

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 with known effect

Each pre-filled syringe contains 30 mg sorbitol (E420) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Solution for injection (injection) with on-body injector (Onpro kit).

Clear, colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

One 6 mg dose (a single pre-filled syringe) of Neulasta is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Special populations

Paediatric population

The safety and efficacy of Neulasta in children has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Patients with renal impairment

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

Method of administration

Neulasta is injected subcutaneously via:

- a pre-filled syringe for manual administration; or
- a pre-filled syringe with on-body injector for automatic administration.

Neulasta 6 mg solution for injection in pre-filled syringe

The manually administered injections should be given into the thigh, abdomen or upper arm.

Neulasta 6 mg solution for injection in pre-filled syringe with on-body injector

The on-body injector must be filled using the co-packed pre-filled syringe. The on-body injector should be applied to intact, non-irritated skin on the back of the arm or abdomen. The back of the arm may only be used if there is a caregiver available to monitor the status of the on-body injector. Approximately 27 hours after the on-body injector is applied to the patient's skin, Neulasta will be delivered over approximately 45 minutes. Once filled, the on-body injector should be used for immediate application and can be applied on the same day as the administration of cytotoxic chemotherapy, as long as application is timed to ensure the on-body injector delivers Neulasta at least 24 hours after administration of cytotoxic chemotherapy.

The on-body injector must only be used with the co-packed pre-filled syringe. The co-packed pre-filled syringe contains additional solution to compensate for residual liquid retained in the on-body injector after delivery. If the pre-filled syringe co-packed with the on-body injector is used for manually administering a subcutaneous injection, the patient will receive more than the recommended dose. If the pre-filled syringe for manual administration is used with the on-body injector, the patient may receive less than the recommended dose.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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 (AML) (see section 5.1). However, the long-term effects of pegfilgrastim have not been established in AML; 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 pegfilgrastim 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 AML.

The safety and efficacy of pegfilgrastim administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established.

The safety and efficacy of pegfilgrastim 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 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 Acute Respiratory Distress Syndrome (ARDS). In such circumstances pegfilgrastim should be discontinued at the discretion of the physician and the appropriate treatment given (see section 4.8).

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 granulocyte-colony stimulating factor 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 4.8).

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 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.

Thrombocytopenia and anaemia

Treatment with pegfilgrastim 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.

Medication error as a result of device failure

There is a risk of medication error, particularly a partial or missed dose of pegfilgrastim, in the event of a device failure or malfunction with the on-body injector. In the event of a partial or missed dose, patients may be at increased risk of events such as neutropenia, febrile neutropenia and/or infection than if the dose had been correctly delivered. The healthcare professional must ensure the patient receives appropriate training about the on-body injector and understands that if they suspect a device

failure or malfunction the patient must immediately inform a healthcare professional as they may need a replacement dose. Comprehensive instructions for use for healthcare professionals and patients are given in the package leaflet. The patient should also be given the Patient Alert Card.

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 4.8). Therefore, physicians should use caution when prescribing pegfilgrastim in patients with sickle cell trait or sickle cell disease, 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 $100 \times 10^9/L$ or greater have been observed in less than 1% of patients receiving pegfilgrastim. 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 $50 \times 10^9/L$ 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 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. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim 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 G-CSF. See also section 4.8.

Other warnings

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

The on-body injector uses an acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in an allergic reaction.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, pegfilgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, 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 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 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 trials have not indicated an interaction of Neulasta with any other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women who become pregnant during Neulasta treatment are encouraged to enrol in Amgen's Pregnancy Surveillance Programme. Contact details are provided in section 6 of the Package leaflet.

Breast-feeding

There is insufficient information on the excretion of pegfilgrastim/metabolites in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from pegfilgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Women who are breast-feeding during Neulasta treatment are encouraged to enrol in Amgen's Lactation Surveillance programme. Contact details are provided in section 6 of the Package leaflet.

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) (see section 5.3).

4.7 Effects on ability to drive and use machines

Pegfilgrastim has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common $\geq 1/10$) and musculoskeletal pain (common $\geq 1/100$ 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 pegfilgrastim (uncommon $\geq 1/1,000$ to $< 1/100$). Serious allergic reactions, including anaphylaxis can occur in patients receiving pegfilgrastim (uncommon) (see section 4.4).

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon ($\geq 1/1,000$ to $< 1/100$) in cancer patients undergoing chemotherapy following administration of granulocyte-colony stimulating factors; see section 4.4 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 4.4).

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 ARDS, which may be fatal (see section 4.4).

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 4.4).

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 ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Very rare ($< 1/10,000$)
Blood and lymphatic system disorders		Thrombocytopenia ¹ Leukocytosis ¹	Sickle cell 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				

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)	Very rare (< 1/10,000)
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) Haemoptysis	Pulmonary haemorrhage	
Gastrointestinal disorders	Nausea ¹				
Skin and subcutaneous tissue disorders		Dermatitis contact ¹	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)			
Renal and urinary disorders			Glomerulonephritis ²		
General disorders and administrative site conditions		Injection site pain ¹ Application site reactions ¹ Non-cardiac chest pain	Injection site reactions ²		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase ¹ ; Transient elevations in LFTs 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 Neulasta 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 pegfilgrastim. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

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

Application site reactions (including events such as haemorrhage, pain, discomfort, bruise, and erythema) have been reported with the use of the on-body injector.

Contact dermatitis and local skin reactions such as rash, pruritus, and urticaria have been reported with the use of the on-body injector, possibly indicating a hypersensitivity reaction to the adhesive.

Common cases of leukocytosis (White Blood Count [WBC] > 100 x 10⁹/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; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving Neulasta following cytotoxic chemotherapy.

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

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

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 4.4).

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 (see section 5.1 and 5.2).

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 via the national reporting system listed in [Appendix V](#).

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 reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factor; 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 to 7 days, and a 30-40% incidence of febrile neutropenia. In one 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 a 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, 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/m² 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 mcg/kg pegfilgrastim following cycle 1 of vincristine, doxorubicin and cyclophosphamide (VAdriaC/IE) chemotherapy, a longer duration of severe neutropenia (neutrophils < 0.5 x 10⁹) was observed in younger children aged 0-5 years (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 years (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).

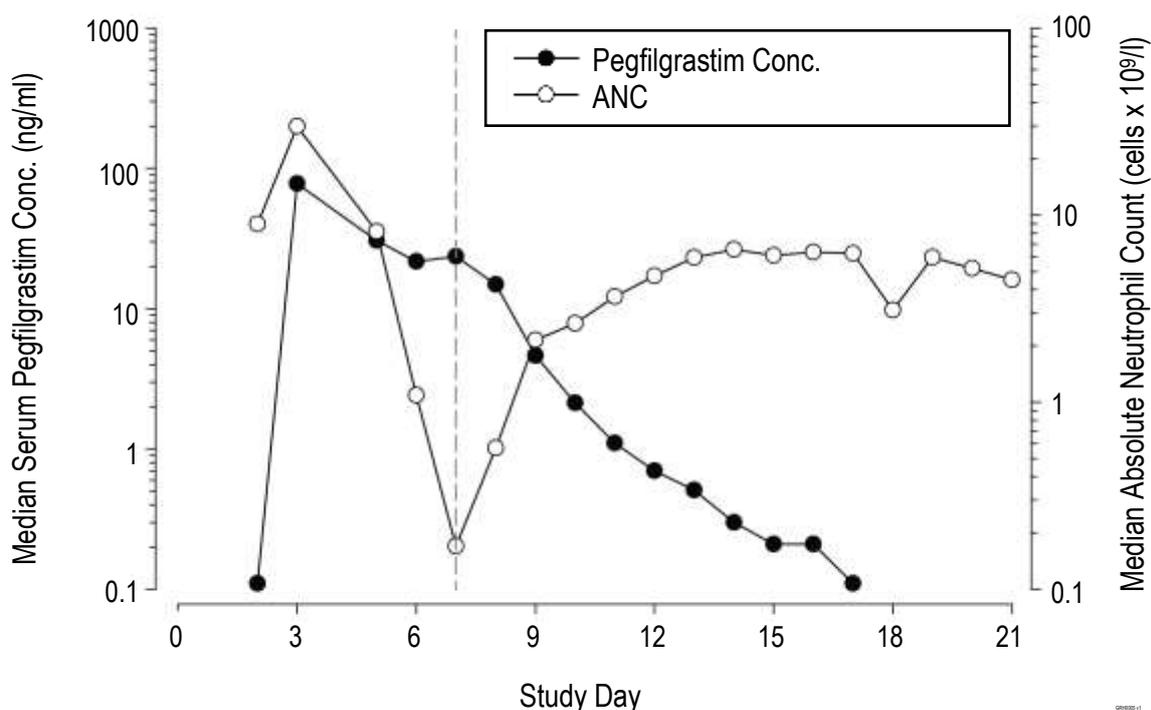
In a phase I (n = 253) randomised, single dose, parallel-group study conducted in healthy subjects the exposure (mean serum concentration-time profiles) of pegfilgrastim delivered by manual injection and by the on-body injector were comparable. The rate (C_{max}) and extent (AUC_{0-inf}) of the absorption of pegfilgrastim delivered by the on-body injector were similar to those from the manual injection of the pre-filled syringe. The least-squares geometric mean ratios (90% CIs) (on-body injector to manual

injection) were 0.97 (0.83, 1.14) for C_{max} and 1.00 (0.84, 1.20) for AUC_{0-inf} within the pre-specified bioequivalence limit of 0.80 to 1.25, and established bioequivalence between the two delivery methods of a single 6 mg dose of pegfilgrastim.

5.2 Pharmacokinetic properties

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.

Elderly

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

Paediatric population

The pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 mcg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (\pm Standard Deviation) (47.9 ± 22.5 mcg·hr/mL) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 mcg·hr/mL).

and 29.3 ± 23.2 mcg·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 mcg/kg pegfilgrastim after the completion of doxorubicin/docetaxel (see sections 4.8 and 5.1).

5.3 Preclinical safety data

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 cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate*
Sorbitol (E420)
Polysorbate 20
Water for injections

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

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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.

The pre-filled syringe for use with the on-body injector may be exposed at room temperature for no longer than 36 hours prior to filling the on-body injector.

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

Pre-filled syringe (Type I glass), with a rubber stopper, stainless steel needle and needle cap with or without an automatic needle guard.

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

On-body injector, the fluid path is made from polypropylene, cyclic olefin copolymer, silicone rubber and fluorinated ethylene propylene (FEP), with a stainless steel 28 gauge needle. The on-body injector contains three silver oxide batteries and includes an adhesive patch made from non-woven polyester tape single coated with a polyacrylate adhesive.

Each pre-filled syringe for manual administration contains 0.6 mL of solution for injection.
Each pre-filled syringe for use with the on-body injector contains 0.64 mL of solution for injection.
Pack size of one pre-filled syringe, in either blistered or non-blistered packaging.
Pack size of one pre-filled syringe in blistered packaging co-packed with an on-body injector.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before use, Neulasta solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected.

The on-body injector must only be used with the Neulasta pre-filled syringe co-packed in the carton. The Neulasta pre-filled syringe for manual administration must not be used with the on-body injector.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

When administering using the manual pre-filled syringe, 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

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

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
EU/1/02/227/005 - 1 pack blistered syringe with blistered on-body injector

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2002
Date of latest renewal: 16 July 2007

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Amgen Inc.
One Amgen Center Drive
Thousand Oaks
CA 91320
USA

Amgen Manufacturing Limited
P.O Box 4060
Road 31 km. 24.6
Juncos
Puerto Rico 00777-4060
USA

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

The MAH shall ensure that in each Member State where Neulasta on-body injector is marketed, all patients/carers who are expected to use Neulasta on-body injector are provided with a patient alert card to be disseminated through the prescribing physicians.

The aim of this patient alert card is to help prevent medication errors including underdose resulting in lack of efficacy with the on-body injector device.

The patient alert card shall contain the following key messages:

- how to monitor the on-body injector
- when to expect dose delivery to begin
- not to remove the on-body injector until after dose delivery is complete
- how to recognise signs from the device (e.g. adhesion issues, fill indicator not moved, no beeping sound, status light has not flashed etc.) that there has been a failure in the delivery of the intended dose
- what action to take in a suspected case of failed delivery or incomplete delivery of the dose and if symptoms of serious infection that may indicate a missed dose present.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg solution for injection
pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 mL (10 mg/mL) solution for injection.
Each pre-filled syringe contains 0.64 mL of solution that delivers 6 mg of pegfilgrastim (10 mg/mL) to be used with the on-body injector.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a single use pre-filled syringe (0.6 mL).
Solution for injection in a single use pre-filled syringe with automatic needle guard (0.6 mL).
Solution for injection in a pack size of one single use pre-filled syringe (0.64 mL) and one on-body injector (Onpro kit).
Pack size of one.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.
Important: read the package leaflet before handling pre-filled syringe.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid vigorous shaking.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the container in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/227/001 - 1 pack
EU/1/02/227/004 - 1 pack with needle guard
EU/1/02/227/005 - 1 pack with on-body injector

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neulasta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK FOR SYRINGE WITH AUTOMATIC NEEDLE GUARD

1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg injection
pegfilgrastim

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER



MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK FOR SYRINGE TO BE USED WITH ON-BODY INJECTOR

1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg injection
pegfilgrastim

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For use with the on-body injector only.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neulasta 6 mg
Pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Amgen Europe B.V.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SYRINGE LABEL FOR USE WITH ON-BODY INJECTOR**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neulasta 6 mg injection
pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.64 ml

6. OTHER

Amgen Europe B.V.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR UNBLISTERED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg solution for injection
pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 mL (10 mg/mL) solution for injection.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a single use pre-filled syringe (0.6 mL).
Pack size of one.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid vigorous shaking.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the container in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/227/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neulasta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
UNBLISTERED SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neulasta 6 mg injection
pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Amgen Europe B.V.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Neulasta 6 mg solution for injection pegfilgrastim

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Whilst wearing the Neulasta on body injector it is important that you keep the Alert Card provided by your doctor, pharmacist or nurse with you. It contains important advice on how to monitor your device for medication errors including under dose leading to lack of effect, and when to seek immediate medical attention.

What is in this leaflet

1. What Neulasta is and what it is used for
2. What you need to know before you use Neulasta
3. How to use Neulasta
4. Possible side effects
5. How to store Neulasta
6. Contents of the pack and other information

1. What Neulasta is and what it is used for

Neulasta contains the active substance pegfilgrastim. Pegfilgrastim is a protein produced by biotechnology in bacteria called *E. coli*. It belongs to a group of proteins called cytokines, and is very similar to a natural protein (granulocyte-colony stimulating factor) produced by your own body.

Neulasta is used to reduce the duration of neutropenia (low white blood cell count) and the occurrence of febrile neutropenia (low white blood cell count with a fever) which can be caused by the use of cytotoxic chemotherapy (medicines that destroy rapidly growing cells). White blood cells are important as they help your body fight infection. These cells are very sensitive to the effects of chemotherapy which can cause the number of these cells in your body to decrease. If white blood cells fall to a low level there may not be enough left in the body to fight bacteria and you may have an increased risk of infection.

Your doctor has given you Neulasta to encourage your bone marrow (part of the bone which makes blood cells) to produce more white blood cells that help your body fight infection.

2. What you need to know before you use Neulasta

Do not use Neulasta

- if you are allergic to pegfilgrastim, filgrastim, or any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Neulasta:

- if you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), redness and flushing, skin rash and areas of the skin that itch.
- if you have an allergy to latex. The needle cap on the pre-filled syringe contains a derivative of latex and may cause severe allergic reactions.
- if you have an allergy to acrylic adhesives. The on-body injector uses acrylic adhesive and may result in an allergic reaction.
- if you experience a cough, fever and difficulty breathing. This can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- if you have any of the following or combination of the following side effects:
 - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness.

These could be symptoms of a condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body. See section 4.

- if you get left upper abdominal pain or pain at the tip of your shoulder. This may be a sign of a problem with your spleen (splenomegaly).
- if you have recently had a serious lung infection (pneumonia), fluid in the lungs (pulmonary oedema), inflammation of the lungs (interstitial lung disease) or an abnormal chest x-ray (lung infiltration).
- if you are aware of any altered blood cell counts (e.g. increase in white blood cells or anaemia) or decreased blood platelet counts, which reduces the ability of your blood to clot (thrombocytopenia). Your doctor may want to monitor you more closely.
- if you have sickle cell anaemia. Your doctor may monitor your condition more closely.
- if you have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing these could be signs of a severe allergic reaction.
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience those symptoms.

Your doctor will check your blood and urine regularly as Neulasta can harm the tiny filters inside your kidneys (glomerulonephritis).

You should talk to your doctor about your risks of developing cancers of the blood. If you develop or are likely to develop cancers of the blood, you should not use Neulasta, unless instructed by your doctor.

Loss of response to pegfilgrastim

If you experience a loss of response or failure to maintain a response with pegfilgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise pegfilgrastim’s activity.

Other medicines and Neulasta

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. Neulasta has not been tested in pregnant women. It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or
- are planning to have a baby.

If you become pregnant during Neulasta treatment, please inform your doctor. You may be encouraged to enrol in Amgen's Pregnancy Surveillance programme. Local representative contact details are provided in section 6 of this leaflet.

Unless your doctor directs you otherwise, you must stop breast-feeding if you use Neulasta.

If you are nursing during Neulasta treatment, you may be encouraged to enrol in Amgen's Lactation Surveillance programme. Local representative contact details are provided in section 6 of this leaflet.

Driving and using machines

Neulasta has no or negligible effect on the ability to drive or use machines.

Neulasta contains sorbitol (E420) and sodium acetate

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

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

3. How to use Neulasta

Neulasta is for use in adults aged 18 and over.

Always take Neulasta exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual dose is one 6 mg subcutaneous injection (injection under your skin) and it should be given at least 24 hours after your last dose of chemotherapy at the end of each chemotherapy cycle.

Injecting Neulasta yourself

Your doctor may decide that it would be more convenient for you to inject Neulasta yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For further instructions on how to inject yourself with Neulasta, please read the section at the end of this leaflet.

Do not shake Neulasta vigorously as this may affect its activity.

Using Neulasta with the on-body injector

Your doctor may decide that it would be more convenient for you to use Neulasta with the on-body injector. For further information on use with the on-body injector, please read the instructions for use at the end of this leaflet.

Check the instructions at the end of this leaflet and contact your healthcare provider if:

- during the monitoring of your on-body injector you are concerned that it is leaking; or
- after the injection is complete you are concerned that you may not have received the full dose.

If you use more Neulasta than you should

If you use more Neulasta than you should contact your doctor, pharmacist or nurse.

If you forget to inject Neulasta

If you are injecting yourself and have forgotten your dose of Neulasta, you should contact your doctor to discuss when you should inject the next dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately if you have any of the following or combination of the following side effects:

- swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

These could be symptoms of an uncommon (may affect up to 1 in 100 people) condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

Very common side effects (may affect more than 1 in 10 people):

- bone pain. Your doctor will tell you what you can take to ease the bone pain.
- nausea and headaches.

Common side effects (may affect up to 1 in 10 people):

- rash, itchy red raised bumps (contact dermatitis/local skin reactions) have been seen with the on-body injector.
- pain at the site of injection.
- application site reactions which may include redness, bleeding, bruising, pain and discomfort have been seen with the on-body injector.
- general aches and pains in the joints and muscles.
- some changes may occur in your blood, but these will be detected by routine blood tests. Your white blood cell count may become high for a short period of time. Your platelet count may become low which might result in bruising.

Uncommon side effects (may affect up to 1 in 100 people):

- allergic-type reactions, including redness and flushing, skin rash, and raised areas of the skin that itch.
- serious allergic reactions, including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face).
- increased spleen size.
- spleen rupture. Some cases of splenic rupture were fatal. It is important that you contact your doctor immediately if you experience pain in the upper left side of the abdomen or left shoulder pain since this may relate to a problem with your spleen.
- breathing problems. If you have a cough, fever and difficulty breathing please tell your doctor.

- Sweet's syndrome (plum-coloured, raised, painful lesions on the limbs and sometimes the face and neck with fever) has occurred but other factors may play a role.
- cutaneous vasculitis (inflammation of the blood vessels in the skin).
- damage to the tiny filters inside your kidneys (glomerulonephritis).
- redness at the site of injection.
- coughing up blood (haemoptysis).

Rare side effects (may affect up to 1 in 1000 people):

- inflammation of aorta (the large blood vessel which transports blood from the heart to the body), see section 2.
- bleeding from the lung (pulmonary haemorrhage).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neulasta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

You may take Neulasta out of the refrigerator and keep it at room temperature (not above 30°C) for no longer than 3 days. Once a syringe has been removed from the refrigerator and has reached room temperature (not above 30°C) it must either be used within 3 days or disposed of.

The syringe for use with the on-body injector must either be used within 36 hours after it has reached room temperature (not above 30°C) or disposed of.

Do not freeze. Neulasta may be used if it is accidentally frozen for a single period of less than 24 hours.

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

Do not use this medicine if you notice it is cloudy or there are particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Neulasta contains

- The active substance is pegfilgrastim. Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 mL of solution.
- The other ingredients are sodium acetate, sorbitol (E420), polysorbate 20 and water for injections. See section 2.

What Neulasta looks like and contents of the pack

Neulasta is a clear, colourless solution for injection in a pre-filled syringe (6 mg/0.6 mL).

Each pack contains 1 glass pre-filled syringe with an attached stainless steel needle and needle cap.

The pre-filled syringe (with or without blister wrapping) may also be provided with either an automatic needle guard or with an on-body injector.

Marketing Authorisation Holder and Manufacturer

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder

Amgen Europe B.V.
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4817 ZK Breda
The Netherlands

Manufacturer

Amgen Technology (Ireland) Unlimited Company
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Dun Laoghaire
Co Dublin
Ireland

Manufacturer

Amgen NV
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1831 Diegem
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

Instructions for injecting with the Neulasta pre-filled syringe

This section contains information on how to give yourself an injection of Neulasta. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse, or pharmacist. If you have questions about how to inject, please ask your doctor, nurse, pharmacist for assistance.

How do you, or the person injecting you, use Neulasta pre-filled syringe?

You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection.

Equipment that you need

To give yourself a subcutaneous injection you will need:

- a pre-filled syringe of Neulasta; and
- alcohol wipes or similar.

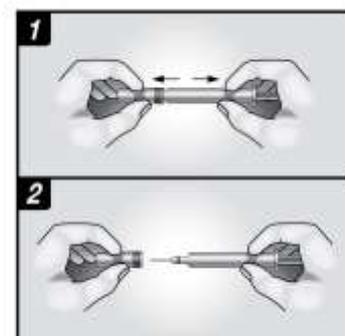
What should I do before I give myself a subcutaneous injection of Neulasta?

1. Remove from the refrigerator.
2. Do not shake the pre-filled syringe.
3. **Do not** remove the cap from the syringe until you are ready to inject.
4. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
5. Check the appearance of Neulasta. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
6. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. **Do not** warm Neulasta in any other way (for example, do not warm it in a microwave or in hot water).
7. **Wash your hands thoroughly.**
8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

How do I prepare my Neulasta injection?

Before you inject Neulasta you must do the following:

1. Hold the syringe barrel and gently take the cap from the needle without twisting. Pull straight as shown in pictures 1 and 2. Do not touch the needle or push the plunger.



2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. You can now use the pre-filled syringe.

Where should I give my injection?



The most suitable places to inject yourself are:

- the top of your thighs; and
- the abdomen, except for the area around the navel.

If someone else is injecting you, they can also use the back of your arms.

How do I give my injection?

1. Clean your skin by using an alcohol wipe.
2. Pinch (without squeezing) the skin using your thumb and forefinger. Insert the needle into the skin.
3. Push the plunger down with a slow constant pressure. Push the plunger all the way down as far as it will go to inject all the liquid.
4. After injecting the liquid, remove the needle and let go of your skin.
5. If you notice a spot of blood at the injection site dab with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
6. Do not use any Neulasta that is left in the syringe.

Remember

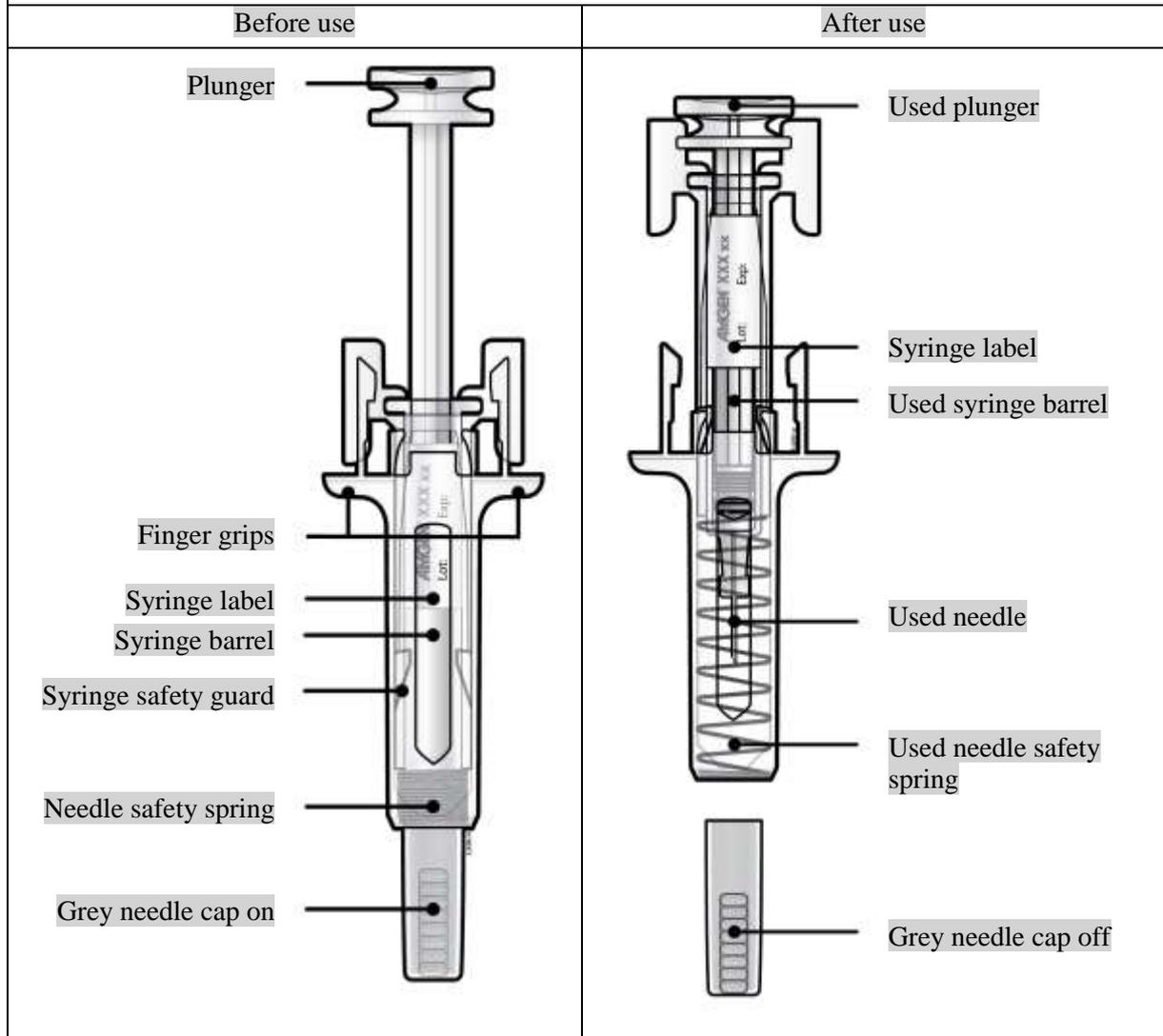
Only use each syringe for one injection. If you have any problems, please ask your doctor or nurse for help and advice.

Disposing of used syringes

- Do not put the cap back on used needles.
 - Keep used syringes out of the sight and reach of children.
 - The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
-

Instructions for use:

Guide to parts



Important

Before you use a Neulasta pre-filled syringe with automatic needle guard, read this important information:

- It is important that you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider.
- Neulasta is given as an injection into the tissue just under the skin (subcutaneous injection).
- Tell your doctor if you have an allergy to latex. The needle cap on the pre-filled syringe contains a derivative of latex and may cause severe allergic reactions.
- ✗ **Do not** remove the grey needle cap from the pre-filled syringe until you are ready to inject.
- ✗ **Do not** use the pre-filled syringe if it has been dropped on a hard surface. Use a new pre-filled syringe and call your doctor or healthcare provider.
- ✗ **Do not** attempt to activate the pre-filled syringe prior to injection.
- ✗ **Do not** attempt to remove the clear pre-filled syringe safety guard from the pre-filled syringe.
- ✗ **Do not** attempt to remove the peelable label on the pre-filled syringe barrel before administering your injection.

Call your doctor or healthcare provider if you have any questions.

Step 1: Prepare

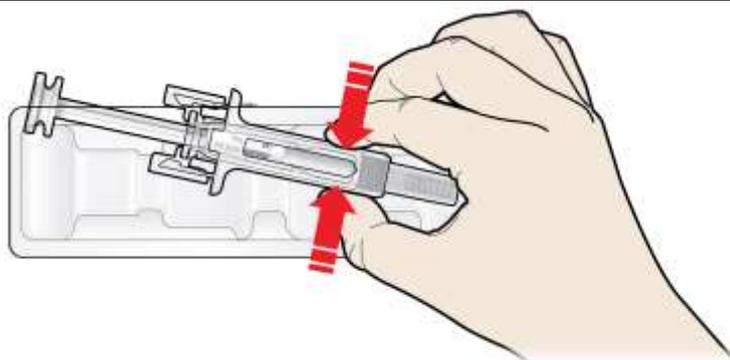
- A Remove the pre-filled syringe tray from the package and gather the supplies needed for your injection: alcohol wipes, a cotton ball or gauze pad, a plaster and a sharps disposal container (not included).

For a more comfortable injection, leave the pre-filled syringe at room temperature for about 30 minutes before injecting. Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the new pre-filled syringe and the other supplies.

- ✗ **Do not** try to warm the syringe by using a heat source such as hot water or microwave.
- ✗ **Do not** leave the pre-filled syringe exposed to direct sunlight.
- ✗ **Do not** shake the pre-filled syringe.
- **Keep pre-filled syringes out of the sight and reach of children.**

- B Open the tray, peeling away the cover. Grab the pre-filled syringe safety guard to remove the pre-filled syringe from the tray.

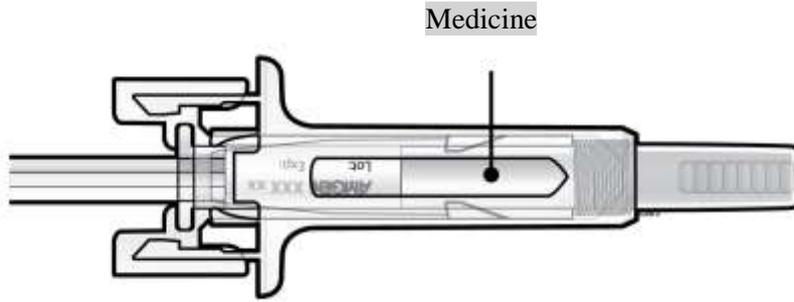


Grab here

For safety reasons:

- ✗ **Do not** grasp the plunger.
- ✗ **Do not** grasp the grey needle cap.

C Inspect the medicine and pre-filled syringe.

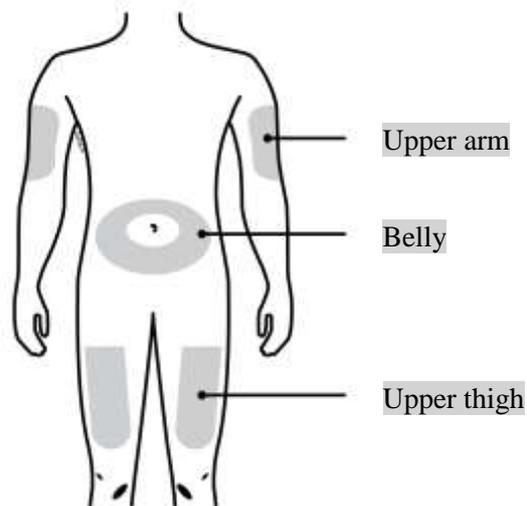


- X Do not** use the pre-filled syringe if:
- The medicine is cloudy or there are particles in it. It must be a clear and colourless liquid.
 - Any part appears cracked or broken.
 - The grey needle cap is missing or not securely attached.
 - The expiry date printed on the label has passed the last day of the month shown.

In all cases, call your doctor or healthcare provider.

Step 2: Get ready

A Wash your hands thoroughly. Prepare and clean your injection site.



You can use:

- Upper part of your thigh.
- Belly, except for a 5 cm (2-inch) area right around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

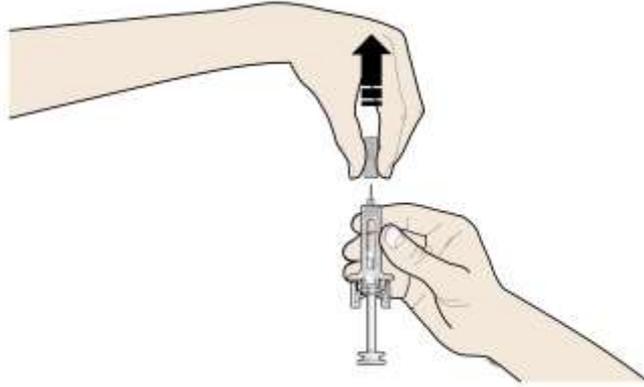
Clean the injection site with an alcohol wipe. Let your skin dry.

- X Do not** touch the injection site before injecting.

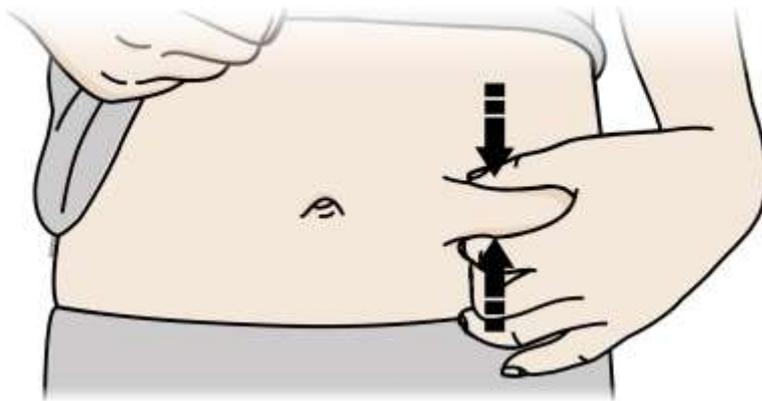


Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

B Carefully pull the grey needle cap straight out and away from your body.



C Pinch your injection site to create a firm surface.



It is important to keep the skin pinched when injecting.

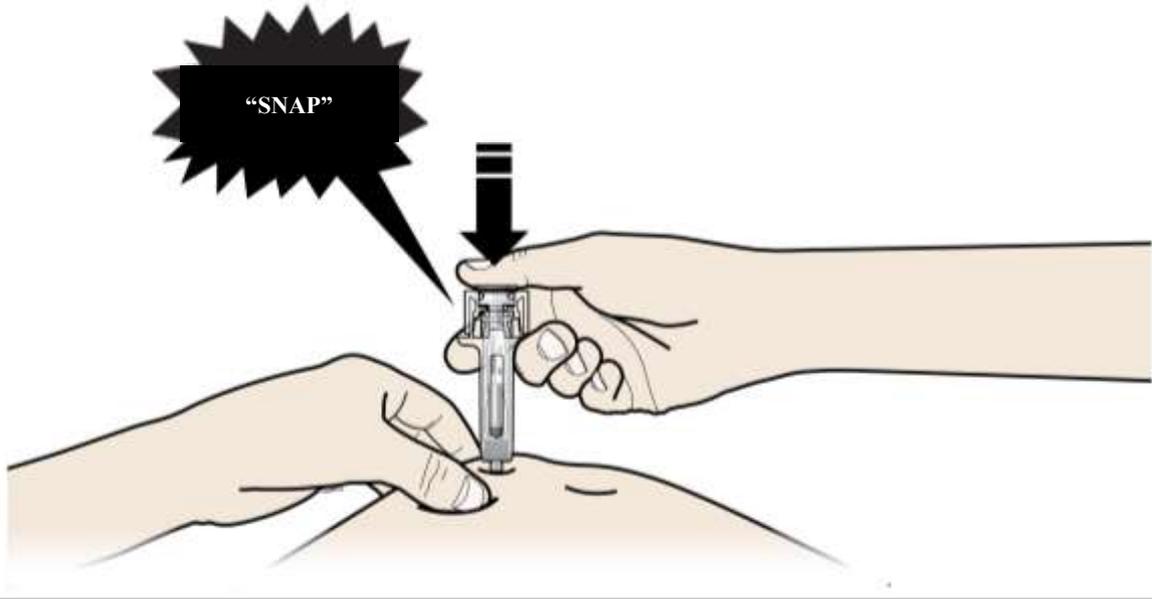
Step 3: Inject

A Hold the pinch. INSERT the needle into skin.



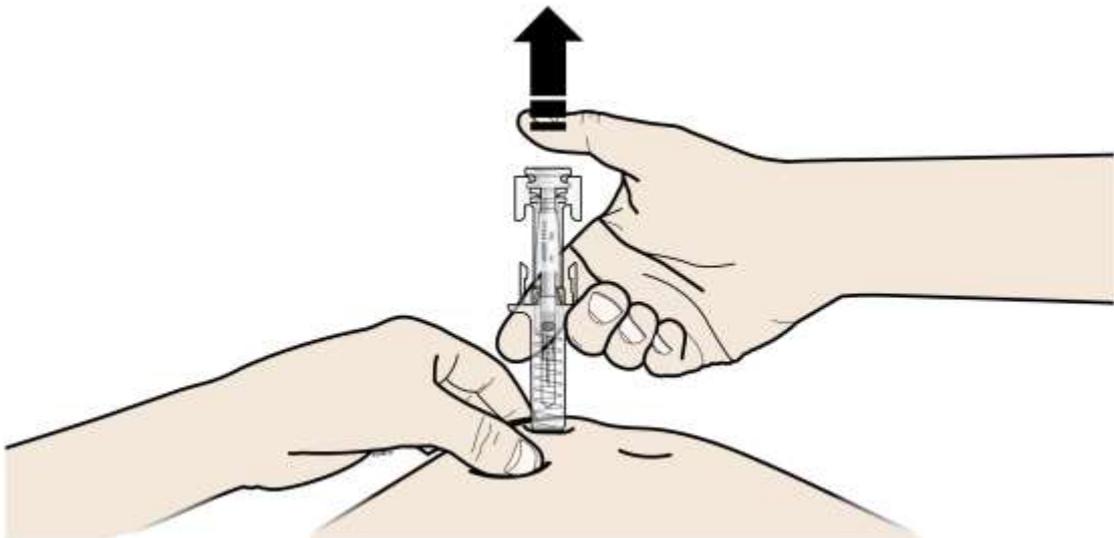
X Do not touch the cleaned area of the skin.

B PUSH the plunger with slow and constant pressure until you feel or hear a “snap”. Push all the way down through the snap.



It is important to push down through the “snap” to deliver your full dose.

C RELEASE your thumb. Then LIFT the syringe off skin.



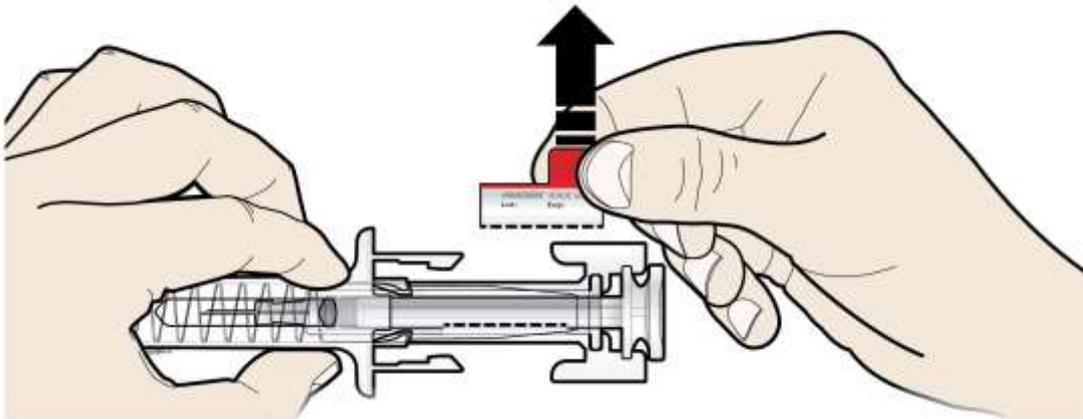
After releasing the plunger, the pre-filled syringe safety guard will safely cover the injection needle.

✗ Do not put the grey needle cap back on used pre-filled syringes.

Healthcare providers only

The trade name of the administered product should be clearly recorded in the patient file.

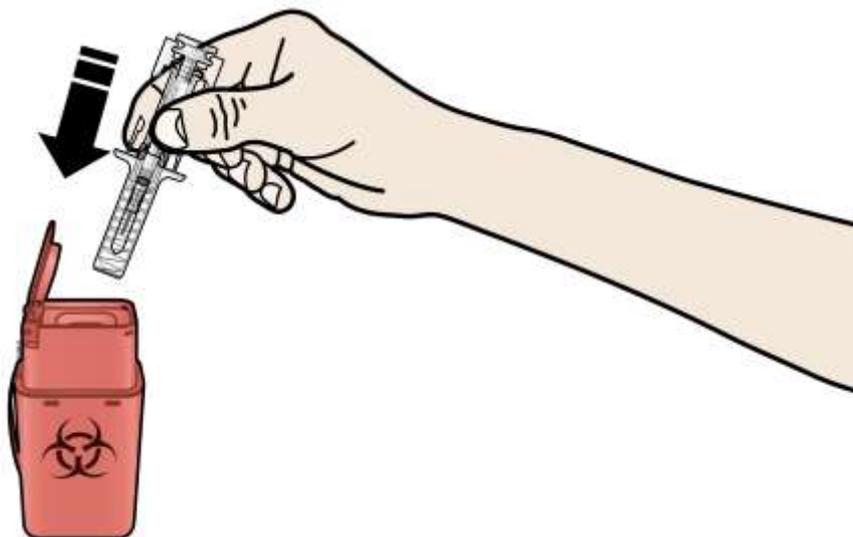
Remove and save the pre-filled syringe label.



Turn the plunger to move the label into a position where you can remove the syringe label.

Step 4: Finish

A Discard the used pre-filled syringe and other supplies in a sharps disposal container.



Medicines should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep the syringe and sharps disposal container out of sight and reach of children.

- ✗ Do not** reuse the pre-filled syringe.
- ✗ Do not** recycle pre-filled syringes or throw them into household waste.

B Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply a plaster if needed.

On-body injector for Neulasta 6 mg solution for injection

Patient instructions for use

Important information

The on-body injector delivers your Neulasta dose with an under-the-skin (subcutaneous) injection. Your healthcare provider will fill the on-body injector with Neulasta and then apply it directly to your skin using an adhesive pad. The adhesive pad is water-resistant but you are advised to avoid submerging the on-body injector in water.

The on-body injector is worn for 27 hours after placement and is programmed to make sure you do not receive Neulasta any sooner than 24 hours after your chemotherapy. The on-body injector will use sounds and lights to let you know its status.

Allergies

- Serious allergic reactions can happen with Neulasta. Ask your caregiver to be nearby for the first use. Plan to be in a place where you or your caregiver can appropriately monitor the on-body injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery.
- Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives. If you have an allergic reaction during the delivery of Neulasta, remove the on-body injector by grabbing the edge of the adhesive pad and peeling off the on-body injector. Get emergency medical help right away.
- Tell your healthcare provider if you have an allergy to latex. A pre-filled syringe is used to fill the on-body injector. The grey needle cap of the pre-filled syringe contains dry natural rubber, which is derived from latex. Latex may be transferred to your skin.

Activity

- **Avoid** knocking or pulling the on-body injector. Consider wearing loose clothing and take care when changing clothes. There is a small cannula which sits just under your skin. If the on-body injector has been knocked or pulled, the cannula may become dislodged. If this happens, you may not receive your dose of Neulasta.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta. For example **AVOID**, travelling, driving, or operating heavy machines during 26-29 hours following application of the on-body injector (this includes the 45-minute dose delivery period plus an hour post-delivery).
- **Do not** use baths, hot tubs, whirlpool baths, or saunas while wearing the on-body injector. This may affect your medicine.
- Only expose the on-body injector to temperatures between 5°C - 40°C.
- **Do not** expose the on-body injector to direct sunlight. If it is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the on-body injector under your clothing.
- **Do not** expose the on-body injector to the following because the on-body injector may be damaged and you could be injured:
 - Diagnostic imaging (e.g. CT scan, MRI, ultrasound, x-ray).
 - Radiation treatment.
 - Oxygen rich environments, such as hyperbaric chambers (a transparent chamber with an increase in atmospheric pressure).

On-body injector becomes loose or falls off

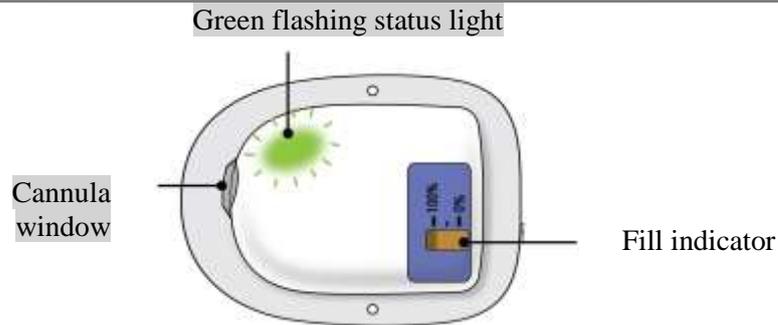
- **Contact your healthcare provider immediately** if the on-body injector comes away from your skin at any time before your full dose has been delivered, **do not** reapply it. There is a small cannula which sits just under your skin. If the on-body injector has been knocked or pulled, the cannula may become dislodged. If this happens, you may not receive your dose of Neulasta.

Electrical equipment

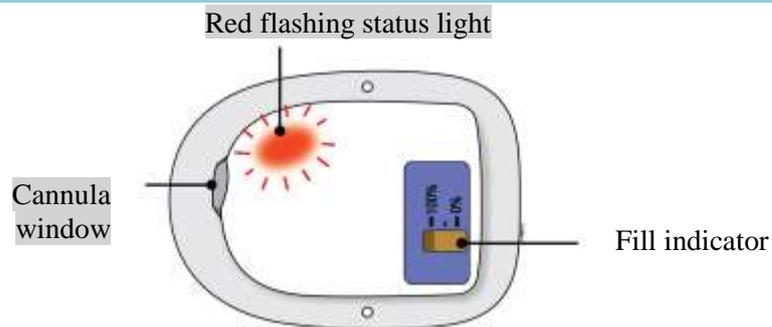
- **Keep the on-body injector at least 10 cm (4 inches) away from electrical equipment** such as mobile phones, cordless telephones, microwaves and other common appliances. Failure to keep the on-body injector at least this recommended distance may interfere with its operation and can lead to a missed or incomplete dose of Neulasta.

If you have any concerns or further questions on the use of this medicine, contact your healthcare provider.

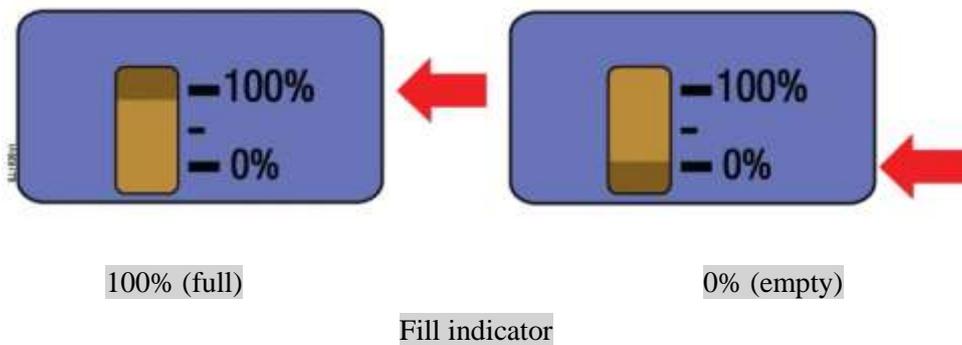
Guide to parts for on-body injector for Neulasta



The on-body injector is working properly.

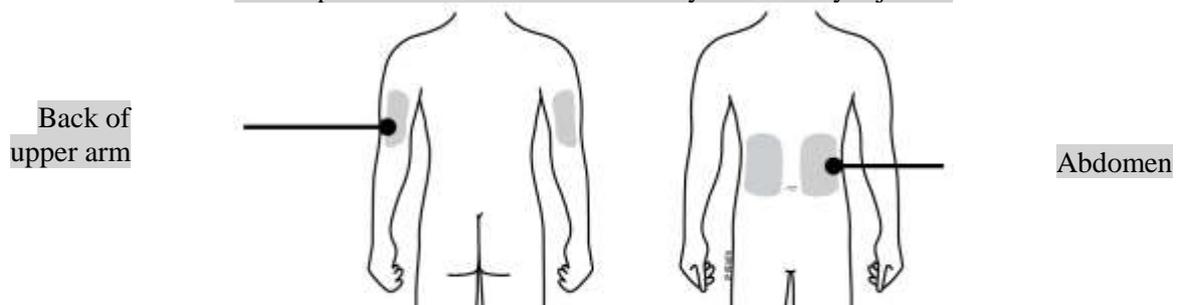


Important: If at any time you hear beeping, check the status light. If it is flashing red, contact your healthcare provider immediately as you may need a replacement dose.



On-body injector placement

Important: Contact your healthcare provider immediately if you have severe pain or skin discomfort around your on-body injector.



- Apply to intact, non-irritated skin on the stomach area abdomen or back of the arm. Use the arm only if a caregiver can help monitor the on-body injector's status.

Step 1: Monitor your on-body injector

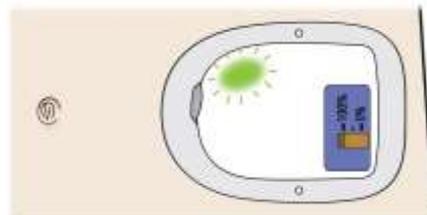
A For the next 27 hours, occasionally check the status light for at least 10 seconds. If the status light is flashing green, it is ok.

Slow flashing light



If the on-body injector was placed on the back of your arm, a caregiver must be available to monitor its status. **Do not** try to do this yourself, as you may accidentally move it and dislodge the cannula from your skin leading to a missed or incomplete dose of Neulasta.

27 hours



- Be careful not to bump or knock the on-body injector off your body.
- The on-body injector has a self-adhesive backing to attach it to the skin, **do not** use additional materials to hold it in place as this could dislodge the cannula leading to a missed or incomplete dose of Neulasta.
- If the on-body injector at any time comes away from your skin before your full dose delivery, **do not** reapply it. Call your healthcare provider immediately as you may need a replacement dose.
- Keep the on-body injector dry for the last 3 hours prior to the start of dose delivery. Avoid getting lotions, creams, oils or cleaning agents near the on-body injector, as these products may loosen the adhesive.
- **Do not** sleep on the on-body injector or apply pressure during wear, especially during dose delivery. This may affect the on-body injector's performance.

Important: If at any time you hear beeping, check the status light.

If it is flashing red, contact your healthcare provider immediately as you may need a replacement dose.

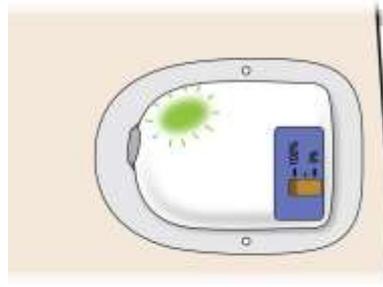
B

After about 27 hours, your on-body injector will produce a series of beeps to let you know your dose delivery is about to begin. Do not remove the on-body injector at this time.

2 minutes before delivery



Fast flashing light



- Dose delivery will start and take about 45 minutes to complete. The on-body injector will flash a fast green light.
- **Do not** remove the on-body injector before the dose delivery is complete. This may result in a missed or incomplete dose of Neulasta.

Important: If at any time you hear beeping, check the status light. If it is flashing red, contact your healthcare provider immediately as you may need a replacement dose.

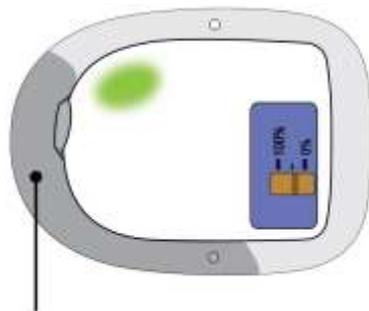
Step 2: Monitor Dose Delivery



For the next 45 minutes, monitor your on-body injector frequently for leaks during dose delivery.

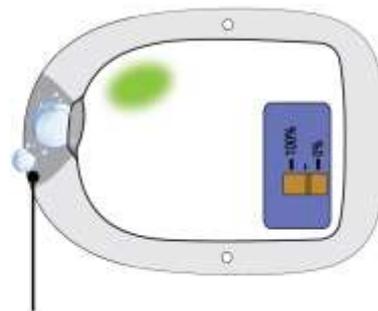
If it was placed on the back of your arm, a caregiver must be available to monitor your on-body injector.

Not working correctly



Noticeably wet (saturated) adhesive

Not working correctly



Dripping fluid from your on-body injector

If the adhesive becomes noticeably wet (saturated) with fluid, or you see dripping, contact your healthcare provider immediately as you may need a replacement dose.

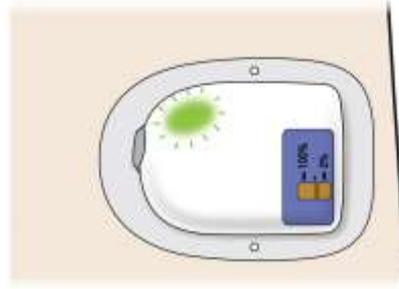
A Your dose delivery will take around 45 minutes to complete.

- During this time, the on-body injector will flash a fast green light.
- You may hear a series of clicks. This is ok.
- When dose delivery is complete, a long beep will sound and the status light will be solid green.

Fast flashing light



45 minutes

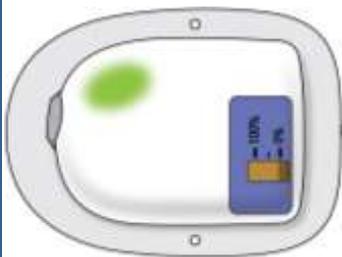


Important: If at any time you hear beeping, check the status light. If it is flashing red, contact your healthcare provider immediately.

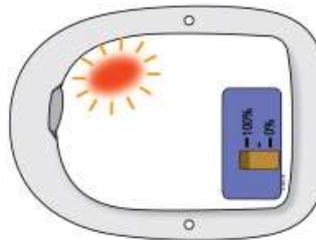
Step 3: Remove your on-body injector when dose delivery is complete

A After the beep, check the colour of the status light.

Correct



Not working correctly

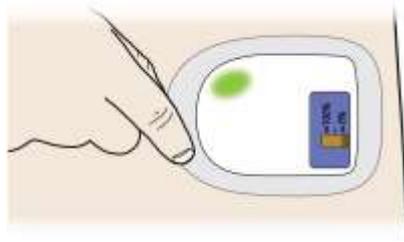


Check to see if the status light is **SOLID GREEN** or has switched off. This means the dose is complete. If the dose is complete, go to the next step.

If you see the status light is flashing red, your on-body injector is not functioning properly. Remember, **any time you see a status light flashing red, call** your healthcare provider immediately, as you may need a replacement dose.

B Grab the edge of the adhesive pad. Slowly peel off the on-body injector.

- If medicine has leaked or the adhesive is noticeably wet (saturated), contact your healthcare provider immediately as you may not have received your full dose and you may need a replacement dose.
- Remove any extra adhesive using soap and water.



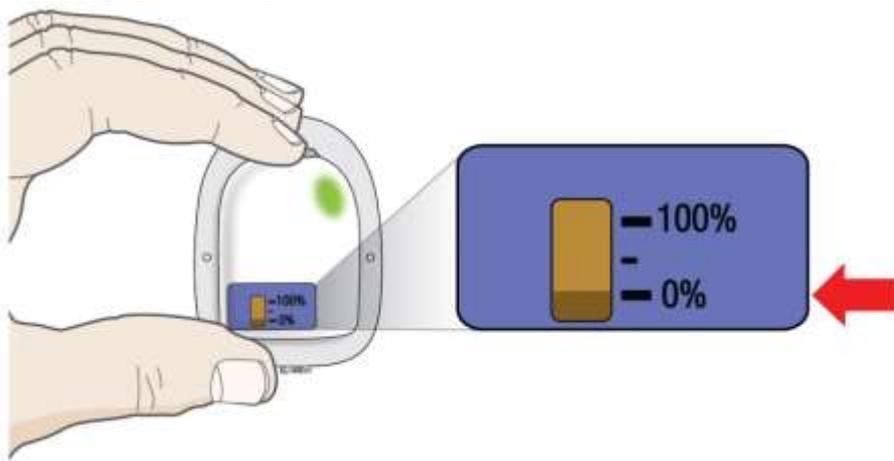
Important: Do not grasp the on-body injector itself to try to pull it off of your body.

Step 4: Finish



Check to see if your on-body injector is empty.

- You should see a black line next to the 0% (empty) indicator to confirm you have received a full dose. If the on-body injector is not empty, contact your healthcare provider immediately as you may need a replacement dose.



- Check your status light again. Watch for at least 10 seconds. If the status light is solid green or it has switched off, it is ok.
- If you hear beeping, or when you check the status light and it is flashing red, contact your healthcare provider immediately.
- If there is blood, press a clean cotton ball or gauze pad on the application site. Apply a plaster if needed.
- Contact your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.
- After your on-body injector removal, place the on-body injector in a sharps disposal container whether the needle is exposed or not. If the needle is exposed, contact your healthcare provider immediately.

A Record the end status of your on-body injector.

- Mark the box of the description that represents your on-body injector after it has been used.
 - Status light is solid green or the status light has switched off. This means that the delivery is complete.
 - The on-body injector leaked, contact your healthcare provider immediately as you may need a replacement dose.
 - Status light is red, contact your healthcare provider immediately as you may need a replacement dose.

B Properly dispose of the on-body injector.

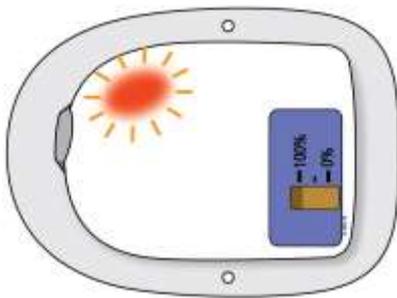
- The on-body injector contains batteries, electronics, and a needle. Dispose of it in a sharps disposal container as instructed by your healthcare provider or in accordance with local requirements.
- Keep children away from the used on-body injector.

Attention!

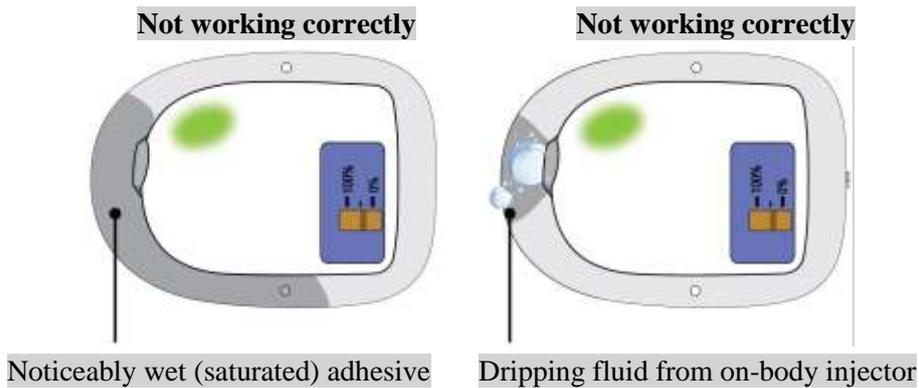
What to do if you hear beeping or when you look at the status light and it is flashing red.

- If the status light is flashing red, you may not have received your full dose and you may need a replacement dose. Contact your healthcare provider immediately.

Not working correctly



What to do if the on-body injector adhesive becomes noticeably wet (saturated) with fluid, or you see dripping.



- If the adhesive becomes saturated with fluid, or you see dripping, your medicine may have leaked out.
- Even with a leak, the status light may remain green and the fill indicator may be at 0% (empty).
- Contact your healthcare provider immediately as you may not have received your full dose and may need a replacement dose.

Note: It is normal to see a few drops of fluid at the application site, but not normal to see a noticeably wet (saturated) adhesive.

What do I do if the on-body injector comes off before the full dose is delivered?

Contact your healthcare provider immediately if the on-body injector comes away from your skin at any time before your full dose has been delivered. There is a small cannula which sits just under your skin. If the on-body injector has been knocked or moved, this may become dislodged. If this happens, you may not receive your dose of Neulasta. Do not reapply it.

What if there is blood at my application site after the on-body injector has been removed?

If there is blood, press a clean cotton ball or gauze pad on the application site. Apply a plaster if needed.

What if my application site is red or tender after on-body injector removal?

Contact your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.