SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Grasustek 6 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).
** The concentration is 20 mg/ml if the PEG moiety is included.

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

Excipient(s) with known effect
Each pre-filled syringe contains 30 mg sorbitol (E 420) (see section 4.4).
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 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.

Special populations

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 dosing recommendations 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

Grasustek 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 ingredient or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Limited clinical data suggest a comparable effect on time to recovery from severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (AML) (see section 5.1). However, the long-term effects of pegfilgrastim have not been established in AML; therefore, it should be used with caution in this patient population.

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

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

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

The safety and efficacy of pegfilgrastim have not been investigated in patients receiving high-dose chemotherapy. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dose regimens.

Pulmonary adverse events

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see section 4.8).

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances, pegfilgrastim should be discontinued at the discretion of the doctor 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 discontinuation of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome

Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include the need for intensive care (see section 4.8).

Splenomegaly and splenic rupture

Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Thrombocytopenia and anaemia

Treatment with pegfilgrastim alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products which are known to cause severe thrombocytopenia.

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

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

Sickle cell anaemia

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

Leucocytosis

White blood cell (WBC) counts of 100×10^9/L or greater have been observed in less than 1 % of patients receiving pegfilgrastim. No adverse events directly attributable to this degree of leucocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicinal product. Consistent with the clinical effects and the potential for leucocytosis, a WBC count should be performed at

regular intervals during therapy. If leukocyte counts exceed 50×10^9/L after the expected nadir, this medicinal product should be discontinued immediately.

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring during initial or subsequent treatment have been reported in patients treated with pegfilgrastim. Pegfilgrastim should be permanently discontinued in patients with clinically significant hypersensitivity. Pegfilgrastim should not be administered 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 are generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after discontinuation of GCSF. See also section 4.8.

Other warnings

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

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.

Excipients

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 6 mg dose, i.e. it is 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 medicinal product 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 Grasustek 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 data on the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Grasustek 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 breast milk. Therefore a risk for new-borns/infants cannot be ruled out. A decision must be made whether to discontinue breast-feeding or to

discontinue/abstain from Grasustek therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area) (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythema, flushing, and hypotension occurred on initial or subsequent treatment with pegfilgrastim (uncommon [≥ 1/1,000 to < 1/100]). Serious allergic reactions, including anaphylaxis can occur in patients receiving pegfilgrastim (uncommon) (see section 4.4).

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of G-CSF; see section 4.4 and section "Description of selected adverse reactions" below.

Splenomegaly, generally asymptomatic, is uncommon.

Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim (see section 4.4).

Uncommon pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or ARDS, which may be fatal (see section 4.4).

Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients) (see section 4.4).

Tabulated list of adverse reactions

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

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)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Myelodysplastic syndrome[1] Acute myeloid leukaemia[1]		
Blood and lymphatic system disorders		Thrombocytopenia[1]; Leukocytosis[1]	Sickle cell anaemia with crisis[2]; Splenomegaly[2]; Splenic rupture[2]		
Immune system Disorders			Hypersensitivity reactions; Anaphylaxis		
Metabolism and nutrition disorders			Elevations in uric acid		
Nervous system Disorders	Headache[1]				
Vascular Disorders			Capillary leak syndrome[1]	Aortitis	
Respiratory, thoracic and mediastinal disorders			Acute Respiratory Distress Syndrome[2]; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis) Haemoptysis	Pulmonary haemorrhage	
Gastrointestinal disorders	Nausea[1]				

Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile neutrophilic dermatosis)[1,2]; Cutaneous Vasculitis[1,2]	Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain)			
Renal and urinary disorders			Glomerulonephritis[2]		
General disorders and administration site conditions		Injection site pain[1] Non-cardiac chest pain	Injection site Reactions[2]		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1]; Transient elevations in LFTs for ALT or AST[1]		

[1] See section "Description of selected adverse reactions" below.
[2] This adverse reaction was identified through post-marketing surveillance of pegfilgrastim 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 erythema (uncommon) as well as injection-site pain (common events) have occurred during initial or subsequent treatment with pegfilgrastim.

Common cases of leucocytosis (White Blood Count [WBC] > 100×10^9/l) have been reported (see section 4.4).

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were uncommon; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving pegfilgrastim following cytotoxic chemotherapy.

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

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

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

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post marketing setting with G-CSF use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medicinal products or undergoing apheresis (see section 4.4).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 factors; ATC Code: L03AA13.

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

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similar to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

In two randomised, double-blind, pivotal studies in patients with high risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to7 days, and a 30-40 % incidence of febrile neutropenia. In one study (n = 157), which used a 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 intravenous 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 %, $p < 0.001$).

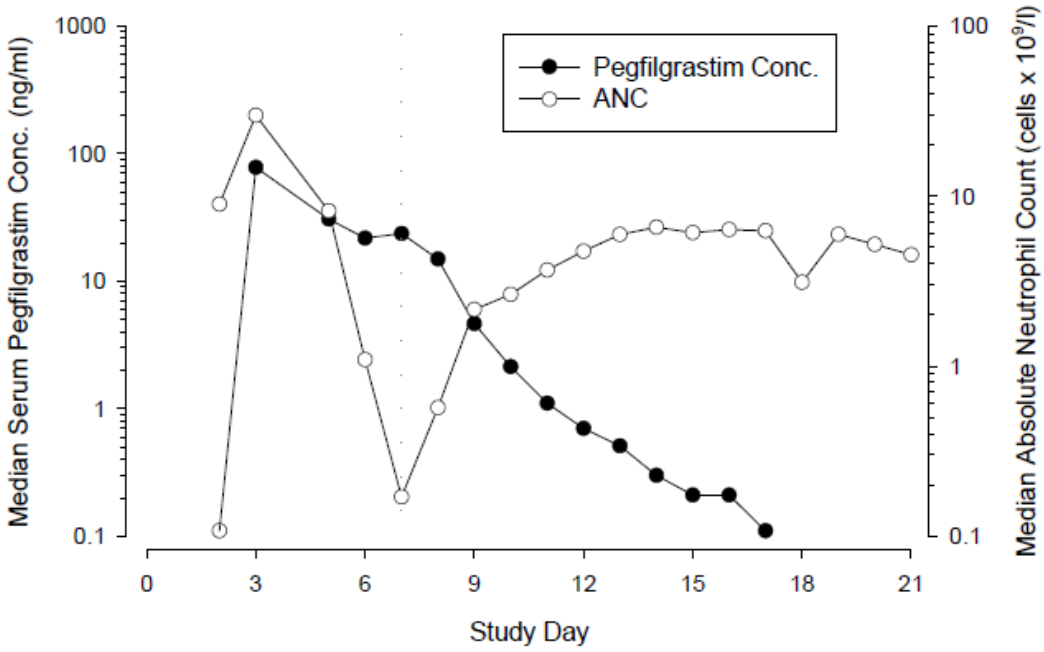
A small (n = 83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 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 years (8.9 days) compared to older children aged 6-11 years and 12-21 years (6 days and 3.7 days, respectively) and adults. Additionally, a higher incidence of febrile neutropenia was observed in younger children aged 0-5 years (75 %) compared to older children aged 6-11 years and 12-21 years (70 % and 33 %, respectively) and adults (see sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see figure 1).

Figure 1. Profile of median pegfilgrastim serum concentration and absolute neutrophil count (ANC) in chemotherapy treated patients after a single 6 mg injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n = 31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Elderly

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

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

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

6.5 Nature and contents of container

Pre-filled syringe (Type I glass), with a (butyl) rubber stopper and a stainless-steel needle with automatic needle guard. The needle has flexible, rigid needle shield.

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

Pack size of one pre-filled syringe with automatic needle guard (0.6 ml) and supplied in a dispensing pack containing one syringe.

6.6. Special precautions for disposal

Before administration, Grasustek solution should be visually inspected 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 for manual administration to come to room temperature for 30 minutes before using the syringe.

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

7 MARKETING AUTHORISATION HOLDER

USV UK Limited
Regus Woburn Place
16 Upper Woburn Place Euston
London WC1H0AF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 32870/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

17/05/2024