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

UDENYCA 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 content only**.

*The active substance is a covalent conjugate of filgrastim produced in *Escherichia coli* cells by recombinant DNA technology with polyethylene glycol (PEG).
** The concentration is 20 mg/ml if the PEG moiety is included.

The potency of this medicinal 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

Excipient with known effect
Each pre--filled syringe contains 30 mg sorbitol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for 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

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

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.

Patients with renal impairment

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

Method of administration
Pegfilgrastim 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.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name 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 (see section 5.1). However, the long-term effects of pegfilgrastim have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

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

The safety and efficacy of pegfilgrastim have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML); therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

The safety and efficacy of 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.

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

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.

Pulmonary adverse reactions
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 hemoconcentration. 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).

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).

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 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.

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

Leukocytosis
White blood cell (WBC) counts of 100 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 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.

Pegfilgrastim contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, pegfilgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, 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 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 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 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). UDENYCA 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 UDENYCA 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

UDENYCA 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) 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 (uncommon). 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 in cancer patients undergoing chemotherapy following administration of G-CSFs; see section 4.4 and section "Description of selected adverse reactions" below.

Aortitis [rare frequency] (see section 4.4).

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 Acute Respiratory Distress Syndrome (ARDS), which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell 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 trials and spontaneous reporting. The adverse reactions are ranked under heading of frequency using 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) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Adverse reactions				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Blood and lymphatic system disorders		Thrombocytopenia[1] Leukocytosis[1]	Sickle cell crisis[2]; Splenomegaly[2]; Splenic rupture[2]		
Immune system disorders			Hypersensitivity reactions; Anaphylaxis		
Metabolism and nutrition disorders			Elevations in uric acid		
Nervous system disorders	Headache[1]				
Vascular disorders			Capillary leak syndrome[1]	Aortitis[2]	
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[2]	
Gastrointestinal disorders	Nausea[1]				
Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile dermatosis)[1,2]; Cutaneous vasculitis[1,2]	Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculo-skeletal pain, neck pain)			
Renal and urinary disorders			Glomerulonephritis[2]		
General disorders and administrative site conditions		Injection site pain[1] Non-cardiac chest pain	Injection site reactions[2]		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1]; Transient elevations in LFT's for ALT or AST[1]		

[1] See section "Description of selected adverse reactions" below.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults. The frequency category was estimated from a statistical calculation based upon 1,576 patients receiving pegfilgrastim in nine randomised clinical trials.

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

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

Injection site reactions, including injection site 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 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.

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 medicinal products or undergoing apheresis (see section 4.4).

Paediatric population
The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain (see section 5.1 and 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses of 300 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m^2 every 3 weeks for 4 cycles). Nine hundred and twenty eight patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p < 0.001$). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p < 0.001$; and 2% versus 10%, $p < 0.001$).

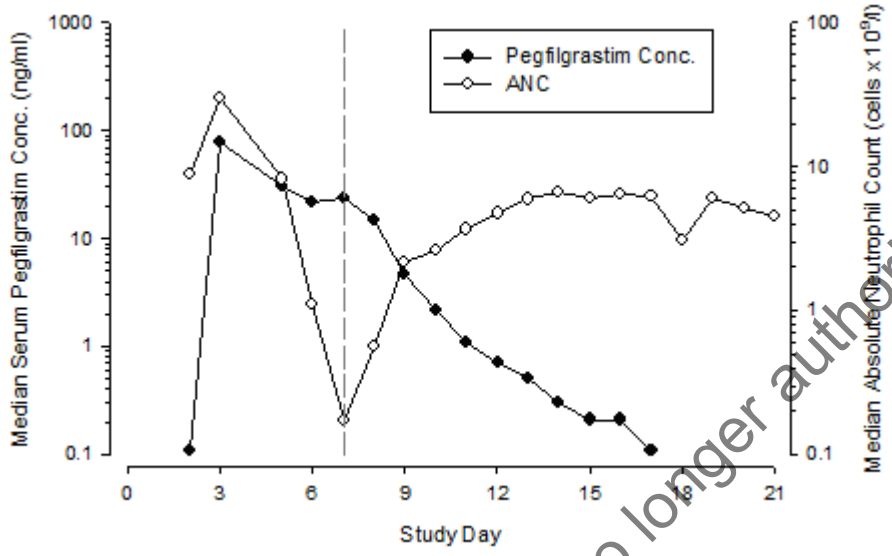
A small (n = 83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see section 4.4).

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

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

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 trihydrate (for pH adjustment)
Acetic acid (for pH adjustment)
Sorbitol (E420)
Polysorbate 20
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

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

UDENYCA may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. When left at room temperature for more than 72 hours it 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 pegfilgrastim.

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

6.5 Nature and contents of container

Pre-filled syringe, with a coated bromobutyl rubber stopper and a stainless steel needle with automatic needle guard.

Each pre-filled syringe contains 0.6 ml of solution for injection.

Pack size: Each carton contains 1 pre-filled syringe with an automatic needle guard blistered in a plastic tray.

6.6 Special precautions for disposal and other handling

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

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

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

7. MARKETING AUTHORISATION HOLDER

ERA Consulting GmbH
Lange Strasse 70
29664 Walsrode
Germany.
Tel: +49 (0) 5161 9890 0
Fax: +49 (0) 5161 9890 18
E-mail: EUAgent@eraconsulting.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1303/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2018

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

KBI Biopharma, Inc.
2500 Central Avenue
Boulder
Colorado
80301
UNITED STATES

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited
Block 7, City North Business Campus,
Stamullen Co. Meath, K32 YD60
Ireland

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**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

UDENYCA 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.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe (0.6 ml).

1 single-use pre-filled syringe with automatic needle guard.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid vigorous shaking.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ERA Consulting GmbH
Lange Strasse 70
29664 Walsrode
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1303/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

UDENYCA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier will be included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY LABEL

1. NAME OF THE MEDICINAL PRODUCT

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

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ERA Consulting GmbH
Lange Strasse 70
29664 Walsrode
Germany

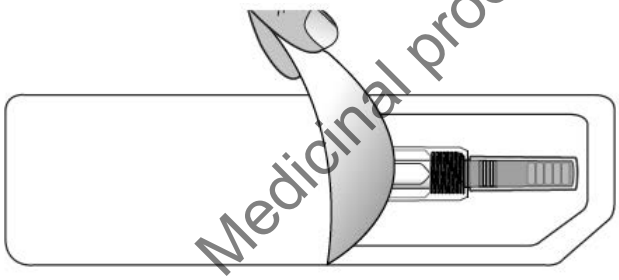
3. EXPIRY DATE

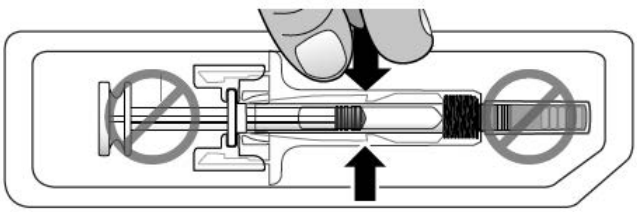
EXP

4. BATCH NUMBER

Lot

5. OTHER





MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

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

UDENYCA 6 mg
pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

ERA, GmbH - Germany

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

1. What UDENYCA is and what it is used for

UDENYCA contains the active substance pegfilgrastim. Pegfilgrastim is a protein produced by biotechnology in bacteria called *E. coli* followed by conjugation with polyethylene glycol (PEG) It belongs to a group of proteins called cytokines. The protein part is very similar to a natural protein produced by your own body.

The medicinal product is used to reduce the duration of low white blood cell count (neutropenia) and the occurrence of low white blood cell count with a fever (febrile neutropenia) 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 UDENYCA 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 UDENYCA

Do not use UDENYCA
- if you are allergic to pegfilgrastim, filgrastim, or any of the other ingredients of this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using UDENYCA 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 itchy skin
- experience a cough, fever and difficulty breathing. This can be a sign of Acute Respiratory Distress Syndrome (ARDS)
- 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 condition called "Capillary Leak Syndrome" which causes blood to leak from the small blood vessels into your body. See section 4.
- 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)
- 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)
- 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
- have sickle cell anaemia. Your doctor may monitor your condition more closely
- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing. These could be signs of a severe allergic reaction
- Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms

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

Severe skin reactions (Stevens-Johnson syndrome) have been reported with the use of UDENYCA. Stop using UDENYCA 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 UDENYCA, unless instructed by your doctor.

Loss of response to pegfilgrastim
If you experience a loss of response or decrease in 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 UDENYCA
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. UDENYCA has not been tested in pregnant women. It is important to tell your doctor if you:
- are pregnant
- think you may be pregnant
- are planning to have a baby

If you become pregnant during UDENYCA treatment, please inform your doctor.

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

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

UDENYCA contains sorbitol (E420) and sodium acetate
UDENYCA contains sorbitol (a type of sugar). Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.
This medicine contains less than 1 mmol (23 mg) sodium per 6 mg dose, that is to say essentially 'sodium-free'.

3. How to use UDENYCA

UDENYCA is for use in adults aged 18 and over.

Always take UDENYCA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

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

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

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

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

If you forget to inject UDENYCA
If you have forgotten a dose of UDENYCA, 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 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.
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- damage to the tiny filters inside your kidneys (glomerulonephritis)
- redness at the site of injection
- coughing up blood (haemoptysis)

Rare side effects (may affect up to 1 in 1,000 people)
- Inflammation of the 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 UDENYCA 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 UDENYCA

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

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

Store in a refrigerator (2°C – 8°C).

You may take UDENYCA out of the refrigerator and keep it at room temperature (not above 30°C) for no longer than 72 hours. Once a syringe has been removed from the refrigerator and has reached room temperature (not above 30°C) it must either be used within 72 hours or disposed of.

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

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

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

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

6. Contents of the pack and other information

What UDENYCA 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 acetic acid and sodium acetate (for pH adjustment), sorbitol (E420), polysorbate 20 and water for injections. See section 2.

What UDENYCA looks like and contents of the pack
UDENYCA 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 syringes are provided with an automatic needle guard.

Marketing Authorisation Holder

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Manufacturer

Millmount Healthcare Limited
Block 7, City North Business Campus,
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Ireland

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

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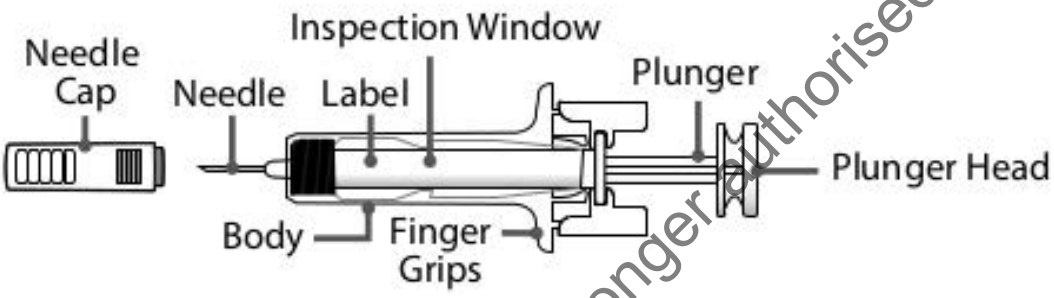
Instructions for use

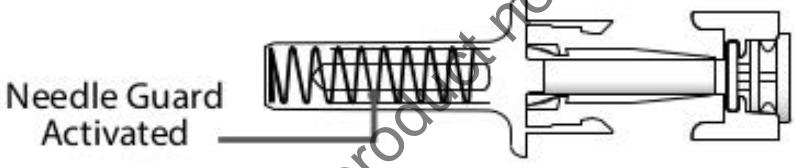
This section contains information on how to give yourself an injection of UDENYCA. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse or pharmacist. If you have questions about how to inject, please ask your doctor, nurse or pharmacist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

About this pre-filled syringe with automatic needle guard

- It is important that you read the instructions before using the syringe so you understand how to administer the injection.
- This medicine comes as a one-time use pre-filled safety syringe that contains a single dose. The syringe should be disposed of after giving the injection.
- The syringe has an automatic needle guard that covers the needle after administering the medicine and designed to prevent needle stick injury



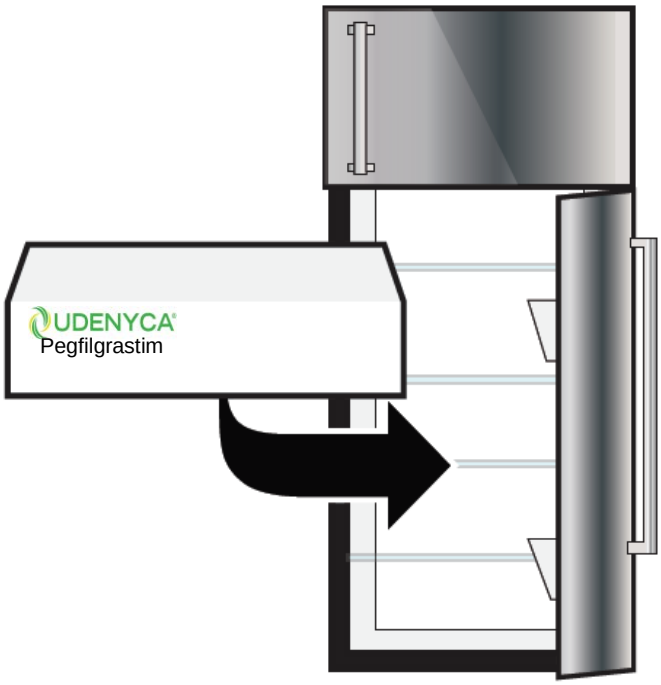
Before use



After use

Storage information

- Store the pre-filled syringes in the refrigerator between 2° to 8° C in its original carton.



DO NOT freeze or shake the pre-filled syringe. If frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

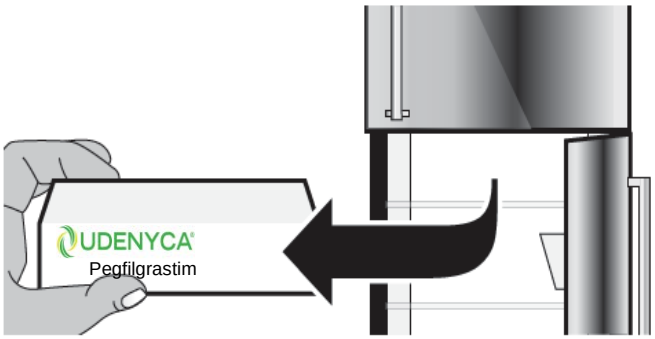
- Store the pre-filled syringe in its original carton to protect from light until you are ready to use it.

DO NOT use the pre-filled syringe if it has been left out at room temperature for more than 72 hours.
DO NOT shake the pre-filled syringe. If shaken vigorously, the solution may appear foamy and should not be used.
DO NOT use this medicine if you are:
- Allergic to pegfilgrastim or any of its ingredients.

Prepare the injection

1 Remove carton from refrigerator and check expiry date.

A: Remove the carton from the refrigerator and check the expiry date printed on the carton. (see Figure 1).
DO NOT use if the expiry date has passed. The expiry date refers to the last day of that month.



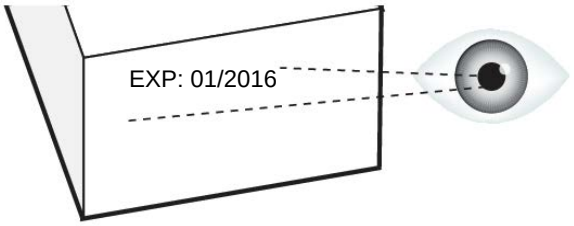


FIGURE 1

B: Open the carton and remove the sealed syringe tray (see Figure 2).

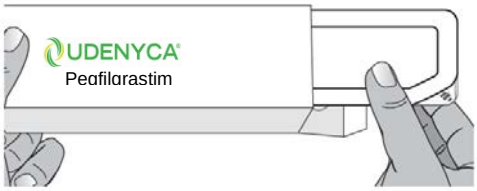


FIGURE 2

2 Allow medicine to reach room temperature and gather supplies.

A: Place the sealed syringe tray on a flat, clean surface and allow it to sit at room temperature for at least 30 minutes (see Figure 3).

FIGURE 3

DO NOT attempt to warm up the syringe in any other way, such as a microwave, hot water, or direct sunlight.

B: Gather the following supplies (see Figure 4).

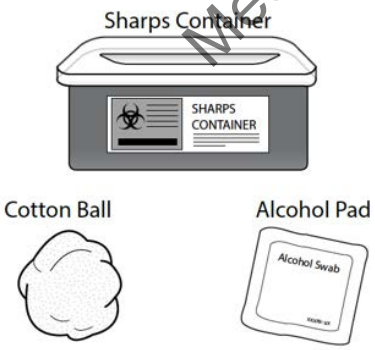


FIGURE 4

3 Wash your hands and remove syringe from tray.

A: Wash your hands with soap and warm water (see Figure 5).

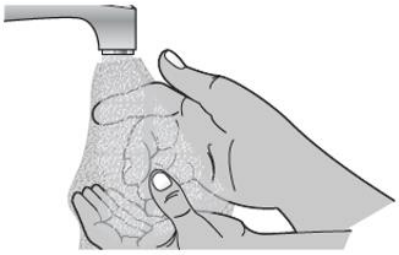


FIGURE 5

B: Remove the syringe from the sealed tray as follows: peel the cover off the tray, remove the syringe by grasping the middle of the syringe body (see Figure 6)
DO NOT handle the syringe by the plunger, plunger head, or needle cap.

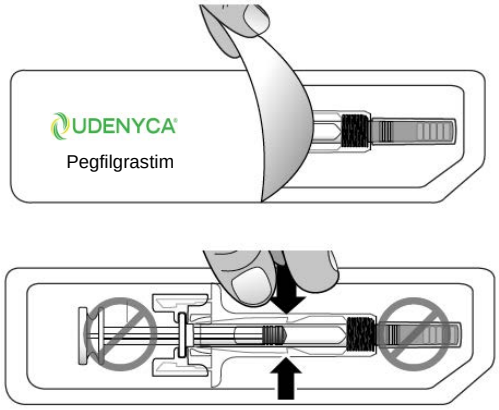


FIGURE 6

4 Inspect the syringe and solution.

Check the solution through the inspection window. The solution should be clear and colourless. It is normal to see one or more air bubbles in the syringe. Removal of the air is not needed (see Figure 7).

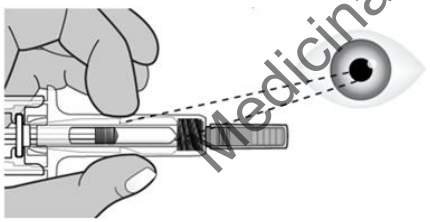


FIGURE 7

DO NOT use if the solution appears discoloured or cloudy.
DO NOT use if the solution contains lumps, flakes, or particles.
DO NOT use the syringe if it appears used or damaged.

<u>Select and clean the injection site</u>

5 Select the injection site.
The recommended injection sites for a subcutaneous injection are the:
- Abdomen (except for a two-inch area surrounding the navel)
- Thighs
- Back of Arms
- Buttocks

(see Figure 8)

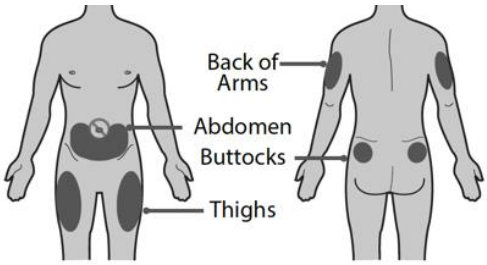


FIGURE 8

DO NOT inject into moles, scars, birthmarks, or areas where the skin is tender, bruised, red, or hard.

6 Clean the injection site.
Clean the injection site with an alcohol swab (see Figure 9).

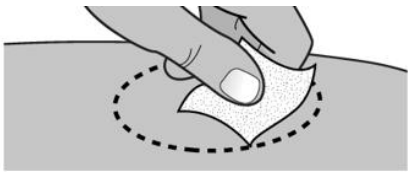


FIGURE 9

Inject the dose

7 Remove needle cap.
Pull the needle cap straight off (see Figure 10).

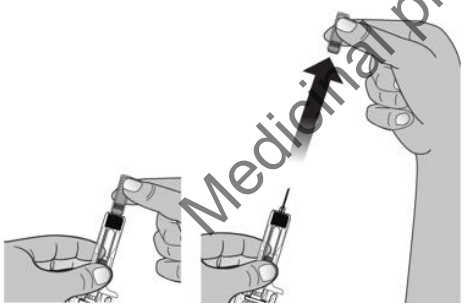


FIGURE 10

DO NOT recap the syringe.
DO NOT use the pre-filled syringe if it has been dropped with the needle cap removed.

8 Position fingers.
Grasp the body of the syringe like a dart (just under the finger grips) with your thumb and index fingers (see Figure 11).

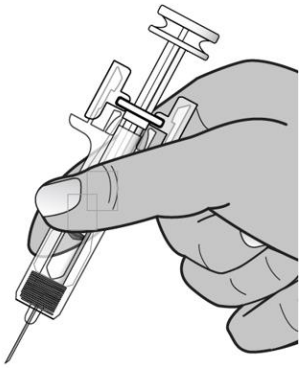


FIGURE 11

DO NOT touch the plunger or grasp the syringe above the finger grips.

9 Pinch the skin and insert the needle.

A: Use your free hand to gently pinch the skin around the injection site (see Figure 12).

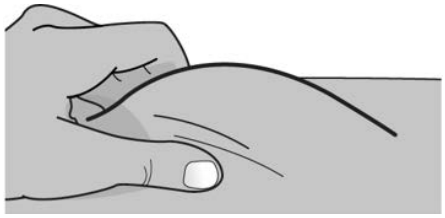


FIGURE 12

B: Insert the needle into the pinched area of the skin at a 45 to 90 degree angle (see Figure 13)

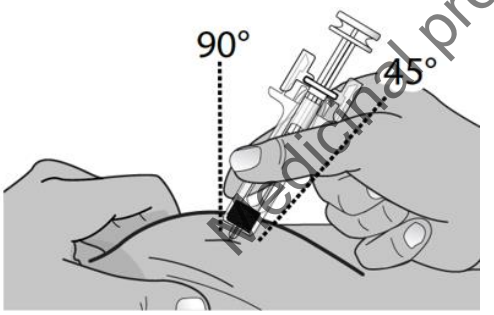


FIGURE 13

DO NOT touch the plunger head while inserting the needle into the skin.

C: After fully inserting the needle, release the pinched skin and use your free hand to stabilise the bottom of the syringe.
Then move your other hand into injection position with your thumb on the plunger head (see Figure 14).

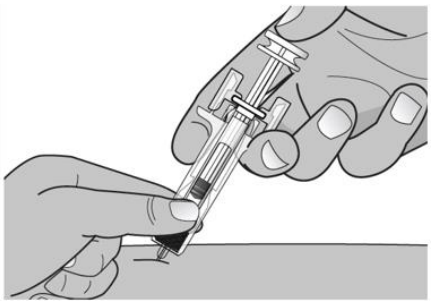


FIGURE 14

10 Push plunger head down to deliver dose.

A: Using your thumb, slowly and steadily push the plunger head down until it will go no further. This will ensure you have received the full dose (see Figure 15).

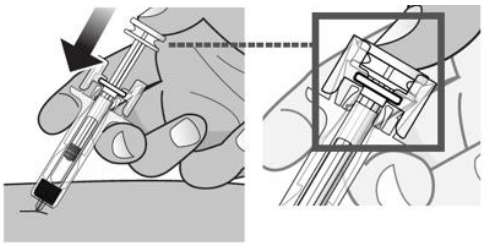


FIGURE 15

B: While the needle is still inserted, slowly move your thumb back, allowing the plunger to rise. This will retract the needle and secure it inside the syringe body. Then remove the syringe from the injection site (see Figure 16).

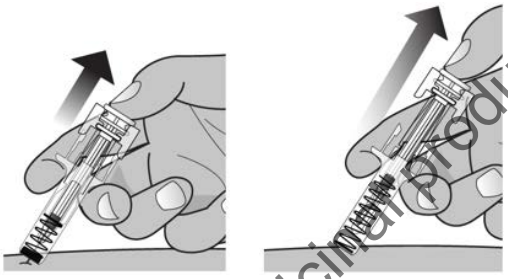


FIGURE 16

C: If you see drops of blood at the injection site, treat by pressing a cotton ball or gauze to the site as needed

11 Dispose of syringe and treat injection site.

Immediately after injecting, discard the used syringe into a sharps disposal container (see Figure 17).

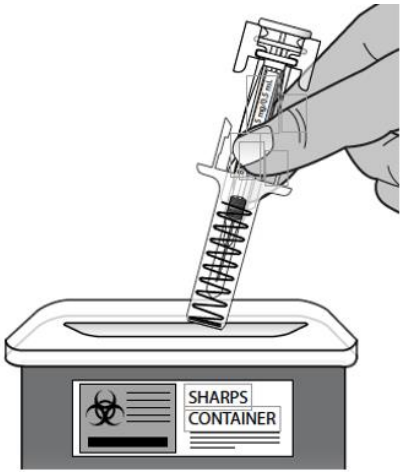


FIGURE 17

DO NOT throw away loose needles and syringes in your household waste.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for pegfilgrastim, the scientific conclusions of the CHMP are as follows:

Three reported cases show a causal relationship between the adverse drug reaction (ADR) Stevens-Johnson syndrome and pegfilgrastim. The number of cases is small, but because of the seriousness of the ADR, the PRAC recommends that the Product Information should be updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for pegfilgrastim the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing pegfilgrastim is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.