Neulastim®
Pegfilgrastim

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Haematopoietic growth factor
Pharmacotherapeutic group: Cytokines, ATC Code: L03AA13

1.2 Type of Dosage Form

Solution for injection in pre-filled syringe.

1.3 Route of Administration

Subcutaneous injection.

1.4 Sterile/Radioactive Statement

Sterile.

1.5 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.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

2.2 Dosage and Administration

Adults (≥ 18 years): One 6 mg dose (a single pre-filled syringe) of pegfilgrastim 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.

2.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 1.5.

2.4 Warnings and Precautions

2.4.1 General

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (see section 3.1.2). However, the long-term effects of Neulastim have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

G-CSF 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 myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (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. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Pulmonary adverse events

Pulmonary adverse reactions, 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 (see section 2.6).

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 (see section 2.6).

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.

Capillary leak syndrome

Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 2.6).

Splenomegaly and splenic rupture

Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 2.6). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Thrombocytopenia and anaemia

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. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients

In the post-marketing observational study setting, pegfilgrastim in conjunction with chemotherapy and/or radiotherapy has been associated with development of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) in breast and lung cancer patients (see section 4.8). Monitor patients treated in these settings for signs and symptoms of MDS/AML.

Sickle cell anaemia

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease (see section 2.6). Therefore, physicians should use caution when prescribing Neulastim in patients with sickle cell trait or sickle cell disease, and only after careful evaluation of the potential risk and benefits. Physicians should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

Leukocytosis

White blood cell (WBC) 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 leukocytosis 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 this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/l after the expected nadir, this medicine should be discontinued immediately.

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with Neulastim. Permanently discontinue Neulastim in patients with clinically significant hypersensitivity. Do not administer Neulastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, has been reported rarely in association with Neulastim treatment. If the patient has developed SJS with the use of Neulastim, treatment with Neulastim must not be restarted in this patient at any time.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against Neulastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of GCSF.

Other warnings

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

The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Increased haematopoietic 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.

Sorbitol

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

Sodium

Neulastim contains less than 1 mmol sodium (23 mg) per 6 mg dose, that is to say essentially 'sodium-free'.

2.4.2 Ability to Drive and Use Machines

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

2.4.3 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 at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, 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.

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

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 trials have not indicated an interaction of Neulastim with any other medicinal products.

2.5 Use in Special Populations

2.5.1 Pregnancy
There are no or limited data from the use of Neulastim in pregnant women.

Studies in animals have shown reproductive toxicity (see section 3.3.3). The potential risk to the human embryo or foetus is unknown.

Neulastim should not be used during pregnancy unless clearly necessary.

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

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

2.5.4 Geriatric Use
See section 3.2.4 (Pharmacokinetics in Special Populations).

2.5.5 Renal Impairment
See section 3.2.4 (Pharmacokinetics in Special Populations).

2.5.6 Hepatic Impairment
See section 3.2.4 (Pharmacokinetics in Special Populations).

2.6 Undesirable Effects

2.6.1 Clinical Trials

Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]) and musculoskeletal pain (common [>1/100 to < 1/10]). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythaema, flushing, and hypotension occurred on initial or subsequent treatment with Neulastim (uncommon [≥ 1/1,000 to < 1/100]). Serious allergic reactions, including anaphylaxis can occur in patients receiving Neulastim (uncommon) (see section 2.4).

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte-colony stimulating factors; see section 2.4 and section “Description of selected adverse reactions” below.

Splenomegaly, generally asymptomatic, is uncommon.

Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim (see section 2.4).

Uncommon pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or Acute Respiratory Distress Syndrome (ARDS), which may be fatal (see section 2.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients) (see section 2.4).

Tabulated list of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	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)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps			Myelodysplastic syndrome[1] Acute myeloid leukaemia[1]	
Blood and lymphatic system disorders		Thrombocytopenia[1] Leukocytosis[1]	Sickle cell anaemia with crisis[2]; Splenomegaly[2]; Splenic rupture[2]	
Immune system disorders			Hypersensitivity reactions; Anaphylaxis	
Metabolism and nutrition disorders			Elevations in uric acid	
Nervous system disorders	Headache[1]			
Vascular disorders			Capillary leak syndrome[1]	Aortitis
Respiratory, thoracic and mediastinal disorders			Acute Respiratory Distress Syndrome[2]; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis)	Pulmonary haemorrhage

MedDRA system organ class	Adverse reactions			
	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)**
Gastrointestinal disorders	Nausea[1]			
Skin and subcutaneous tissue disorders		Dermatitis contact[1]	Sweet's syndrome (acute febrile neutrophilic dermatosis)[1,2]; Cutaneous vasculitis[1,2]	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculo-skeletal pain, neck pain)		
Renal and urinary disorders			Glomerulonephritis[2]	
General disorders and administrative site conditions		Injection site pain[1] Non-cardiac chest pain	Injection site reactions[2]	
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1] Transient elevations in LFT's for ALT or AST[1]	

[1] See section "Description of selected adverse reactions" below.
[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults. The frequency category was estimated from a statistical calculation based upon 1,576 patients receiving Neulastim in nine randomised clinical trials.

Description of selected adverse reactions

Uncommon cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Uncommon events of cutaneous vasculitis have been reported in patients treated with Neulastim. The mechanism of vasculitis in patients receiving Neulastim is unknown.

Injection site reactions, including injection site erythaema (uncommon) as well as injection site pain (common events) have occurred on initial or subsequent treatment with Neulastim.

Common cases of leukocytosis (White Blood Count [WBC] > 100 × 109/L) have been reported (see section 2.4).

Reversible, mild to moderate elevations in uric acid, with no associated clinical effects, were common, 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.

Nausea and headaches were very commonly observed in patients receiving chemotherapy.

Uncommon elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

An increased risk of MDS/AML following treatment with Neulasta in conjunction with chemotherapy and/or radiotherapy has been observed in an epidemiological study in breast and lung cancer patients (see section 2.4).

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post-marketing setting with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 2.4).

Paediatric population

The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions as per local regulations.

2.7 Overdose

Single doses of 300 μg/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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

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

3.1.1 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. Neulastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Neulastim is a sustained duration form of filgrastim due to decreased renal clearance.

Increase of white blood cell count (leukocytosis) is the predicted consequence of Neulastim 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 Neulastim.

Neulastim 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 Neulastim 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.

3.1.2 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 Neulastim, 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 Neulastim the mean duration of grade 4 neutropenia for the Neulastim 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 μg/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 Neulastim 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 Neulastim 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 Neulastim 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 Neulastim 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 Neulastim (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 2.4.1).

3.2 Pharmacokinetic Properties

3.2.1 Absorption

After a single subcutaneous dose of Neulastim, the peak serum concentration of Neulastim occurs at 16 to 120 hours after dosing.

3.2.2 Distribution

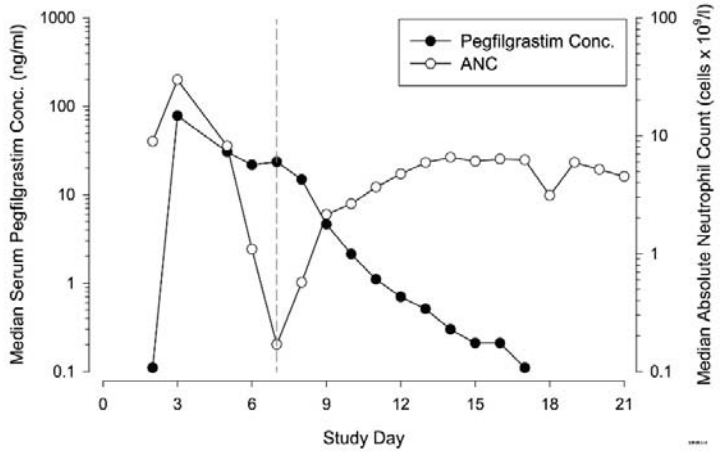
Serum concentrations of Neulastim are maintained during the period of neutropenia after myelosuppressive chemotherapy.

The distribution of Neulastim was limited to the plasma compartment.

3.2.3 Elimination

The elimination of Neulastim is non-linear with respect to dose; serum clearance of Neulastim decreases with increasing dose. Neulastim 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 Neulastim declines rapidly at the onset of neutrophil recovery (see Figure 1).

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



3.2.4 Pharmacokinetics in Special Populations

Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of Neulastim is not expected to be affected by renal or hepatic impairment.

Limited data indicate that the pharmacokinetics of Neulastim in elderly subjects (> 65 years) is similar to that in adults.

3.3 Preclinical Safety

3.3.1 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 carcinogenetic potential of Neulastim 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 1,000 µg/kg of Neulastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

3.3.2 Mutagenicity

Mutagenesis studies have not been conducted.

3.3.3 Teratogenicity

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

loss) at low subcutaneous doses. In rat studies, it was shown that Neulastim may cross the placenta. The relevance of these findings for humans is not known.

3.3.4 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.

4. PHARMACEUTICAL PARTICULARS

4.1 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.

4.2 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 Neulastim, 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.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

4.3 Packs

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

Medicine: keep out of reach of children

Current at Jan 2021

Manufactured by:
Amgen Manufacturing Limited
State Road 31, Km 24.6, Juncos,
Puerto Rico, 00777-4060, United States

SGNLAPI02

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