilgrastim serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy-treated patients after a single 6 mg injection

Figure 1: Profile of median pegfilgrastim serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy-treated patients after a single 6 mg injection



Pharmacokinetics in Special Populations

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

Paediatrics:

The pharmacokinetics of NEULASTIM were studied in 37 paediatric patients with sarcoma. The systemic exposure ($AUC_{0\text{-}inf}$, mean ± Standard Deviation) of NEULASTIM after subcutaneous administration at 100 µg/kg was 22,0 (± 13,1) µg·hr/ml in the 6-11 years age group (n = 10), 29,3 (± 23,2) µg·hr/ml in the 12-21 years age group (n = 13) and 47,9 (± 22,5) µg·hr/ml in the youngest age group (0-5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20,2 (± 11,3) hours, 21,2 (± 16,0) hours and 30,1 (± 38,2) hours, respectively. Note that the systemic exposure is much higher and the $T_{1/2}$, longer in children aged 0 - 6 years. See DOSAGE and DIRECTIONS FOR USE, SIDE-EFFECTS AND SPECIAL PRECAUTIONS.

INDICATIONS

To reduce the duration of neutropenia and the incidence of febrile neutropenia and the incidence of infection as manifested by febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

CONTRA-INDICATIONS

Hypersensitivity to pegfilgrastim, filgrastim, *E. coli* derived proteins, or to any excipients.

WARNINGS AND SPECIAL PRECAUTIONS

Cases of splenic rupture, in some cases fatal, have been reported following administration of pegfilgrastim. Spleen size should be carefully monitored. Patients receiving pegfilgrastim who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.
NEULASTIM can promote growth of myeloid cells including malignant cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.
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. See INTERACTIONS.

In animal models concomitant administration of NEULASTIM and 5-fluorouracil (5-FU) or other anti-metabolites has been shown to potentiate myelosuppression.
NEULASTIM is incompatible with sodium chloride solutions.
The safety and efficacy of NEULASTIM in patients with acute leukaemia have not been sufficiently investigated to enable treatment recommendations.
NEULASTIM can promote growth of myeloid cells, including malignant 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 myelogenous leukaemia, and in patients with secondary AML; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.
The safety and efficacy of NEULASTIM have not been investigated in patients receiving high dose chemotherapy.
The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). In such circumstances NEULASTIM should be discontinued at the discretion of the medical practitioner and the appropriate treatment given.
Treatment with NEULASTIM alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule.
Regular monitoring of platelet count and haematocrit is recommended.
NEULASTIM should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.
Sickle cell crises have been associated with the use of NEULASTIM in patients with sickle cell disease. Medical practitioners should exercise caution when considering the use of NEULASTIM in patients with sickle cell disease, and only after careful evaluation of the potential risk and benefits.
White blood cell counts of 100 x 10^9/l or greater have been observed in less than 1 % of patients receiving NEULASTIM. No adverse events directly attributable to this degree of leucocytosis have been reported. Such elevation in white blood cells is transient, typically seen 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 blood progenitor cells in patients has not been adequately evaluated.

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. Concomitant use of NEULASTIM with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of NEULASTIM and 5-fluorouracil (5-FU) or other anti-metabolites has been shown to potentiate myelosuppression.
Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.
Possible interactions with other haematopoietic 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 an interaction would be harmful.
The safety and efficacy of NEULASTIM have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression eg, nitrosoureas.
Specific interaction or metabolism studies have not been performed, however clinical studies have not indicated an interaction of NEULASTIM with any other medicinal products.

PREGNANCY AND LACTATION
Safety in pregnancy has not been established. Studies in animals have shown reproductive toxicity. The potential risk to the human embryo or foetus is unknown. NEULASTIM should not be used during pregnancy. NEULASTIM should not be administered to women who are breast-feeding.

DOSAGE AND DIRECTIONS FOR USE
Adults (≥ 18 years) One 6 mg dose (a single pre-filled syringe) of NEULASTIM is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.
Children and Adolescents: There are insufficient data to recommend the use of NEULASTIM in children and adolescents under 18 years of age.
NEULASTIM therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
NEULASTIM pre-filled syringe is for single use only.
NEULASTIM is a sterile but unpreserved solution.
Before administration, 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE-EFFECTS
In randomised clinical studies in patients with malignancy receiving NEULASTIM after cytotoxic chemotherapy, most adverse events were caused by the underlying malignancy or cytotoxic chemotherapy.
The most frequently reported and very common study-drug related undesirable effect was bone pain. Bone pain was generally of mild-to-moderate severity, transient and could be controlled in most patients with standard analgesics.
Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension, occurring on initial or subsequent treatment have been reported both with NEULASTIM and with the parent compound of NEULASTIM, filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship.
Cases of splenic rupture have been reported during treatment with NEULASTIM.
Reversible, mild to moderate elevations in uric acid, alkaline phosphatase and lactate dehydrogenase, with no associated clinical effects, occurred in 7 %, 10 % and 20 % respectively of patients receiving NEULASTIM following cytotoxic chemotherapy. Nausea was observed in healthy volunteers (11 %) and < 1 % of patients receiving chemotherapy. Very common (≥ 10 %) and common (≥ 1 %, < 10 %) undesirable effects in clinicl studies were:

Body system		**Undesirable effects**
Musculoskeletal and connective tissue disorders	very common	Bone pain
	common	Arthralgia, myalgia, and back, limb, musculo-skeletal, and neck pain
General disorders and application site disorders	common	Injection site pain and erythema, chest pain (non-cardiac), pain
Central nervous system disorders	common	Headache

Post Marketing
Immune system disorders: Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea, hypotension, erythema and flushing, occurring on initial or subsequent treatment have been reported in patients receiving NEULASTIM. Symptoms have recurred with rechallenge, suggesting a causal relationship. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. NEULASTIM should be permanently discontinued in patients who experience a serious allergic reaction.
Gastrointestinal disorders: Cases of splenic rupture, have been reported during treatment with NEULASTIM.
Skin and subcutaneous tissue disorders: Sweet's syndrome (acute febrile dermatosis) have been reported. Cutaneous vasculitis have been reported in patients with cancer receiving NEULASTIM.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Single doses of 300 µg/kg have been administered to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse effects. The adverse events were similar to those in subjects receiving lower doses of NEULASTIM.

IDENTIFICATION
A clear and colourless liquid, practically free from particles.

PRESENTATION
1 ml clear colourless Type I glass pre-filled syringe (containing 0,6 ml) with a stainless steel needle, for single use only. Cartons with 1 or 5 syringes.

STORAGE INSTRUCTIONS
Store at 2– 8 ˚C (in a refrigerator).
Do not freeze.
Keep the container in the outer carton, in order to protect from light.
Keep out of reach and sight of children.
Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of NEULASTIM.
NEULASTIM may be exposed to room temperature (not above 30 ˚C) for a maximum single period of up to 72 hours. NEULASTIM left at room temperature for more than 72 hours should be discarded.
Do not use after the expiry date (EXP) shown on the pack.

REGISTRATION NUMBER
42/8.5/0598

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DATE OF PUBLICATION OF THIS PACKAGE INSERT
12 June 2015