ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Stimufend 6 mg solution for injection in pre-filled syringe

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).

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

Stimufend 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 Stimufend is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Special populations

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

renal disease.

Paediatric population
The safety and efficacy of pegfilgrastim 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.

Method of administration

Stimufend is injected subcutaneously. The injections should be given into the thigh, abdomen or upper arm.

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 listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 (G-CSF) can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

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

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

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

Sickle cell anaemia

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease (see section 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 medicinal product with splenic enlargement and vaso-occlusive crisis.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in less than 1% of patients receiving 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 medicinal product. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, this medicinal product 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.

Stevens-Johnson syndrome

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against 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 pegfilgrastim 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.

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging findings. This should be considered when interpreting bone-imaging results.

Sorbitol

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) 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 studies, pegfilgrastim has been safely administered 14 days before chemotherapy. Concomitant use of pegfilgrastim with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of pegfilgrastim 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 pegfilgrastim 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 pegfilgrastim 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.

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.

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 [≥ 1/10]) and musculoskeletal pain (common [≥ 1/100 to < 1/10]). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythaema, flushing, and hypotension occurred on initial or subsequent treatment with pegfilgrastim (uncommon [≥ 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 (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of G-CSFs; 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 list of adverse reactions

The data in the table below describe adverse reactions reported from clinical studies and spontaneous reporting. The table is according to the MedDRA system organ classification. Frequencies have been evaluated according to the following convention: 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).Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Neoplasm benign, malignant and unspecified (incl cysts and polyps)			Myelodysplastic syndrome[1] Acute myeloid leukaemia[1]	
Blood and lymphatic system disorders		Thrombocytopenia[1] Leukocytosis[1]	Sickle cell anaemia with crisis[2]; Splenomegaly[2]; Splenic rupture[2]	
Immune system disorders			Hypersensitivity reactions; Anaphylaxis	
Metabolism and nutrition disorders			Elevations in uric acid	
Nervous system disorders	Headache[1]			
Vascular disorders			Capillary leak syndrome[1]	Aortitis
Respiratory, thoracic and mediastinal disorders			Acute Respiratory Distress Syndrome[2]; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis) Haemoptysis	Pulmonary haemorrhage

Gastrointestinal disorders	Nausea[1]			
Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile neutrophilic dermatosis)[1,2] Cutaneous vasculitis[1,2]	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain)		
Renal and urinary disorders			Glomerulonephritis[2]	
General disorders and administrative site conditions		Injection site pain[1] Non-cardiac chest pain	Injection site reactions[2]	
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1]; Transient elevations in 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 studies in adults. The frequency category was estimated from a statistical calculation based upon 1,576 patients receiving pegfilgrastim in nine randomised clinical studies.

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 erythaema (uncommon) as well as injection site pain (common) have occurred on initial or subsequent treatment with pegfilgrastim.

Common 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; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving pegfilgrastim 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.

An increased risk of MDS/AML following treatment with pegfilgrastim in conjunction with chemotherapy and/or radiotherapy has been observed in an epidemiological study in breast and lung cancer patients (see section 4.4).

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post-marketing setting with G-CSF 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 sections 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 factors; ATC Code: L03AA13

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

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/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%, $p < 0.001$).

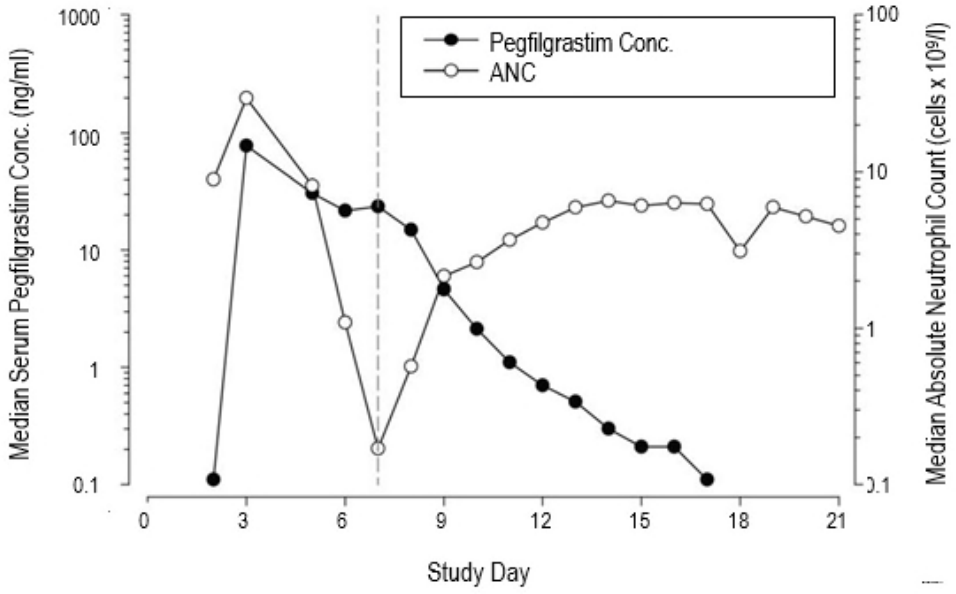
A small (n = 83), phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 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 mcg/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/L) 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).

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) (± 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
Glacial acetic acid
Water for injections

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).

Stimufend may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Stimufend left at room temperature for more than 72 hours should be discarded.

Do not freeze.

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 bromobutyl fluorotec stopper, stainless steel needle, needle cap and an automatic needle guard.
The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex) (see section 4.4).

Each pre-filled syringe contains 0.6 mL of solution for injection.
Pack size of one pre-filled syringe, in a blistered packaging.

6.6 Special precautions for disposal and other handling

Before use, Stimufend 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 come to room temperature for 30 minutes before using the syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
61352 Bad Homburg v.d.Hoehe
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1632/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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(S) 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(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM Diosynth Biotechnologies UK Ltd
Belasis Avenue
Billingham TS23 1LH
United Kingdom

Name and address of the manufacturer(s) responsible for batch release

Fresenius Kabi Austria GmbH
Hafnerstrasse 36
8055 Graz
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Stimufend 6 mg solution for injection in pre-filled syringe
pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

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.
Do not use if seal is broken or missing.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton 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

Fresenius Kabi Deutschland GmbH
Else-Kroener-Strasse 1
61352 Bad Homburg v.d.Hoehe
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1632/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Stimufend

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

Stimufend 6 mg injection
pegfilgrastim

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use
0.6 mL
1 single-dose pre-filled syringe

EU/1/22/1632/001

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

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

Stimufend 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

Fresenius Kabi Deutschland GmbH

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Stimufend 6 mg solution for injection in pre-filled syringe
pegfilgrastim

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 signs 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.

What is in this leaflet

1. What Stimufend is and what it is used for

Stimufend 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.

Stimufend 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 Stimufend 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 Stimufend

Do not use Stimufend
- if you are allergic to pegfilgrastim, filgrastim or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Stimufend:

- 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 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 are a patient with breast cancer or lung cancer, Stimufend in combination with chemotherapy and/or radiation therapy may increase your risk of a precancerous blood condition called myelodysplastic syndrome (MDS) or a blood cancer called acute myeloid leukaemia (AML). Symptoms may include tiredness, fever, and easy bruising or bleeding.
- 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.
- if you have symptoms of inflammation of aorta (the large blood vessel which transports blood from the heart to the body), this 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 Stimufend can harm the tiny filters inside your kidneys (glomerulonephritis).

Severe skin reactions (Stevens-Johnson syndrome) have been reported with the use of pegfilgrastim. Stop using pegfilgrastim and seek medical attention immediately if you notice any of the symptoms described in section 4.

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 Stimufend, 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 Stimufend
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. Stimufend 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 Stimufend treatment, please inform your doctor.

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

Driving and using machines
Stimufend has no or negligible effect on the ability to drive or use machines.

Stimufend contains sorbitol (E420) and sodium acetate
This medicine contains 30 mg sorbitol in each 6 mg dose, which is equivalent to 50 mg/ml.
This medicine contains less than 1 mmol sodium (23 mg) per 6 mg dose, that is to say essentially 'sodium-free'.

3. How to take Stimufend

Stimufend is for use in adults aged 18 and over.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 6 mg subcutaneous injection (injection under your skin) using a pre-filled syringe and it should be given at least 24 hours after your last dose of chemotherapy at the end of each chemotherapy cycle.

Injecting Stimufend yourself
Your doctor may decide that it would be more convenient for you to inject Stimufend 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 Stimufend, please read the section at the end of this leaflet.

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

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

If you forget to inject Stimufend
If you are injecting yourself and have forgotten your dose of Stimufend, 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):
- pain at the site of injection.
- 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)
- blood disorders (myelodysplastic syndrome [MDS] or acute myeloid leukaemia [AML]).

Rare side effects (may affect up to 1 in 1,000 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).
- Stevens-Johnson syndrome, which can appear as reddish target-like or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. Stop using Stimufend if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

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 Stimufend

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).

Stimufend may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Stimufend left at room temperature for more than 72 hours should be discarded. For all questions about storage, ask your doctor, nurse or pharmacist.

Do not freeze.

Keep the pre-filled syringe 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 protect the environment.

6. Contents of the pack and other information

What Stimufend 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, glacial acetic acid and water for injections. See section 2 ‘Stimufend contains sorbitol (E420) and sodium acetate’.

What Stimufend looks like and contents of the pack
Stimufend 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 is provided with an automatic needle guard.

Marketing Authorisation Holder
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Germany

Manufacturer
Fresenius Kabi Austria GmbH
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8055 Graz
Austria

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 use Stimufend (pegfilgrastim)

Single-dose pre-filled syringe for subcutaneous injection

Important:
Read the package leaflet for important information you need to know about Stimufend before using this instructions for use Stimufend.

Before you use a Stimufend pre-filled syringe, read this important information.

Storing Stimufend pre-filled syringes:
- Store Stimufend in the refrigerator between 2°C to 8°C.
- **Do not** freeze.
- Keep the pre-filled syringe in the original carton to protect from light.
- Throw away (dispose of) any Stimufend that has been left at room temperature, not above 30°C, for more than 72 hours.
- Keep the Stimufend pre-filled syringe out of the reach of children.

Using the pre-filled syringe:
- It is important that you do not try to inject Stimufend unless you or your caregiver has received training from your healthcare professional.
- You should not inject Stimufend to children.
- A dose less than 6 mg/0.6 mL cannot be accurately measured using the Stimufend pre-filled syringe.
- **Do not** use a pre-filled syringe after the expiry date on the label because it could lead to illness.
- **Do not** shake the pre-filled syringe.
- **Do not** remove the needle cap from the pre-filled syringe until you are ready to inject.
- **Do not** use the pre-filled syringe if the carton is open or damaged.
- **Do not** use the pre-filled syringe if it has been dropped on a hard surface. The pre-filled syringe may be broken even if you cannot see the break. Use a new pre-filled syringe.
- **Do not** use Stimufend that has been frozen or left in direct sunlight.
- The needle cover on the pre-filled syringe contains dry natural rubber (latex). Tell your healthcare professional if you are allergic to latex. You should not give Stimufend using the pre-filled syringe if you have latex allergies.
- Stimufend pre-filled syringe has clear needle guard that covers the needle after the injection is complete.
- **Do not** try to activate the clear needle guard before injecting.
- **Do not** insert your fingers into the opening of the clear needle guard because the needle could injure you.
- **Do not** try to reuse the Stimufend pre-filled syringe because it could lead to an infection.

Call your healthcare professional if you have any questions.

Step 1: Get ready for your injection

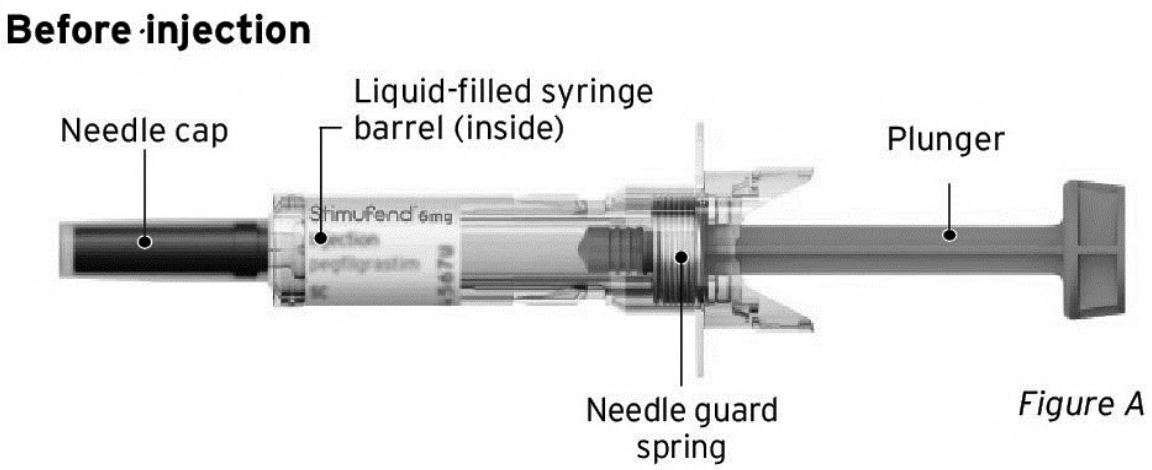


Figure A

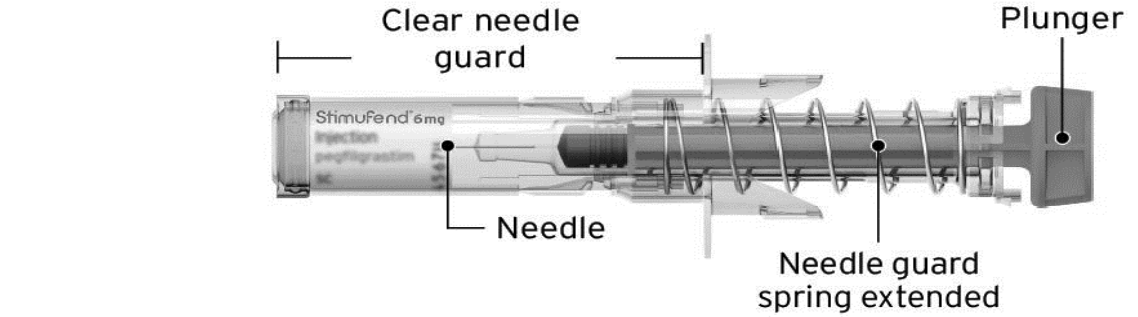


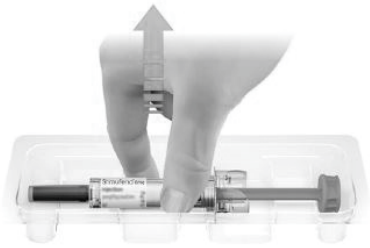
Figure B

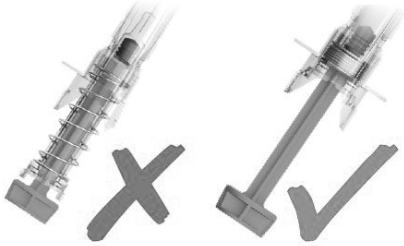
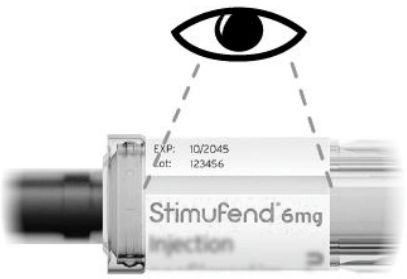
1.1 Prepare your materials

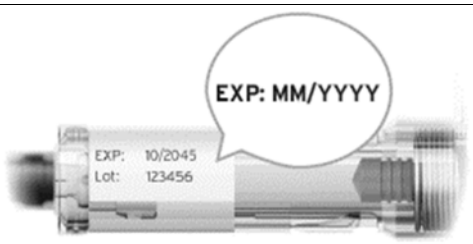
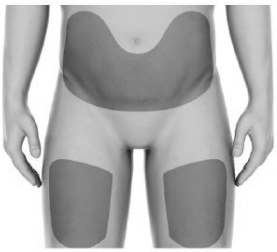
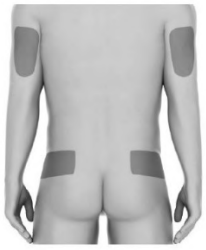
- Prepare a clean flat surface, such as a table or countertop, in a well-lit area.
- You will also need (not included) (Figure C):
  - 1 alcohol pad
  - 1 cotton ball or gauze, and
  - a sharps disposal container.

Figure C

- Remove the carton from the refrigerator.
- Take out the sealed plastic tray from the carton.
- Put the syringe in its sealed plastic tray on a clean flat surface.

• Leave the syringe in its sealed plastic tray and let it come to room temperature for 30 minutes before the injection (Figure D). Injecting cold medicine can be painful.	 *Figure D*
• **Do not** warm the syringe any other way, such as in a microwave, hot water, or direct sunlight.	
• **Do not** remove the needle cap while allowing the syringe to reach room temperature.	
Step 2: Wash your hands	
2.1 Wash your hands	
• Wash your hands well with soap and water and dry them with a clean towel (Figure E). • Wearing gloves does not replace the need to wash your hands.	 *Figure E*
Step 3: Check your syringe	
3.1 Remove pre-filled syringe from the sealed plastic tray	
• Peel off the seal from the sealed plastic tray.	
• Place two fingers on either side, in the middle of the clear needle guard. Pull the pre-filled syringe straight up and out of the tray (Figure F). **Do not** pick up the pre-filled syringe by plunger, or needle cap. Doing so could damage the syringe or activate clear needle guard.	 *Figure F*
3.2 Check your syringe	
• Check that the pre-filled syringe, the clear needle guard and the needle cap are not cracked or damaged (Figure G).	 *Figure G*

• Check that the needle cap is securely attached (Figure H).	 *Figure H*
• Check that the needle guard spring is not extended (Figure I).	 *Figure I*
Do not use the pre-filled syringe if it shows any sign of damage. If so, throw away the syringe in your sharps disposal container (see Step 6) and contact your healthcare professional or pharmacist right away.	
3.3 Check liquid	
• Check the liquid through the clear window of the label to make sure that the medicine is clear, colourless, and free of particles and flakes (Figure J).	 *Figure J*
Do not use the pre-filled syringe if the medicine is cloudy or coloured or if it has particles or flakes in it. If so, throw away the syringe in your sharps disposal container (see Step 6) and call your healthcare professional or pharmacist right away.	
3.4 Check label	
• Check the label **on the syringe** to make sure that:	
- The name on the label says Stimufend (Figure K). - The expiry date has not passed (Figure L). - The dose strength is 6 mg/0.6 mL	 *Figure K*

Do not use the pre-filled syringe if: • The name on the label is not Stimufend. • The expiry date on the label has passed. • The dose strength is not 6 mg/0.6 mL.	 *Figure L*
If so, throw away the syringe in your sharps disposal container (see Step 6) and call your healthcare professional or pharmacist right away.	
Step 4: Prepare to inject	
4.1 Choose an injection site (Figure M)	
You can use: • Top of the thighs, or • Stomach area (lower abdomen) except for a 5 centimetres away from the navel (belly button).	 *Figure M*
• If you are injecting into someone else, you may use the back of the arm or the upper outer areas of the buttocks (Figure N). • Only inject into the sites shown.	 *Figure N*
Do not inject into an area that is sore (tender), bruised, red, hard, scarred or where you have stretch marks or tattoos.	
Do not inject through your clothes.	
4.2 Clean the injection site	
• Wipe the skin of your injection site with an alcohol pad to clean it (Figure O). Let the skin dry. **Do not** touch the injection site again before injecting.	 *Figure O*
Step 5: Inject medicine	
5.1 Remove the needle cap	

- Hold the syringe by the clear needle guard.
- Use your other hand to remove the needle cap by pulling the cap straight off (Figure P).
- Throw away the needle cap in your sharps disposal container.

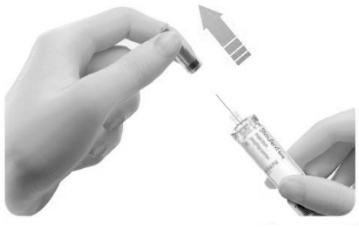


Figure P

Do not touch the needle or let it touch any surface after removal of the needle cap.

5.2 Pinch the skin

- Gently pinch skin around the area where you plan to inject (without squeezing or touching the cleaned area) to avoid injecting into muscle (Figure Q).

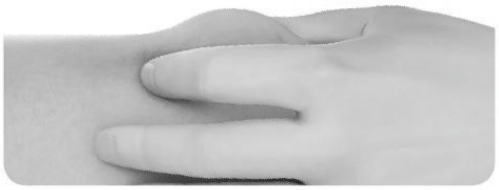


Figure Q

5.3 Insert the needle

- Hold the syringe in the other hand like a pencil.
- Quickly insert the needle straight into the skin at a 45 to 90-degree-angle (Figure R).

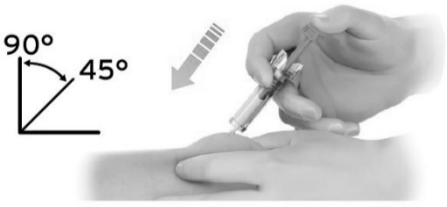


Figure R

5.4 Inject

- Use your thumb to gently push the plunger all the way down to inject the full dose (Figure S).

Figure S

- The plunger must be pushed down fully to ensure the full dose has been injected (Figure T).
- Hold the syringe firmly without moving it.

Figure T

Do not remove the needle from the skin when the plunger reaches the end.

5.5 Finish injection

- Slowly release your thumb upward. This will allow the needle to move up into the clear needle guard and cover the entire needle (Figure U).

Figure U

Important: Call your healthcare professional or pharmacist right away if:
- you did not inject the full dose or
- the clear needle guard does not activate after a full injection.

Injecting an incorrect amount of medicine could affect or delay your treatment.

Do not reuse a syringe in case of partial injection.

Do not try to recap the needle as it could lead to needle stick injury.

- If there is blood or liquid on the injection site, gently press a cotton ball or gauze on the skin (Figure V). You may use an adhesive bandage if needed.

Figure V

Do not rub the injection site.

Step 6: Throw away your pre-filled syringe

6.1 Put your used pre-filled syringes in a sharps disposal container right away after use (Figure W).

Do not throw away (dispose of) pre-filled syringes in your household trash.

Figure W

- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic;
  - can be closed with a tight-fitting, puncture-resistant lid; without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

Do not recycle your used sharps disposal container.