

## 1. NAME OF THE MEDICINAL PRODUCT

Pelgraz 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 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.

### Excipients with known effect

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

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

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

### Special populations

Paediatric population

The safety and efficacy of Pelgraz in children and adolescents has not yet been established.

Patients with renal impairment

No dose change is recommended in patients with renal impairment.

#### Method of administration

Pelgraz is for subcutaneous use. The injections should be given subcutaneously into the thigh, abdomen or upper arm.

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

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Traceability

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

#### Acute myeloid leukaemia (AML)

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

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

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

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

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

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

#### Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

#### Capillary leak syndrome

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

#### Splenomegaly and splenic rupture

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

#### Thrombocytopenia and anaemia

Treatment with pegfilgrastim alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic medicinal products 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 medicinal product with splenic enlargement and vaso-occlusive crisis.

#### Leukocytosis

White blood cell (WBC) counts of  $100 \times 10^9/L$  or greater have been observed in less than 1% of patients receiving pegfilgrastim. No adverse reactions directly attributable to this degree of leukocytosis have been reported. Such elevation in WBCs is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicinal product. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed  $50 \times 10^9/L$  after the expected nadir, this medicinal product should be discontinued immediately.

#### Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with pegfilgrastim. Permanently discontinue pegfilgrastim in patients

with clinically significant hypersensitivity. Do not administer pegfilgrastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

### Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

### Aortitis

Aortitis has been reported after filgrastim or pegfilgrastim 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 WBC count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of filgrastim or pegfilgrastim. See also section 4.8.

### Mobilisation of PBPC

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

### Other special precautions

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 with known effect

This medicinal product contains 50 mg sorbitol in each unit volume, which is equivalent to 30 mg per 6 mg dose.

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

### All patients

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

## **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 Pelgraz with any chemotherapeutic 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 Pelgraz 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). Pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

##### Breast-feeding

There is insufficient information on the excretion of pegfilgrastim/metabolites in human milk, a risk to the newborns/infants cannot be excluded. Pegfilgrastim should not be administered to women who are breast-feeding.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

##### Summary of the safety profile

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

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

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

Splenomegaly, generally asymptomatic, is uncommon.

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

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

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

Tabulated 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 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)
<b>Blood and lymphatic system disorders</b>		Thrombocytopenia <sup>a1</sup> Leukocytosis <sup>1</sup>	Sickle cell crisis <sup>2</sup> ; Splenomegaly <sup>2</sup> ; Splenic rupture <sup>2</sup>		
<b>Immune system disorders</b>			Hypersensitivity reactions; Anaphylaxis		
<b>Metabolism and nutrition disorders</b>			Elevations in uric acid		
<b>Nervous system disorders</b>	Headache <sup>1</sup>				
<b>Vascular disorders</b>			Capillary leak syndrome <sup>1</sup>	Aortitis	
<b>Respiratory, thoracic and mediastinal disorders</b>			Adult Respiratory Distress Syndrome <sup>2</sup> ; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis) Haemoptysis	Pulmonary haemorrhage	
<b>Gastrointestinal disorders</b>	Nausea <sup>1</sup>				
<b>Skin and subcutaneous tissue disorders</b>			Sweet's syndrome (acute febrile dermatosis) <sup>1,2</sup> Cutaneous vasculitis <sup>1,2</sup>		

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)
<b>Musculoskeletal and connective tissue disorders</b>	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain)			
<b>Renal and urinary disorders</b>			Glomerulonephritis <sup>2</sup>		
<b>General disorders and administrative site conditions</b>		Injection site pain <sup>1</sup> Non-cardiac chest pain	Injection site reactions <sup>2</sup>		
<b>Investigations</b>			Elevations in lactate dehydrogenase and alkaline phosphatase <sup>1</sup> ; Transient elevations in LFTs for ALT or AST <sup>1</sup>		

<sup>1</sup> See section “Description of selected adverse reactions” below.

<sup>2</sup> 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 erythema (uncommon) as well as injection site pain (common events) have occurred on initial or subsequent treatment with pegfilgrastim.

Common cases of leukocytosis (WBC > 100 x 10<sup>9</sup>/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.

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post-marketing setting with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy 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.

### **4.9 Overdose**

Single doses of 300 mcg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse reactions 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

Pelgraz is a biosimilar medicinal product.

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 PEG molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

In two randomised, double-blind, pivotal studies in patients with high-risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to 7 days, and a 30-40% incidence of febrile neutropenia. In one study (n = 157), which used a 6 mg fixed dose of pegfilgrastim the mean duration

of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference 7%, 95% CI of -19%, 5%). In a second study (n = 310), which used a weight-adjusted dose (100 mcg/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%, -1.1%).

In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m<sup>2</sup> 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* AML 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 randomized, active-controlled, assessor-blind, comparative, phase III study, clinical efficacy and safety of Pelgraz, US-Neulasta<sup>®</sup> and EU-Neulasta<sup>®</sup> was evaluated in patients with early breast cancer and receiving TAC (docetaxel, doxorubicin, and cyclophosphamide) anticancer chemotherapy in an adjuvant setting. A total of 589 patients were randomized and administered Pelgraz (n=294), US-Neulasta<sup>®</sup> (n=148) or EU-Neulasta<sup>®</sup> (n=147) in 2:1:1 ratio, as a single subcutaneous injection of 6 mg once every 3 weeks for up to 6 cycles. The primary objective was to demonstrate an equivalent efficacy of Pelgraz as compared to each of US-Neulasta<sup>®</sup> and EU-Neulasta<sup>®</sup>. The primary efficacy endpoint was duration of severe neutropenia (DSN) in cycle 1. Severe neutropenia was defined as occurrence of ANC below  $0.5 \times 10^9/L$ . Equivalence was demonstrated if 2-sided 95% confidence interval (CI) for the difference (Pelgraz minus Neulasta<sup>®</sup>) of DSN in Cycle 1 lie within equivalence range of -0.5 to +0.5 day. The conclusion of equivalence for the primary endpoint was based on the analysis of the FAS-As Randomized (all patients who were randomized, received at least one dose of active treatment and who had any follow-up data for the primary target variable). The analysis of per-protocol (PP) population (excluding patients with protocol deviations with impact on the integrity of the primary endpoint data and the safety/well-being in cycle 1) was a confirmatory analysis for the primary endpoint. The FAS-As randomized included 589 patients – 294 in Pelgraz, 148 in US-Neulasta<sup>®</sup> and 147 in EU-Neulasta<sup>®</sup> group. The PP (cycle 1) population included 543 patients - 275 in Pelgraz, 133 in US-Neulasta<sup>®</sup> and 135 in EU-Neulasta<sup>®</sup> group. Secondary efficacy endpoints included the assessment of the frequency of Grade 3 and Grade 4 severe neutropenia, the rate of febrile neutropenia, characteristics of the ANC-time profile in cycle 1 (nadir, time to nadir, time until recovery etc.), frequency and type of (culture-confirmed) infections, incidence of intravenous antibiotic therapy and hospitalization, mobilization of CD34+ cells (in selected centers only), incidence of bone pain, and occurrence and/or resolution of chemotherapy-induced mucositis, need for TAC dose-reduction, and delays in TAC administration.

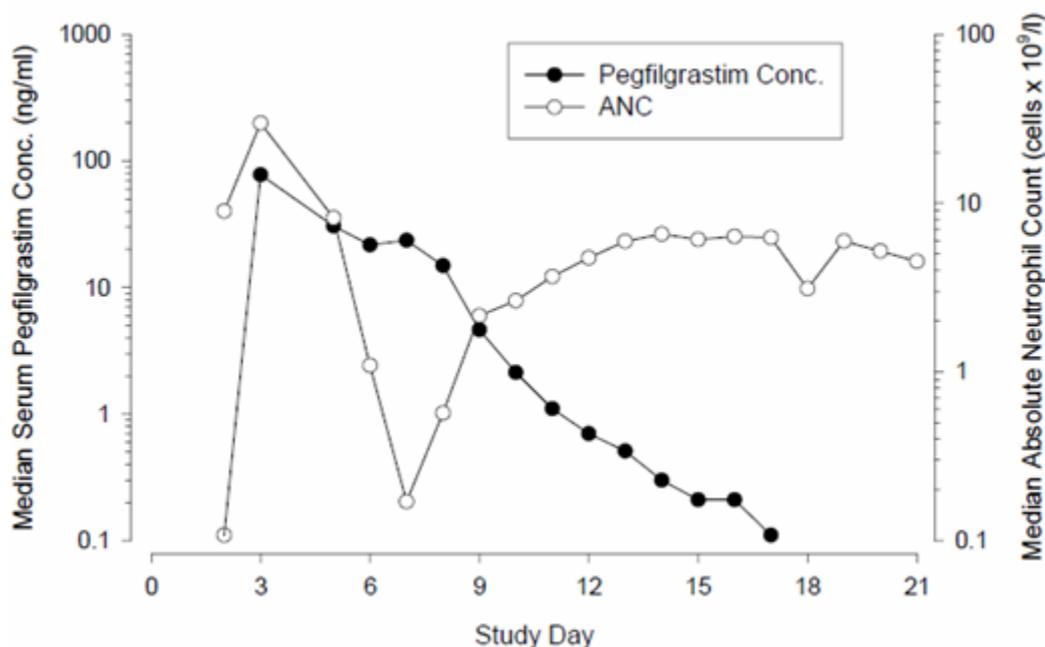
The mean (SD) DSN in cycle 1 was 1.6 (1.48) days for Pelgraz, 1.4 (1.17) days for US-Neulasta<sup>®</sup> and 1.6 (1.34) days for EU-Neulasta<sup>®</sup> groups. The 95% CI for the least square mean difference for DSN in cycle 1 was -0.03 to +0.51 day for comparison between Pelgraz and US-Neulasta<sup>®</sup>, and -0.25 to +0.30 day for comparison between Pelgraz and EU-Neulasta<sup>®</sup>. These results were confirmed by analysis of PP population: 95% CI for the least square mean difference for DSN in cycle 1 was -0.07 to +0.46 day for comparison between Pelgraz and US-Neulasta<sup>®</sup>, and -0.32 to +0.20 day for comparison between Pelgraz and EU-Neulasta<sup>®</sup>. The results of secondary endpoints confirmed similarity in clinical efficacy of Pelgraz, US-Neulasta<sup>®</sup> and EU-Neulasta<sup>®</sup>.

## 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.

### Elderly

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

## 5.3 Preclinical safety

### 5.3.1 Carcinogenicity

Certain malignant cells have been shown to express granulocyte-colony stimulating factor (G-CSF) receptors. The possibility that pegfilgrastim can act as a growth factor for any tumour type cannot be excluded.

The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies.

In a toxicity study of 6 month duration in rats given once weekly subcutaneous injections of up to 1,000

µg/kg of pegfilgrastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

### **5.3.2 Mutagenicity**

Mutagenesis studies have not been conducted.

### **5.3.3 Teratogenicity**

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 low subcutaneous doses. In rat studies, it was shown that pegfilgrastim may cross the placenta. The relevance of these findings for humans is not known.

### **5.3.4 Other**

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.

## **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 Interchangeability**

Biosimilarity of Pelgraz has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Pelgraz has been developed as a biosimilar product to a reference product named Neulastim. Biosimilar product is similar but not identical to the reference product. It is recommended to consult with healthcare practitioner on the risk of substitution of reference product with biosimilar product.

If a physician wishes to change a patient's treatment to a biosimilar, careful monitoring of clinical response of the individual patient is advised.

### **6.4 Shelf life**

3 years.

### **6.5 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

Pelgraz may be exposed to room temperature (Not above 30 °C) for a maximum single period of up

to 72 hours. Pelgraz 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 Pelgraz.

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

## **6.6 Nature and contents of container**

Pre-filled syringe (type I glass) with a permanently attached stainless steel injection needle, with a needle safety guard.

The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4).

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

## **6.7 Special precautions for disposal and other handling**

Before use, Pelgraz 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.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. The plunger should be slowly and evenly depressed until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, the syringe should be removed from the injection site. The needle safety guard will cover the needle when releasing the plunger.

Disposal

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

## **7. NAME AND ADDRESS OF PRODUCT REGISTRANT**

Accord Healthcare Private Limited  
6 Shenton Way, OUE Downtown #38-01  
Singapore, 068809

## **8. NAME AND ADDRESS OF MANUFACTURER**

### **Manufactured by:**

Intas Pharmaceuticals Ltd. Biopharma Division  
Plot No. 423 / P / A, Sarkhej Bavla Highway  
Village – Moraiya, Taluka – Sanand  
District. Ahmedabad –  
382213 Gujarat  
INDIA