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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 10/11/2011

SPC NEULASTA

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Legal Categories
POM – Prescription Only Medicine

Active Ingredients/Generics
pegfilgrastim

1. Name of the medicinal product

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Neulasta® 6 mg solution for injection.

2. Qualitative and quantitative composition

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Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only**.

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).

** The concentration is 20 mg/ml if the PEG moiety is included.

The potency of this product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1

Excipients:

Excipients known to have a recognised action: sorbitol E420, sodium acetate (see section 4.4).

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

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Solution for injection.

Clear, colourless solution for injection.

4. Clinical particulars

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4.1 Therapeutic indications

Go to top of the page

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).

4.2 Posology and method of administration

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

One 6 mg dose (a single pre-filled syringe) of Neulasta is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

Paediatric patients

The experience in children is limited (see section 4.8, 5.1 and 5.2).

Renal impairment

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

4.3 Contraindications

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Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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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 5.1). However, the long-term effects of Neulasta have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

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

The safety and efficacy of Neulasta have not been investigated in patients receiving high dose chemotherapy. Neulasta should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Uncommon (≥1/1000 to < 1/100) 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 (see section 4.8).

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 Neulasta should be discontinued at the discretion of the physician and the appropriate treatment given (see section 4.8).

Uncommon (≥ 1/1000 to < 1/100) but generally asymptomatic cases of splenomegaly and uncommon (≥ 1/1000 to < 1/100) cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.8). 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.

Treatment with Neulasta 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.

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease (see section 4.8). Therefore, physicians should exercise caution when administering Neulasta in patients with sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of Neulasta with splenic enlargement and vaso-occlusive crisis.

White blood cell (WBC) counts of 100 x 10^9/l or greater have been observed in less than 1% of patients receiving Neulasta. 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 Neulasta. Consistent with the clinical effects of Neulasta 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, Neulasta should be discontinued immediately.

If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Neulasta should be permanently discontinued in patients who experience a serious allergic reaction (see section 4.8).

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

The needle cover 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.

Neulasta contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Neulasta contains less than 1 mmol (23 mg) sodium per 6 mg dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neulasta should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical studies, Neulasta has been safely administered 14 days before chemotherapy. Concomitant use of Neulasta with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Neulasta 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 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 Neulasta 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 Neulasta with any other medicinal products.

4.6 Pregnancy and lactation

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There are no adequate data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Neulasta should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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a. Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]) and musculoskeletal pain (very common [≥ 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 Neulasta (uncommon [≥ 1/1000 to < 1/100]). Serious allergic reactions, including anaphylaxis can occur in patients receiving Neulasta (uncommon [≥ 1/1000 to < 1/100]) (see section 4.4).

Splenomegaly, generally asymptomatic, is uncommon (≥ 1/1000 to < 1/100) (see section 4.4).

Splenic rupture including some fatal cases is uncommonly (≥ 1/1000 to < 1/100) reported following administration of pegfilgrastim (see section 4.4).

Uncommon (≥ 1/1000 to < 1/100) pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly (≥ 1/1000 to < 1/100), cases have resulted in respiratory failure or Adult Respiratory Distress Syndrome (ARDS), which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell disease (uncommon [≥ 1/1000 to < 1/100] in sickle cell patients) (see section 4.4).

b. Tabulated summary 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 **(≥ 1/1000 to <** 1/100)	Rare **(≥** 1/10,000 to < 1/1000)	Very rare (< 1/10,000)
Blood and lymphatic system disorders		Thrombocytopenia[1]	Sickle cell crisis[2]; Leukocytosis[1]		
Immune system disorders			Hypersensitivity reactions; Anaphylaxis		
Metabolism and nutrition disorders			Elevations in uric acid		
Nervous system disorders	Headache[1]				
Respiratory, thoracic and mediastinal disorders			Adult Respiratory Distress Syndrome[2]; Pulmonary adverse effects (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis)		

Gastrointestinal disorders	Nausea[1]		Splenomegaly[2]; Splenic rupture[2];		
Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile dermatosis)[1,2]; Cutaneous vasculitis[1, 2]		
Musculoskeletal and connective tissue disorders	Bone pain Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain)				
General disorders and administrative site conditions		Injection site reaction (including injection site pain)[1]	Non-cardiac chest pain		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1]; Transient elevations in LFT's for ALT or AST[1]		

[1] See Section C.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults that supported the marketing authorisation. The frequency category was estimated from a statistical calculation based upon 932 patients receiving Neulasta in seven randomized clinical trials.

c. Description of selected adverse reactions

Uncommon (≥ 1/1000 to < 1/100) cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Uncommon (≥ 1/1000 to < 1/100) events of cutaneous vasculitis have been reported in patients treated with Neulasta. The mechanism of vasculitis in patients receiving Neulasta is unknown.

Injection site reactions, including injection site pain and injection site erythaema (common (≥ 1/100 to < 1/10)) have occurred on initial or subsequent treatment with Neulasta.

Uncommon (≥ 1/1000 to < 1/100) cases of leukocytosis (White Blood Count [WBC] > 100 x 10^9/l) have been reported (see section 4.4).

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were uncommon (≥ 1/1000 to < 1/100); reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon (≥ 1/1000 to < 1/100) in patients receiving Neulasta following cytotoxic chemotherapy.

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

Uncommon (≥ 1/1000 to < 1/100) 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.

Common (≥ 1/100 to < 1/10) cases of thrombocytopenia have been reported.

d. Paediatric population

The experience in children is limited. A higher frequency of serious adverse events 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 (see section 5.1 and 5.2).

4.9 Overdose

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There is no experience with overdose of Neulasta in humans.

5. Pharmacological properties

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5.1 Pharmacodynamic properties

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Pharmacotherapeutic group: Cytokines, ATC Code: L03AA13

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 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. 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. 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*.

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 to7 days, and a 30-40% incidence of febrile neutropenia. In one study (n = 157), which used a 6mg 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 a second study (n = 310), which used a weight-adjusted dose (100 micrograms/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, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m^2 every 3 weeks for 4 cycles). Nine hundred and twenty eight 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 lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p < 0.001$). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p < 0.001$; and 2% versus 10%, $p < 0.001$).

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).

In a phase II (n = 37) multicentre, randomised, open-label study of paediatric sarcoma patients receiving 100 µg/kg pegfilgrastim following cycle 1 of vincristine, doxorubicin and cyclophosphamide (VAdriaC/IE) chemotherapy, a longer duration of severe neutropenia (neutrophils < 0.5 x 10^9) was observed in younger children aged 0-5 yrs (8.9 days) compared to older children aged 6-11 years and 12-21 years (6 days and 3.7 days, respectively) and adults. Additionally a higher incidence of febrile neutropenia was observed in younger children aged 0-5 yrs (75%) compared to older children aged 6-11 years and 12-21 years (70% and 33%, respectively) and adults (see sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

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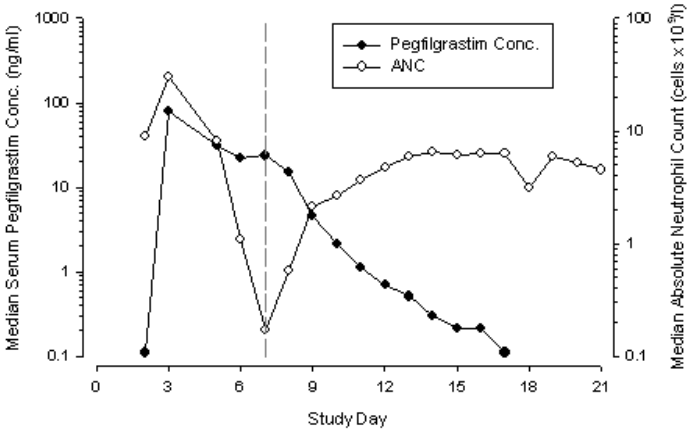
After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which 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



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 stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

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

Paediatric patients

The pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 µg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (± Standard Deviation) (47.9 ± 22.5 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·hr/ml, respectively) (see section 5.1). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel (see sections 4.8 and 5.1).

5.3 Preclinical safety data

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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.

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.

6. Pharmaceutical particulars

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6.1 List of excipients

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Sodium acetate*

Sorbitol (E420)

Polysorbate 20

Water for injections

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

6.2 Incompatibilities

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This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

6.3 Shelf life

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3 years.

6.4 Special precautions for storage

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Store in a refrigerator (2°C – 8°C).

Neulasta may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Neulasta 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 Neulasta.

Keep the container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

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0.6 ml of solution for injection in a pre-filled syringe (Type I glass), with a rubber stopper, and with a stainless steel needle. Pack size of one, in either blistered, with or without an automatic needle guard or non-blistered packaging. Single use only.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) (see section 4.4).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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Before administration, Neulasta solution should be inspected visually for particulate matter. 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.

7. Marketing authorisation holder

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Amgen Europe B.V.

Minervum 7061

4817 ZK Breda

The Netherlands

8. Marketing authorisation number(s)

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EU/1/02/227/001 1 pack blistered syringe

EU/1/02/227/002 1 pack unblistered syringe

EU/1/02/227/004 1 pack blistered syringe with needle guard

9. Date of first authorisation/renewal of the authorisation

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Date of first authorisation: 22 August 2002

Date of last renewal: 16 July 2007

10. Date of revision of the text

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24 October 2011

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

More information about this product

- Patient Information Leaflets (PILs):
  NEULASTA with needle guard
- Alternative format Patient Information Leaflets (X-PILs):
  NEULASTA with needle guard
- Medicine Guides:
  Neulasta

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