1. NEULASTIM (6 mg in 0.6 mL solution for injection)

Neulastim® 6 mg in 0.6 mL solution for injection (pre-filled syringe)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

6 mg of pegfilgrastim in 0.6 mL (10 mg/mL*) solution for injection. The concentration is 20 mg/mL if the PEG moiety is included.

* Based on protein only.

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).

Excipient(s) with known effect

Each pre-filled syringe contains 30 mg sorbitol (E420).

Each pre-filled syringe contains less than 1 mmol (*23* mg) sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Neulastim is a clear, colourless solution for injection in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 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).

4.2 Dose and method of administration

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

Dose

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.

Paediatric population

The safety and efficacy of Neulastim in children aged below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a dosage can be made.

Method of administration

Subcutaneous injection.

For instructions on handling the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to pegfilgrastim, filgrastim, *E. coli*-derived proteins, or to any excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Neulastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

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

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with pegfilgrastim. Permanently discontinue pegfilgrastim in patients with clinically significant hypersensitivity. Do not administer pegfilgrastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim.

Use in leukaemia and myelodysplasia

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 section 5.1). 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.

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients

In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. Monitor patients for signs and symptoms of MDS/AML in these settings.

Acute Respiratory Distress Syndrome

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 Acute Respiratory Distress Syndrome (ARDS). In such circumstances Neulastim should be discontinued at the discretion of the physician and the appropriate treatment given.

Splenic Rupture and Splenomegaly

Splenic rupture, in some cases fatal, has 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.

Capillary leak syndrome

Capillary leak syndrome, characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration, has been reported very rarely. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate medical attention.

Sickle Cell Crisis

Sickle cell crisis has been associated with the use of Neulastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing the use of Neulastim in patients with sickle cell trait or sickle cell disease.

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

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Considering all sources of data on immunogenicity, rates of generation of antibodies against pegfilgrastim are generally low. Binding antibodies do develop as expected with all biologics however were not associated with neutralising antibodies and adverse clinical consequences.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pegfilgrastim with the incidence of antibodies to other products may be misleading.

Aortitis

Aortitis has been reported in patients receiving Neulastim and may present with generalised signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known aetiology.

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving pegfilgrastim. Platelet counts should be monitored closely.

Laboratory tests

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.

Monitoring of Complete Blood Count (CBC) during Neulastim therapy is recommended.

Paediatric population

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

Use in the elderly patients

See section 5.2.

Renal impairment

See section 5.2.

Hepatic impairment

See section 5.2.

4.5 Interaction with other medicines and other forms of interaction

Cytotoxic chemotherapy

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.

Bone Imaging

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.

Lithium

The potential for pharmacodynamic 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.

Other

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B3

There are no data from the use of Neulastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to the human embryo or fetus is unknown.

Neulastim should not be used during pregnancy unless clearly necessary.

Breast-feeding

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

Fertility

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]) and musculoskeletal pain (common). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Tabulated list of adverse reactions

The adverse drug reactions (ADRs) presented in the table below were reported from clinical trials and spontaneously.

Table 1 Adverse Reactions with Neulastim

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Not known*
Blood and lymphatic system disorders		Leucocytosis, Thrombo-cytopenia		Splenomegaly		Sickle cell anaemia with crisis, Myelodys-plastic syndrome, Acute myeloid leukaemia, Splenic rupture
Immune system disorders				Anaphylactic reactions		
Nervous system disorders		Headache				
Vascular disorders						Aortitis
Respiratory, thoracic and mediastinal disorders			Haemoptysis	Pulmonary haemorrhage		

Skin and subcutaneous tissue disorders		Erythema				Acute febrile neutrophilic dermatosis, Cutaneous vasculitis
Musculo-skeletal and connective tissue disorders	Bone pain	Arthralgia, Myalgia, Back, Limb, Musculo-skeletal, and Neck pain				
Renal and urinary disorders						Glomerulo-nephritis
General disorders and administration site disorders		Chest pain (non-cardiac), Pain	Injection site pain			
Investigations			Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased	Blood uric acid increased		

*Not known (cannot be estimated from the available data') per the NZ guidance.

Description of selected adverse reactions

Adverse reactions from 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.

Musculoskeletal and connective tissue disorders

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.

Blood and lymphatic system disorders

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in patients with non-myeloid malignancies receiving pegfilgrastim.

Gastrointestinal disorders

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

Investigations

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.

Adverse reactions from spontaneous reporting

Blood and lymphatic system disorders

Sickle cell crisis, in some cases fatal, have been reported in patients with sickle cell disease.

Cases of splenomegaly have been reported commonly (≥ 1/100 to < 1/10) in patients treated with filgrastim.

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.

Skin and subcutaneous tissue disorders

Uncommon 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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factor; ATC code: L03AA13

Pharmacodynamic effects

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 and safety

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^2 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 section 4.4).

5.2 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

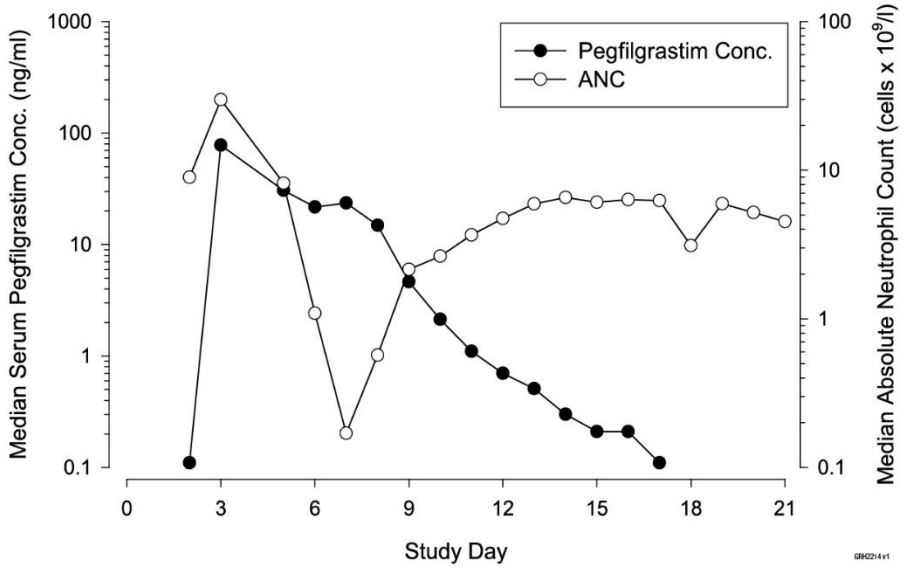
Serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy.

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



Paediatric population

The safety and pharmacokinetics of Neulastim were studied in 37 paediatric patients with sarcoma. The systemic exposure (AUC 0 - inf, mean ± Standard Deviation) of Neulastim after subcutaneous administration at 100 mcg/kg was 22.0 (± 13.1) mcg·hr/mL in the 6 - 11 years age group (n = 10), 29.3 (± 23.2) mcg·hr/mL in the 12 - 21 years age group (n = 13) and 47.9 (± 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 (± 11.3) hours, 21.2 (± 16.0) hours and 30.1 (± 38.2) hours, respectively. The most common adverse reaction was bone pain, as in adults (see sections 4.8 and 4.2).

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.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate**

Sorbitol

Polysorbate 20

Water for injections

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

6.2 Incompatibilities

Neulastim is incompatible with sodium chloride solutions.

6.3 Shelf life

36 months

6.4 Special precautions for 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.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Neulastim is a sterile but unpreserved solution.

Neulastim pre-filled syringe is for single use only.

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.

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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Amgen New Zealand Limited

Level 22, PwC Tower

15 Customs Street West

Auckland 1010 NEW ZEALAND

Medical Information: 0800 443 885

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
7 June 2007

10. DATE OF REVISION OF THE TEXT

18 November 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of MDS/AML in patients with lung cancer
8	Address update