

# Data Sheet

## Neulastim<sup>®</sup>

*Pegfilgrastim 6 mg in 0.6 mL (pre-filled syringe), solution for injection*

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### Description

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#### ***Therapeutic/Pharmacologic Class of Medicine***

Haematopoietic growth factor

Pharmacotherapeutic group: Cytokines, ATC Code: L03AA13

#### ***Type of Dosage Form***

Solution for injection in a pre-filled syringe.

#### ***Route of Administration***

Subcutaneous injection.

#### ***Sterile/Radioactive Statement***

Sterile.

#### ***Qualitative and Quantitative Composition***

6 mg of pegfilgrastim in 0.6 mL (10 mg/mL\*) solution for injection.

\* Based on protein only. The concentration is 20 mg/mL if the PEG moiety is included.

Pegfilgrastim is composed of filgrastim (recombinant methionyl human G-CSF) with a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is produced by recombinant DNA technology in *E coli* (K12).

Excipients: Sodium acetate\*\*, Sorbitol, Polysorbate 20, Water for injections

\*\* Sodium acetate is formed by titrating glacial acetic acid with sodium hydroxide

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## Clinical Particulars

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### ***Therapeutic Indications***

Reduction in the duration of neutropenia, 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).

### ***Dosage and Administration***

#### **Adults ( $\geq 18$ 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.

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

### ***Contraindications***

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

### ***Warnings and Precautions***

#### **General**

Limited clinical data suggest that the effect on time to recovery of severe neutropenia between pegfilgrastim and filgrastim is comparable in patients with *de novo* acute myeloid leukaemia (see Clinical/efficacy studies). However, the long-term effects of Neulastim have not been established in acute myeloid leukaemia (AML); therefore, it should be used with caution in this patient population.

Granulocyte-colony stimulating factor 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 administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established.

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 physician and the appropriate treatment given.

Very rare cases of splenic rupture, in some cases fatal, have been reported following administration of Neulastim. 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.

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. Physicians 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.

The safety and efficacy of Neulastim for the mobilisation of blood progenitor cells in patients has not been adequately evaluated.

### **Ability to drive and use machines**

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

### **Laboratory tests**

White blood cell counts of  $100 \times 10^9/L$  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.

## ***Interactions with other Medicinal Products and other Forms of Interaction***

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 antimetabolites 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 e.g. 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.

## ***Use in Special Populations***

### **Pregnancy**

Pregnancy Category B3.

There are no data from the use of Neulastim in pregnant women. Studies in animals have shown reproductive toxicity (see Teratogenicity). The potential risk to the human embryo or foetus is unknown.

Neulastim should not be used during pregnancy unless clearly necessary.

### **Nursing mothers**

There is no clinical experience with lactating women; therefore Neulastim should not be administered to women who are breast-feeding.

### **Paediatric use**

There are insufficient data to recommend the use of Neulastim in children and adolescents under 18 years of age.

### **Geriatric use**

See Pharmacokinetics in special populations.

### **Renal impairment**

See Pharmacokinetics in special populations.

### **Hepatic impairment**

See Pharmacokinetics in special populations.

## ***Undesirable Effects***

### **Clinical trials**

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.

### ***Gastrointestinal disorders***

Nausea was observed in healthy volunteers more frequently than in patients receiving chemotherapy.

Very common ( $\geq 10\%$ ) and common ( $\geq 1\%$ ,  $< 10\%$ ) undesirable effects in clinical 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
Nervous system disorders	common	Headache

### ***Laboratory abnormalities***

Reversible, mild to moderate elevations in uric acid, with no associated clinical effects, were common, and reversible, mild to moderate elevations in alkaline phosphatase and lactate dehydrogenase, with no associated clinical effects, were very common in patients receiving Neulastim following cytotoxic chemotherapy.

### **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 rarely been reported in patients receiving Neulastim. In some cases, 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***

Very rare cases of splenic rupture have been reported during treatment with Neulastim.

#### ***Skin and subcutaneous tissue disorders***

Rare cases of Sweet's syndrome (acute febrile dermatosis) have been reported.

Reactions of cutaneous vasculitis have been reported in patients with cancer receiving Neulastim (estimated reporting rate: 0.00038%).

### **Overdose**

Single doses of 300 mcg/kg have been administered subcutaneously 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.

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## Pharmacological Properties and Effects

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### **Pharmacodynamic Properties**

#### **Mechanism of action**

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.

Increase of white blood cell count (leukocytosis) is the predicted consequence of pegfilgrastim administration. No adverse events directly attributable to leukocytosis have been reported. The increase in white blood cells is transient, and is consistent with the pharmacodynamic effects of pegfilgrastim.

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. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

#### **Clinical / efficacy studies**

In two randomised, double-blind, pivotal studies in patients with high risk stage II - IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once-per-cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to 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 for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference -7%, 95% CI of -19%, 5%).

In the second study ( $n = 310$ ), which used a weight-adjusted dose (100 mcg/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 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% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference -9%, 95% CI of -16.8%, -1.1%).

In a placebo-controlled study the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen (docetaxel 100 mg/m<sup>2</sup> every 3 weeks for 4 cycles) which has been reported to be associated with a febrile neutropenia rate of 10 – 20%. In this study 928 patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (i.e. on Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was significantly lower for patients randomised to receive pegfilgrastim compared with

placebo (1% versus 17%,  $p \leq 0.001$ , respectively). The incidence of hospitalisation and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in the pegfilgrastim group compared with placebo (1% versus 14%,  $p < 0.001$ ; and 2% versus 10%,  $p < 0.001$  respectively).

A small ( $n = 83$ ), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see Warnings and Precautions).

## 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

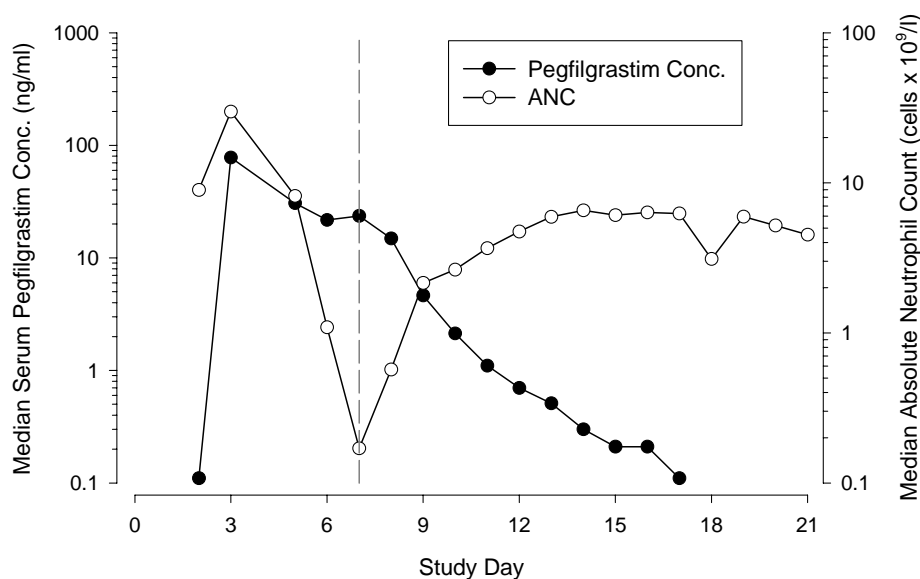
Serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy.

The distribution of pegfilgrastim is 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**



## 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.

### **Paediatric**

The safety and pharmacokinetics of Neulastim were studied in 37 paediatric patients with sarcoma. The systemic exposure ( $AUC_{0-\infty}$ , mean  $\pm$  Standard Deviation) of Neulastim after subcutaneous administration at 100 mcg/kg was 22.0 ( $\pm$  13.1) mcg·hr/mL in the 6-11 years age group ( $n = 10$ ), 29.3 ( $\pm$  23.2) mcg·hr/mL in the 12 - 21 years age group ( $n = 13$ ) and 47.9 ( $\pm$  22.5) mcg·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 ( $\pm$  11.3) hours, 21.2 ( $\pm$  16.0) hours and 30.1 ( $\pm$  38.2) hours, respectively. The most common adverse reaction was bone pain, as in adults (see Undesirable Effects and Use in Special Populations – Paediatric Use).

## Preclinical Safety

### **Carcinogenicity**

Certain malignant cells have been shown to express granulocyte colony-stimulating factor (G-CSF) receptors. The possibility that pegfilgrastim can act as a growth factor for any tumour type cannot be excluded.

The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies.

In a toxicity study of 6 month duration in rats given once weekly subcutaneous injections of up to 1000 mcg/kg of pegfilgrastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

### **Mutagenicity**

Mutagenesis studies have not been conducted.

### **Teratogenicity**

There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal 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.

### **Other**

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

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## Pharmaceutical Particulars

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### **Storage**

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

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

Keep the container in the outer carton, in order to protect from light. This medicine should not be used after the expiry date (EXP) shown on the pack.

### **Special Instructions for Use, Handling and Disposal**

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.

### **Incompatibility**

Neulastim is incompatible with sodium chloride solutions.

### **Packs**

Type I glass pre-filled syringe of 0.6 mL with a stainless steel needle, for single use only.

### **Disposal of Medicines**

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

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## Medicine Classification

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Prescription Medicine



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## **Name and Address**

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NEW ZEALAND

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## **Date of Preparation**

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