For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

READ PACKAGE INSERT CAREFULLY BEFORE USE

Filpegla 6mg/0.6ml Solution for Injection in pre-filled syringe

Pegfilgrastim 6mg/0.6ml Solution for Injection

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Colony stimulating factor

Pharmacotherapeutic group: immunostimulants, ATC Code: L03AA13

Filpegla 6mg/0.6ml Solution for Injection in pre-filled syringe has been developed as a similar biological product to NEULASTIM®

1.2 Type of Dosage Form

Solution for injection in pre-filled syringe

1.3 Route of Administration

Subcutaneous injection

1.4 Sterile/Radioactive Statement

Sterile

1.5 Qualitative and Quantitative Composition

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 nonpegylated protein of the same therapeutic class, see section 3.1.

Excipients: D-Sorbitol, Polysorbate 20, Sodium Hydroxide*** , Glacial Acetic Acid and Water for Injection.

***The Sodium content formed by titration of Sodium Hydroxide and Glacial Acetic acid is 0.02 mg.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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

2.2 Dosage Administration

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

Posology

Adults (≥ 18 years): One 6 mg dose (a single pre-filled syringe) of Filpegla is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

Method of administration

Filpegla 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 *Instruction for use.*

Special populations

Paediatric population

The safety and efficacy of Pegfilgrastim injection in children has not yet been established. Currently available data are described in sections 2.6, 3.1 and 3.2 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.

2.3 Contraindications

Hypersensitivity to pegfilgrastim, filgrastim, *E. coli* derived proteins, or to any excipients.

2.4 Warnings and Precautions

2.4.1 General

Filpegla 6 mg / 0.6 mL Solution for Injection in Pre-filled Syringe is a biosimilar product of Neulastim® and interchangeability or auto-substitution between Filpegla and Neulastim® is not allowed.

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

Granulocyte-colony stimulating factor can promote growth of myeloid cells *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.

<u>Pulmonary adverse events</u>

Uncommon (≥ 1/1,000 to < 1/100) pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after granulocyte colony stimulating factor (G-CSF) administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see section *Undesirable Effects*).

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 Filpegla should be discontinued at the discretion of the physician and the appropriate treatment given (see section *Undesirable Effects*).

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis are 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 *Undesirable Effects*).

Splenomegaly and splenic rupture

Uncommon but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. (see section *Undesirable Effects*). 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.

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

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment has 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 neutralizing activity at present.

Aortitis

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

Other warnings

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.

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

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.

2.4.2 Ability to Drive and Use Machines

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

2.4.3 Laboratory Tests

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

2.4.4 Interactions 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, Pegfilgrastim injection 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 injection 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 Pegfilgrastim injection 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 Pegfilgrastim injection with any other medicinal products.

2.5 Fertility, pregnancy and lactation

2.5.1 Pregnancy

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

2.5.2 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.

2.5.3 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)

2.6 Undesirable Effects

Summary of the safety profile

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

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

Clinical Trials

In Cancer Patients

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy

following administration of granulocyte-colony stimulating factors; see section *Warnings and Precautions* and section "Description of selected adverse reactions" below.

In Normal Donors undergoing peripheral blood progenitor cell mobilization
Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors.

Splenomegaly, generally asymptomatic, is uncommon.

Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim (see section *Warnings and Precautions*).

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

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 *Warnings and Precautions*).

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

MedDRA system organ class	**Adverse reactions**				
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Blood and lymphatic system		Thrombocytopenia[1] Leukocytosis[1]	Sickle cell crisis[2]; Splenomegaly[2]; Splenic rupture[2]		

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)**
disorders					
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)		

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

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)**
			LFT's for ALT or AST[1]		
Renal and urinary disorders			Glomerulonephritis[2]		

[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 Pegfilgrastim injection in nine randomized 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 injection is unknown.

Injection site reactions, including injection site erythaema (uncommon (≥ 1/1,000 to < 1/100)) as well as injection site pain (common events ≥ 1/100 to < 1/10) have occurred on initial or subsequent treatment with Pegfilgrastim injection.

Common (≥ 1/100 to < 1/10) cases of leukocytosis (White Blood Count [WBC] > 100 x 10^9/l) have been reported (see section *Warnings and Precautions*).

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 ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.
Common cases of thrombocytopenia have been reported.

Post Marketing

Vascular disorders

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

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 *Pharmacodynamics and Pharmacokinetics*).

Reporting of suspected adverse reactions

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

2.7 Overdose

Single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic properties

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 with Neulastim®, 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). [1] 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 µg/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%, -1.1%).[1]

In a placebo-controlled study, double-blind study in patients with breast cancer, the effect of pegfilgrastim (Neulastim®) 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%, $p \leq 0.001$). 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%, $p < 0.001$).[1]

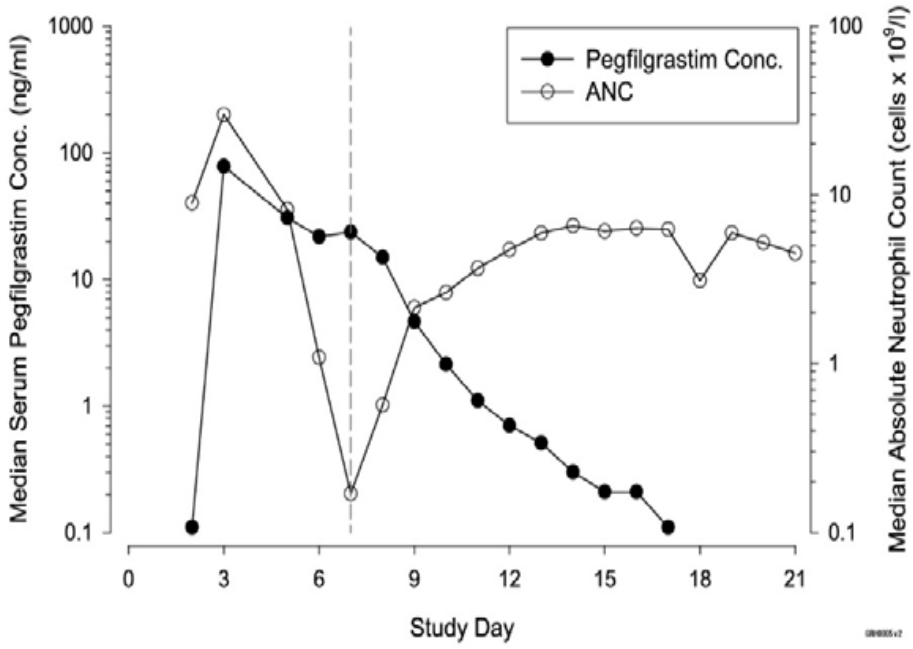
A small (n = 83), Phase II, randomised, double-blind study in patients receiving chemotherapy for de novo acute myeloid leukaemia compared pegfilgrastim (Neulastim®, single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see section 2.4). [1]

In a phase II (n = 37) multicentre, randomised, open-label study of paediatric sarcoma patients receiving 100 µg/kg pegfilgrastim (Neulastim®) 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 2.6 and 3.2). [1]

3.2 Pharmacokinetic properties

After a single subcutaneous dose of pegfilgrastim (Neulastim®), 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 nonlinear 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). [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. [1]

Elderly people

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults. [1]

Paediatric population

The pharmacokinetics of pegfilgrastim (Neulastim®) were studied in 37 paediatric patients with sarcoma, who received 100 µg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (± Standard Deviation) (47.9 ± 22.5 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·hr/ml, respectively) (see section *Pharmacodynamics*). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel (see sections *Undesirable Effects and Pharmacodynamics*). [1]

[1]: This data has been obtained from clinical trial experience of Neulastim® Pre-filled Syringes 6 mg/mL

3.3 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.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Store in a refrigerator (2°C – 8°C).

Filpegla 6 mg / 0.6 mL solution for injection in pre-filled syringe may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Filpegla 6 mg / 0.6 mL solution for injection in pre-filled syringe left at room temperature for more than 72 hours should be discarded.

Do not freeze. Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of Filpegla 6 mg / 0.6 mL solution for injection in pre-filled syringe.

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

4.2 Special Instructions for Use, Handling and Disposal

Before administration, Filpegla 6 mg / 0.6 mL solution for Injection in pre-filled syringe should be inspected visually for particulate matter. Only a solution that is clear and colorless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.
Any unused product or waste material should be disposed of in accordance with local requirements.

Kindly refer attached complete Instruction for Use.

4.3 Packs

Filpegla 6mg/0.6ml Solution for Injectionin in pre-filled syringe is supplied as a sterile, clear and colourless preservative-free solution for injection with pH value in the range of 3.8 to 4.3 in a 1 mL USP Type 1 glass pre-filled syringe (PFS). The syringe staked with 27-gauge, ½ inch stainless steel needle with rigid needle shield and passive needle safety guard (UltraSafe needle guard from Becton Dickinson).
Each PFS contains 6 mg Pegfilgrastim in 0.6 ml solution.

Medicine: Keep out of reach of children

Date of Revision: September 2020 Version: 01

Product Registration Holder

Cipla Malaysia Sdn Bhd
Suite 1101, Amcorp Tower,
Amcorp Trade Centre,
18 Persiaran Barat 46050,
Petaling Jaya, Selangor
Malaysia

Manufactured and Released By:

USV Private Limited

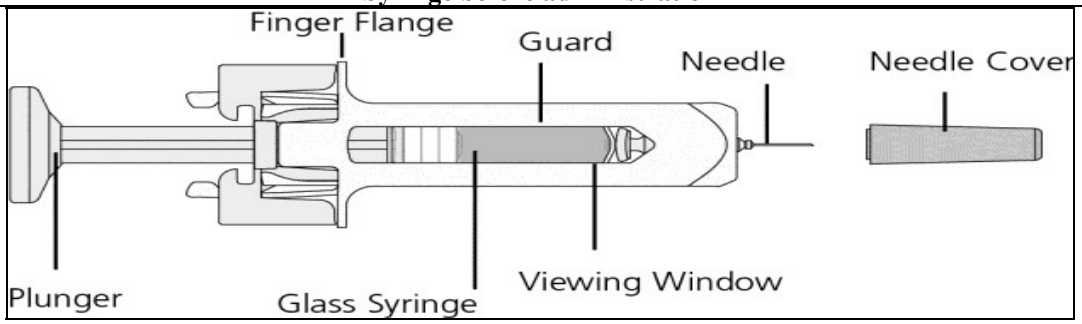
H-13, 16, 16A, 17, 18, 19, 20, 21 & E-22, OIDC,

Mahatma Gandhi Udyog Nagar, Dabhel, Daman-396210, India.

Instructions for use:

Guide to parts

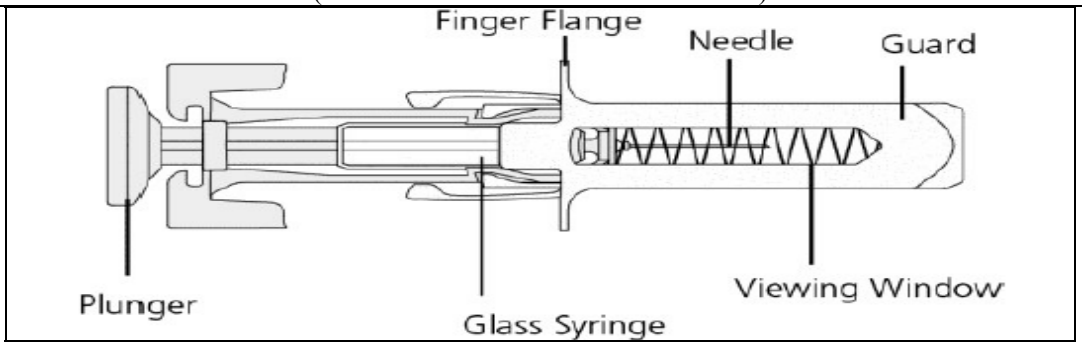
Syringe before administration



Caution: *Avoid contact with the plunger and needle during the preparation of the syringe, The safety device is normally activated by pressure from the plunger on the syringe.*

Syringe after administration

(Guard is released and covers the needle)



Important

Before you use a Filpegla 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.
- Filpegla is given as an injection into the tissue just under the skin (subcutaneous use).

✘ **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.

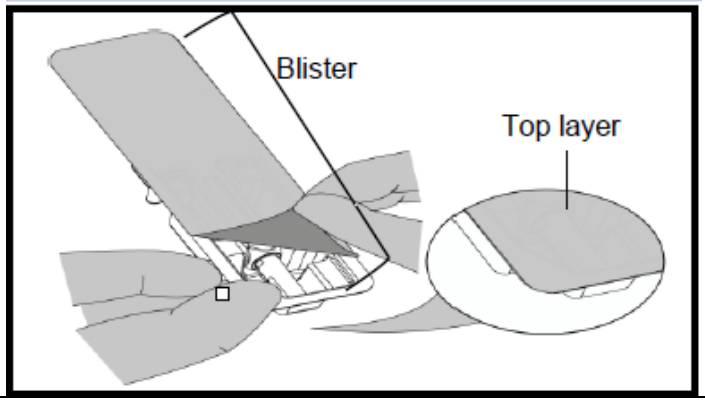
✘ **Do not** try to warm the syringe by using a heat source such as hot water or microwave.

✘ **Do not** leave the pre-filled syringe exposed to direct sunlight.

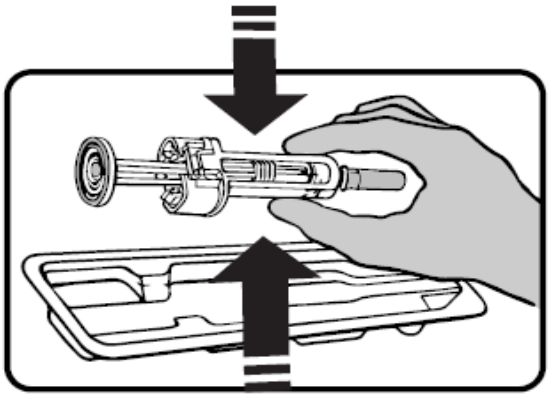
✘ **Do not** shake the pre-filled syringe.

Keep pre-filled syringes out of the sight and reach of children.

B.	Warning/Precaution: Check to ensure there is no loose fragment or fluid inside the pack. In case of doubt DO NOT open this pack and take another pack instead. Open the blister by peeling back the top layer all the way off the blister as shown.



C.	Warning/Precaution: DO NOT lift the product by the plunger or needle cover. **Remove the pre-filled syringe from blister as shown.**



D.	**Inspect the medicine content through the viewing window of the pre-filled syringe.**

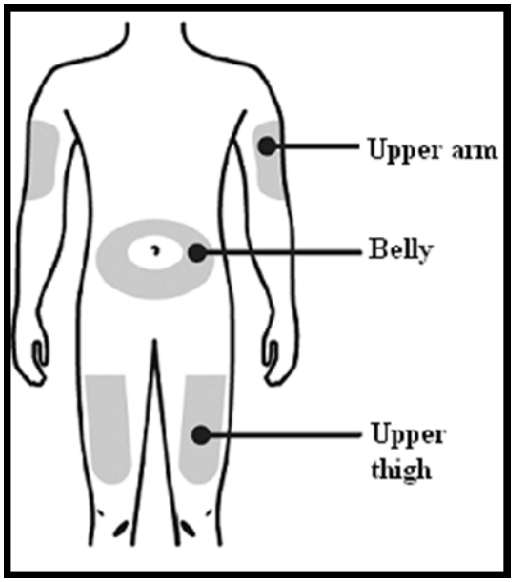
✘ **Do not** use the pre-filled syringe if:

- 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:

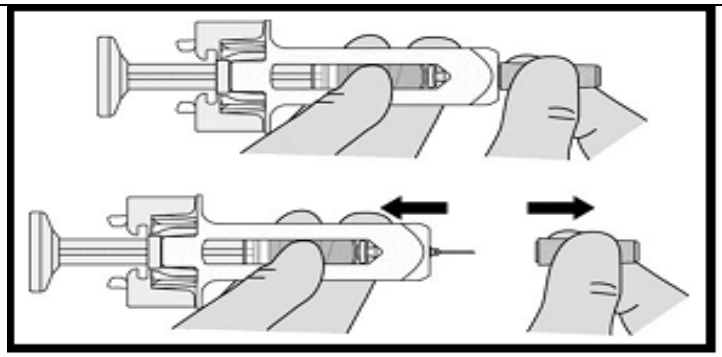
- Upper part of your thigh
- Belly, except for a 5 cm (2-inch) area right around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

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

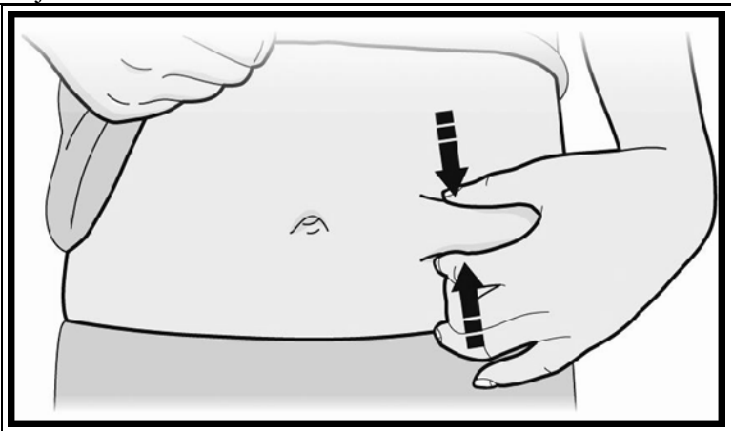
✘ **Do not** touch the injection site before injecting.

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

B.	Warning/Precaution: DO NOT twist the needle cover or touch the needle or plunger. Pull the needle cover straight off as shown and handle the guard to avoid injuries or bending the needle.



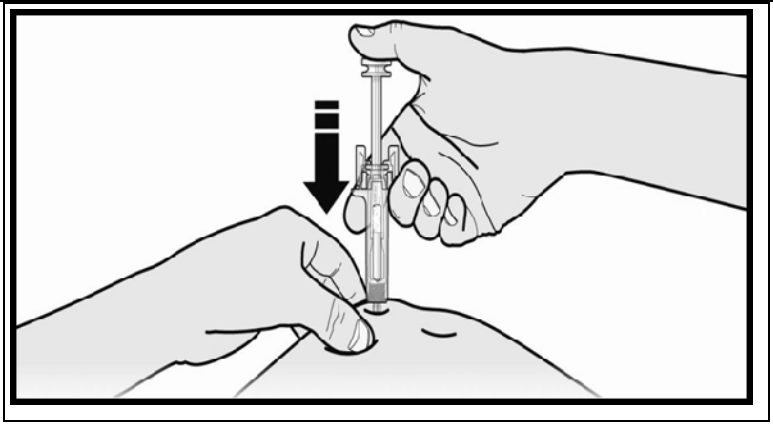
C.	Pinch your injection site to create a firm surface.



It is important to keep the skin pinched when injecting.

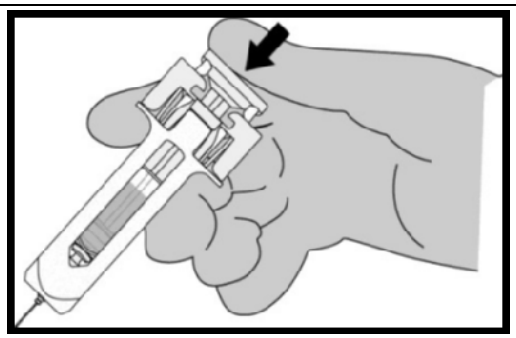
Step 3: Inject

A.	INSERT the needle into skin. Push the plunger while grasping the finger flanges. Push the plunger all the way down as far as it will go to inject all of the solution.

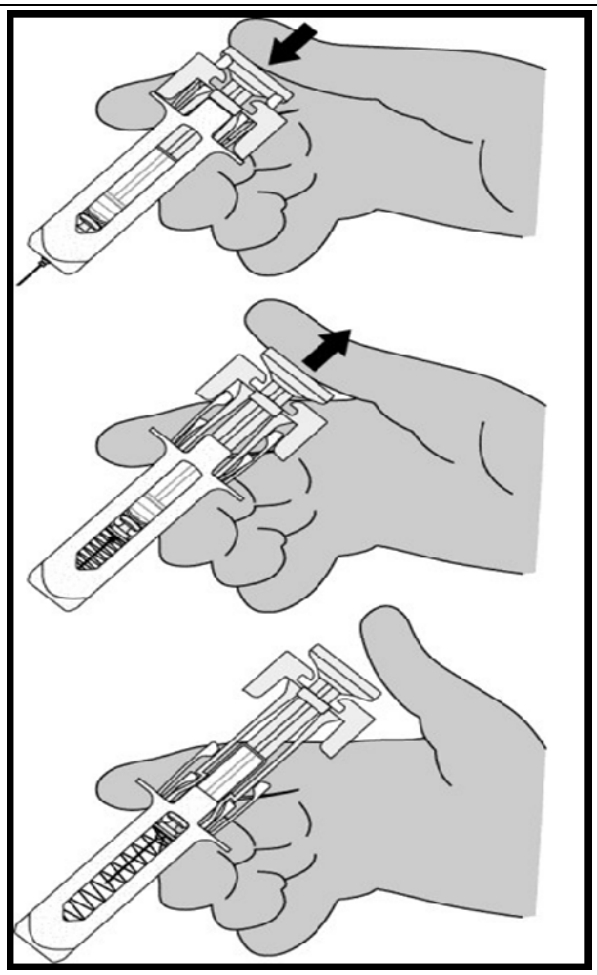


✘ **Do not** touch the injection site before injecting.

B.	The entire dose has to be administered to trigger the guard.

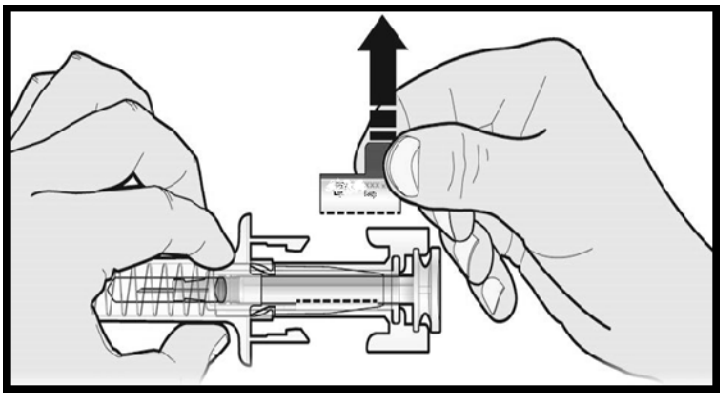


C.	After the injection is complete, one of the below alternatives can be followed: -Remove the needle from the injection site and release the plunger until the entire needle is covered by the guard. -Release the plunger until the needle is covered and then remove the syringe from the injection site



Warning/Precaution: If the guard is not activated or only partially activated, discard the syringe without replacing the needle cover.

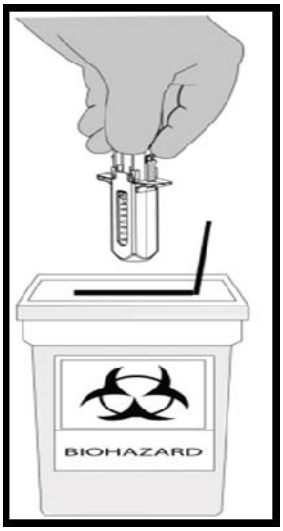
Healthcare professionals only
The trade name of the medicine should be clearly recorded in the patient file.



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

Step 4: Finish

A.	Dispose of the used medicine immediately in a Sharps container or as instructed by your healthcare provider.



Medicines should be disposed of in accordance with local requirements. Ask your pharmacist how to throw away medicines you no longer use. These measures will help 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 away via 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.