

**EU Risk Management Plan for
Grasustek 6 mg solution for injection in pre-filled syringe
(Pegfilgrastim)**

RMP version to be assessed as part of this application:

RMP Version number	3.1
Data lock point for this RMP	31 Dec 2025
Date of final sign off	12-Aug-2026

Note:

- 1. In clinical/non-clinical study data, the product brand name/ name of finished product/ name of study treatment has been mentioned as "USV Pegfilgrastim" instead of "Grasustek" to be in-line the product brand name with the finalized protocols/clinical study reports.
- 2. Throughout the RMP, "USV Pegfilgrastim" to be referred as "Grasustek".

Rationale for submitting an updated RMP: Request in supplementary information” (RfSI) from EMA

Summary of significant changes in this RMP:

- Part II module SVII.1.1 and SVII.1.2: Restored all information of initially approved RMP (version 1.2, dated 29Jan2019), as GVP module V rev. 2 states that this section is expected to be “locked” and not change after the approval of the initial RMP.
- Annex 7: Updated references

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version	Procedure	Date of approval
2.0	EMA/H/C/004556/0000 (MA. No. EU/1/19/1375/001)	16 Aug 2023

QPPV name: Dr. Nicole Niemeier-Siegl

QPPV signature:

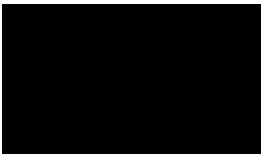


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Part I: Product(s) Overview

Table 1: Product overview

Active substance(s) (INN or common name)	Pegfilgrastim
Pharmacotherapeutic group(s)(ATC Code)	Immunostimulants, Pegylated form of the Recombinant Human Granulocyte Colony Stimulating Factor (L03AA13)
Marketing Authorisation Holder	Juta Pharma GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Grasustek 6 mg solution for injection in pre-filled syringe
Marketing authorisation procedure	EMA/H/C/004556/0000 (MA. No. EU/1/19/1375/001)
Brief description of the product	Chemical class: Hematopoietic Agents (immunostimulants, colony stimulating factor) Summary of mode of action: Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly, to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, in vitro and similar effects may be seen on some non-myeloid cells in vitro. <u>Important information about its composition</u> 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. <i>Excipient(s) with known effect:</i> Each pre-filled syringe contains 30 mg sorbitol (E 420)
Hyperlink to the PI	Refer Module 1.3.1 for SmPC and PIL.

Indication(s) in the EEA	Current 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).
Dosage in the EEA	Current Pegfilgrastim therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. <u>Posology</u> 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. <u>Method of administration</u> Pegfilgrastim is injected subcutaneously. The injections should be administered into the thigh, abdomen, or upper arm.
Pharmaceutical form(s) and strengths	Solution for injection 6 mg
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Part II: Module SII - Non-clinical part of the safety specification

Table 2: Non-clinical studies of Grasustek

Key Safety findings (from non- clinical studies)	Relevance to human usage
<u><i>In vivo comparative studies in neutropenic and non-neutropenic rats</i></u> In vivo comparative studies in neutropenic and non-neutropenic rats were performed to compare the pharmacokinetic / pharmacodynamic (PK / PD) profile of Grasustek and reference product. The results demonstrated that the PK / PD profile of Grasustek was comparable to the reference product.	Preclinical data revealed no special hazard likely for humans.
<u><i>A comparative 4-week sub-chronic toxicity study by repeated subcutaneous administration once weekly to CD rats</i></u> A comparative 4-week sub-chronic toxicity study by repeated subcutaneous administration once weekly to CD rats, using reference product, showed a consistent toxicological and immunological profile of Grasustek and reference product.	Preclinical data revealed no special hazard likely for humans.

Key Safety findings (from non- clinical studies)	Relevance to human usage
<u>The local tolerance study in rabbits was conducted by five routes (intraarterial, intramuscular, intravenous, paravenous and subcutaneous administration)</u> The local tolerance study in rabbits was conducted by five routes (intraarterial, intramuscular, intravenous, paravenous and subcutaneous administration) of administration to evaluate the local reactions following administration of Grasustek. Grasustek was well tolerated by all five routes of administration.	Preclinical data revealed no special hazard likely for humans.

Part II: Module SIII - Clinical trial exposure

Table 3: Clinical studies of Grasustek

Clinical Study Design	Study treatment	Comment
Phase I (PEGF/USV/P1/001) A randomised, double-blind, two treatment, two period, two sequence crossover phase I study to compare PK and PD of single SC injection of Grasustek and Neulasta® in healthy male and female subjects'	Reference product: Neulasta® EU, administered as a single 6 mg SC injection (Batch numbers 1028972A and 1029467C) Test product: Grasustek, administered as a single 6 mg SC injection (Batch number DS12010) There was washout period of at least 28 days between period 1 and period 2.	Study status: Completed Of the total 156 healthy male and female subjects, 71 subjects had completed the study in each sequence. Safety Conclusion: The incidence and frequency of AEs, either overall or IMP-related, was comparable between treatments (Grasustek and Neulasta®). Back pain and headache were the most frequent AEs reported during the study followed by extremity pain and musculoskeletal pain, followed by arthralgia, neck pain, musculoskeletal pain, upper respiratory tract infection, nausea, abdominal pain, increased alanine aminotransferase all of which are commonly reported ARs for pegfilgrastim. The majority of AEs recorded during the study were considered mild in severity; no difference between treatments was noted in the incidence of moderately severe adverse events reported (13.3% and 15.4% of subjects after dosing with Grasustek and Neulasta®, respectively).

Clinical Study Design	Study treatment	Comment
Phase I (PEGF/USV/P1/003) (EudraCT No: 2016-003157-15) A Randomised, Double-Blind, Two-Treatment, Two-Period, Two-Sequence, Crossover Study to Compare the Pharmacodynamics and Pharmacokinetics of a Single Subcutaneous Injection of 2 mg of Grasustek and 2 mg Neulasta® (EU Approved) in Healthy Male Subjects	<u>Test product:</u> Grasustek 0.2 mL Solution for Subcutaneous Injection (10 mg/mL); to give a single dose of 2 mg <u>Reference product:</u> EU-approved Neulasta® 0.2 mL Solution for Subcutaneous Injection (10 mg/mL); to give a single dose of 2 mg	Study site: United Kingdom Study status: Completed Number of Subjects: Planned: 64; Randomised: 64 (32 subjects each to Sequence AB and BA); Dosed: 64; Completed: 60; Withdrawn: 4. All 64 subjects were included in the safety, PD and PK populations, and 60 subjects were included in the PD and PK analysis datasets. <u>Safety Conclusion:</u> Single 2 mg SC doses of USV Pegfilgrastim and Neulasta® were well tolerated under the conditions of the study, and there were no notable differences in safety results between treatments. The incidence of AEs, both overall and IMP-related, was similar between treatments. Back pain and headache were the most frequently reported IMP-related AEs. There were no safety concerns related to vital signs, ECGs, or sonographic spleen examination findings for either treatment.
Phase III (PEGF/USV/P3/001) A Phase III, Randomized, Multicentric, Open-label, Equivalence Design Study to Compare the Safety and Efficacy of Grasustek and Neulasta® in Patients Receiving Doxorubicin and Docetaxel as a Combination Chemotherapy for Breast Cancer	<u>Test product:</u> Grasustek (6 mg) by s.c. injection: 60 subjects <u>Reference product:</u> EU-approved Neulasta® (6 mg) by s.c. injection: 60 subjects.	Study site: India Study status: Completed Number of subjects enrolled: 120 Number of subjects completed: 94 All the 120 subjects randomized received at least one dose of either USV Pegfilgrastim or Neulasta®. Efficacy and safety conclusions: Primary Endpoint: Duration of Severe Neutropenia (DSN) during first chemotherapy cycle, defined as the number of days with grade 4 neutropenia with an ANC <0.5x10⁹/L [<500/mm³]. DSN was found to be 0.793 (0.987) day and 1.254 (1.469) days in the USV Pegfilgrastim and Neulasta® groups respectively. The difference in mean DSN in cycle 1 was -0.461 days. DSN ranged from 0 to 3 days in the USV Pegfilgrastim and from 0 to 6 days in Neulasta® group in cycle 1.

Clinical Study Design	Study treatment	Comment
Phase III (PEGF/USV/P3/003) A Randomised, Multi-Centre, Assessor-Blinded, Active-Controlled, Parallel-Group, Equivalence Phase III Study Comparing the Safety and Efficacy of Grasustek and Neulasta® in Breast Cancer Patients Undergoing Myelo-suppressive Chemotherapy	<u>Test product:</u> Grasustek (6 mg) by s.c. injection: 170 subjects <u>Reference product:</u> EU-licensed Neulasta® (6 mg) by s.c. injection: 85 subjects	Study site: European Region Study status: Completed Number of Subjects: Planned enrolment: 255 Actual enrolment: 254 A total of 254 chemotherapy-naïve female subjects suffering from breast cancer were randomized in a ratio of 2:1 to receive one of the two treatments: • USV Pegfilgrastim (test treatment): 172 subjects • EU-licensed Neulasta® (active control treatment): 82 subjects. However, 6 subjects were not dosed and therefore the full analysis set (FAS) included 248 subjects (166 in USV Pegfilgrastim and 82 in Neulasta®). <u>Efficacy and safety Conclusions:</u> In conclusion, the data based on the primary and the secondary efficacy endpoints, demonstrate the equivalence of efficacy USV Pegfilgrastim and EU-licensed Neulasta® in a clinical setting. Secondly, USV Pegfilgrastim demonstrated a safety profile similar to EU-licensed Neulasta®. Importantly, no new AEs were observed compared with the known AE profile for EU-licensed Neulasta®. No SUSARs were reported. The immunogenicity findings confirmed the low immunogenic potential of USV Pegfilgrastim and support the biosimilarity of USV Pegfilgrastim and EU-licensed Neulasta®. The totality of the efficacy and safety results support the biosimilarity and as such the lack of clinically meaningful differences between USV Pegfilgrastim and EU-licensed Neulasta®.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 4: Exclusion criteria in Grasustek studies

Exclusion criteria	Missing information	Rational for being an exclusion criteria (if not missing information)
Subjects with distant metastasis	No	This condition could potentially interfere with the aim of the study
Subjects with severe chronic neutropenia (congenital, cyclic, or idiopathic)	No	This condition could potentially interfere with the aim of the study
History of chronic myeloid leukaemia or myelodysplastic syndrome	No	This condition could potentially interfere with the aim of the study
History of sickle cell disease	No	This condition could potentially interfere with the aim of the study
Subjects with active infections [including positive serology for human immunodeficiency virus (HIV) and active hepatitis B and C infection]. Subjects with infections bacterial or fungal not controlled by antibiotic therapy; or history of uncontrolled seizures, or diabetes, or central nervous system disorders should be excluded as per the clinical judgment of the investigator precluding informed consent	No	This condition could potentially interfere with the aim of the study
Previous or concurrent malignancy except non-invasive skin cancer (excluding melanoma), in situ carcinoma of the cervix, or other solid tumour treated with curative intent with no recurrence within two years prior to study entry	No	This condition could potentially interfere with the aim of the study
Hormonal therapy (e.g., tamoxifen or aromatase inhibitors), immunotherapy and monoclonal antibodies or biological therapy concurrent or within 30 days of screening	No	This condition could potentially interfere with the aim of the study
Significant neurologic or psychiatric disorders that would prohibit the understanding and giving of the informed consent	No	This condition could potentially interfere with the aim of the study
Previous therapy with any recombinant human granulocyte colony stimulating factor (rhG-CSF) product, Lipegfilgrastim, or Pegfilgrastim preparation	No	This condition could potentially interfere with the aim of the study
Concurrent radiotherapy	No	This condition could potentially interfere with the aim of the study
Clinically significant cardiac dysfunction at the time of screening, history of myocardial infarction, heart failure, uncontrolled hypertension, severe valvular heart disease, unstable angina pectoris, pericardial disease, electrocardiographic evidence of acute ischemic changes or unstable arrhythmia within six months preceding the first treatment cycle	No	This condition could potentially interfere with the aim of the study
History of pulmonary infiltrates or pneumonia within two years of study entry	No	This condition could potentially interfere with the aim of the study

Exclusion criteria	Missing information	Rational for being an exclusion criteria (if not missing information)
Known hypersensitivity to any of the chemotherapy drugs used in TAC regime or <i>E. coli</i> proteins or any of the excipients used in the IMP	No	This condition could potentially interfere with the aim of the study
Major organ allograft or condition requiring chronic immunosuppression (i.e., kidney, liver, lung, heart, bone marrow transplant, or autoimmune diseases). Subjects who received corneal transplants or cadaver skin or bone transplants are eligible	No	This condition could potentially interfere with the aim of the study
Peripheral neuropathy > Grade 1	No	This condition could potentially interfere with the aim of the study
Ongoing drug abuse or alcohol addiction and/or chronic alcoholism	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Participation in any other clinical study using an IMP within three months prior to the screening visit	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Pregnancy or breast feeding	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Any condition that by consideration of the investigators might affect the safety of the subject or interfere with the efficacy assessments of this study	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Participation in any other clinical study using an IMP within three months prior to the screening visit	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Ongoing drug abuse or alcohol addiction or chronic alcoholism	No	Standard exclusion criteria followed under the requirements of GCP for the conduct of any clinical trials in humans
Female (in Study PEGF/USV/P1/003) and Male (in Study PEGF/USV/P3/003)	No	This condition could potentially interfere with the aim/objective of the study

Exclusion criteria	Missing information	Rational for being an exclusion criteria (if not missing information)
Absolute Neutrophil Count (ANC) outside the reference range of 2.0-7.5 x10 ⁹ /L and platelet count outside the limits of the reference range of 150-400 x10 ⁹ /L at screening and Treatment Period 1. Marginal abnormalities may have been acceptable if deemed clinically insignificant as judged by the investigator for Treatment Period 2.	No	This condition could potentially interfere with the aim of the study
Palpable splenic enlargement or splenic enlargement on ultrasound judged as clinically relevant by the investigator	No	This condition could potentially interfere with the aim of the study

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table 5: Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Risk associated with the drug exposure in paediatric population (having age less than 18 years) is not known since patients with less than 18 years of age were not enrolled.	The safety and effectiveness of pegfilgrastim in paediatric patients have not been established in clinical trials.	None, as the indication includes adult patients only.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 6: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: - Patients with hepatic impairment - Patients with renal impairment - Patients with cardiovascular impairment - Immunocompromised patients - Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Post-authorisation exposure is calculated based on the sales volume since marketing authorisation on 20 June 2019 until 31 Dec 2025. The defined daily dose (DDD) provided by the WHO collaborating Centre for Drug Statistics, 0.3 mg. Strength of dose: 6mg

Total cumulative unit sold till the 31Dec 2025 = is 246409 units.

DDD= 0.3mg

Patient exposure per year = total unit sold*strength of dose/ DDD * total days in year

Patient exposure per year: 246409*6/03*365= 13502 patients years.

Cumulative sales indicate a total of 13502 patient years.

All patients have been exposed in the European Union.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

SVI.2 Potential for transmission of infectious agents

There is no potential for transmission of infectious agents via manufacturing of Grasustek.

SVI.3 Potential for immunogenicity

There is a potential for immunogenicity, as with all therapeutic proteins. Rate 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. The safety and efficacy of pegfilgrastim for the mobilization 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.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, frequency: uncommon ($\geq 1/1000$ to $< 1/100$). These are listed event in Summary of Product Characteristic (SmPC) section 4.8.
- Reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, frequency: uncommon ($\geq 1/1000$ to $< 1/100$). This is a listed event in SmPC section 4.8.
- Reversible, mild to moderate nausea and headaches; frequency: very common ($\geq 1/10$). These are listed event in SmPC section 4.8.
- Reversible, mild to moderate bone pain (very common [$\geq 1/10$]) and musculoskeletal pain (common [$\geq 1/100$ to $< 1/10$]), both are most frequently reported adverse reactions. These are listed event in SmPC section 4.8.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase). These elevations are transient and return to baseline. Frequency: uncommon ($\geq 1/1000$ to $< 1/100$). These are listed event in SmPC section 4.8.
- Injection site reactions, including injection site erythema (uncommon ($\geq 1/1000$ to $< 1/100$)). These are listed event in SmPC section 4.8.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- None

Known risks that do not impact the risk-benefit profile:

– None

Other reasons for considering the risks not important:

– None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 7: Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Important Identified Risks	
Severe Splenomegaly/splenic rupture	This risk was not reported in clinical trials with USV Pegfilgrastim. Severe splenomegaly/splenic rupture is uncommon in patients taking Neulasta. Severe splenomegaly is an uncommon risk but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. 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 left shoulder tip pain. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. This safety concern has been identified from post-marketing adverse event reporting with Neulasta. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Cutaneous vasculitis	This risk was not reported in clinical trials with USV Pegfilgrastim. 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 1576 patients receiving Neulasta® in nine randomized clinical trials. Uncommon events of cutaneous vasculitis have been reported in patients treated with Neulasta®. The mechanism of vasculitis in patients receiving Neulasta® is unknown. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Sweet's syndrome (Acute Febrile dermatosis)	This risk was not reported in clinical trials with USV Pegfilgrastim. 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 1576 patients receiving Neulasta® in nine randomized clinical trials. Uncommon cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Anaphylactic reaction	This risk was not reported in clinical trials with USV Pegfilgrastim. Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment has been reported in patients treated with Neulasta®. It is recommended to permanently discontinue Pegfilgrastim in patients with clinically significant hypersensitivity. Do not administer USV 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. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Capillary leak syndrome	This risk was not reported in clinical trials with USV Pegfilgrastim. Capillary Leak Syndrome has been reported as uncommon ($\geq 1/1,000$ to $< 1/100$) in cancer patients undergoing chemotherapy following administration of granulocyte colony-stimulating factors. Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony-stimulating factor use 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. Capillary Leak Syndrome can be life-threatening. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Serious pulmonary adverse events (including Interstitial pneumonia and ARDS)	This risk was reported in clinical trials with USV Pegfilgrastim (PEGF/USV/P3/003) with following frequency: : – Acute respiratory distress syndrome: 1 subject from USV Pegfilgrastim treatment arm (0.6%). – Acute respiratory distress syndrome was assessed as an SAE. During the Treatment Period, one fatal SAE reported in the USV Pegfilgrastim treatment arm due to acute respiratory distress syndrome. – Acute respiratory distress syndrome is severe and assessed as unlikely related to the USV Pegfilgrastim. Uncommon ($\geq 1/1,000$ to $< 1/100$) 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. 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. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Sickle cell crisis in patients with sickle cell disease	This risk was not reported in clinical trials with USV Pegfilgrastim. 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 1576 patients receiving Neulasta® in nine randomized clinical trials. Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients). 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. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Musculoskeletal pain-related symptoms	Frequency: PEGF/USV/P1/001: – Back pain: 87 patients (58.0%) from USV pegfilgrastim and 84 patients (56.4%) from Neulasta. – Pain in extremity: 27 patients (18.0%) from USV pegfilgrastim and 22 patients (14.8%) from Neulasta. – Musculoskeletal chest pain: 13 patients (8.7%) from USV pegfilgrastim and 9 patients (6.0%) from Neulasta. – Neck pain: 8 patients (5.3%) from USV pegfilgrastim and 5 patients (3.4%) from Neulasta. – Musculoskeletal pain: 4 (2.7%) from USV pegfilgrastim and 4 (2.7%) from Neulasta. – Arthralgia 15 (10.0) from USV pegfilgrastim and 10 (6.7) from Neulasta PEGF/USV/P1/003: – Back pain was the most frequently reported AE. PEGF/USV/P3/003: – Bone pain: 54 (32.5%) subjects from USV pegfilgrastim and 27 (32.9%) subjects from Neulasta. PEGF/USV/P1/001: Investigational medicinal product related adverse events were considered moderate in severity. – Back pain: Related in 5 subjects and possibly related in 3 subjects with USV pegfilgrastim and related in 6 subjects and possibly related in 1 subject with Neulasta. – Pain in extremity: Related in 1 subject with USV pegfilgrastim and related in 1 subject with Neulasta. – Musculoskeletal chest pain: Related in 1 subject with USV pegfilgrastim. – Neck pain: Related in 2 subjects with USV

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
	pegfilgrastim. – Musculoskeletal pain: Related in 1 subject with Neulasta. PEGF/USV/P1/003: – Back pain was the most frequently reported Investigational medicinal product related AE. The vast majority of AEs recorded during the study were considered mild in severity. PEGF/USV/P3/003: – Most of the reported bone pain events (mostly located in the leg) were assessed as moderate and mild. Severe bone pain was reported in 9.6% of subjects in the USV Pegfilgrastim treatment arm which was marginally higher than in the Neulasta treatment arm where the number of subjects was 7.3%. None of the reported bone pain events were assessed as serious adverse events (SAEs). The most frequently reported adverse reactions were bone pain (very common [$\geq 1/10$]) and musculoskeletal pain (common). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Leukocytosis	Frequency: PEGF/USV/P3/003: The associated investigational medicinal product/comparator related treatment emergent adverse event (TEAE) (Leukocytosis) is the recognized side effect of pegfilgrastim treatment. 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 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. WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed $50 \times 10^9/l$ after the expected nadir, this medicine should be discontinued immediately. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. This safety concern has been identified from post-marketing adverse event reporting with Neulasta. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Thrombocytopenia	Frequency: PEGF/USV/P1/001: (i) 01 subject had an AE of asymptomatic thrombocytopenia, moderate in severity and related to USV pegfilgrastim. 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. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Glomerulonephritis	Not reported in clinical trials with USV pegfilgrastim. Glomerulonephritis has been reported as uncommon (affecting less than 1 patient in 100) with pegfilgrastim treatment. Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Important Potential Risks	

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS]	Not reported in clinical trials with USV pegfilgrastim. 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 risk association between G-CSF and development of AML or MDS in patients with non-myeloid malignancies has not been established. Conversely, patients treated intensively with chemotherapy and no GCSF treatment have a 100-fold or more increased risk of MDS and AML compared with the risk in the general population (Pedersen-Bjergaard et al, 2002a¹). Granulocyte-colony stimulating factor can promote growth of myeloid cells in vitro. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Cytokine release syndrome	Not reported in clinical trials with USV pegfilgrastim. This risk has been identified from PRAC review of case reports submitted for Neulasta[®] in EudraVigilance. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Medication errors including overdose	Not reported in clinical trials with USV pegfilgrastim. Pegfilgrastim should be administered at least 24-hours after administration of cytotoxic chemotherapy. There is potential for medication error and administration of the product just after chemotherapy, which may actually increase the risk of neutropenia. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Drug interaction with lithium	Not reported in clinical trials with USV pegfilgrastim. 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. This risk has been identified from post-marketing adverse event reporting with Neulasta[®]. Neulasta[®] (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Off-label use (Use outside of its approved indications)	Frequency in USV pegfilgrastim clinical trials is not applicable. This risk has been identified from post-marketing adverse event reporting with Neulasta[®].

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	Frequency: PEGF/USV/P1/001 No true positive results were recorded for anti-drug antibodies (ADA) during the study. PEGF/USV/P1/003: Three (10.0%) subjects (all randomised to USV Pegfilgrastim in Period 1 and Neulasta in Period 2) had positive confirmatory assay results for Pegfilgrastim ADA post-dose. However, for all 3 subjects, the results of the NAb assay were negative, and the positive immune response had no notable impact on their PK, PD and safety profiles. PEGF/USV/P3/003: In the USV Pegfilgrastim arm, one subject tested positive for Pegfilgrastim antibodies post-dose, only at one time-point i.e. end of trial (EoT) Visit after 6 cycles of treatment. Although this subject was ADA (anti-drug antibody) positive with neutralizing activity, the titer of ADA as well as NAb (neutralising antibody) activity was low (titer =2). Although the subject had higher duration of severe neutropenia than the treatment arm mean, this difference was already present before Cycle 4 when ADAs were not present. The pre-existing antibodies to pegfilgrastim were detected in one subject prior to treatment, however the subject did not remain positive after exposure to USV Pegfilgrastim. Neulasta® exposure did not result in the induction of neutralizing antibodies to Pegfilgrastim. This risk has been identified from post-marketing adverse event reporting with Neulasta®. As with all therapeutic proteins, there is a potential for immunogenicity. Rate 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. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94%

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
	across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Extramedullary haematopoiesis	Not reported in clinical trials with USV pegfilgrastim. This risk has been identified from post-marketing adverse event reporting with Neulasta®. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials. No additional pharmacovigilance and risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Missing information	
Risks in children under 18 years of age	The safety and efficacy of Pegfilgrastim in children has not yet been established. 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. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials.
Risks during pregnancy and lactation	There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Neulasta is not recommended during pregnancy and in women of childbearing potential not using contraception. There is insufficient information on the excretion of pegfilgrastim/ metabolites in human milk, a risk to the newborns/infants cannot be excluded. Neulasta® (Pegfilgrastim) reduces the incidence of neutropenic events (febrile neutropenia) by 94% across multiple endpoints in pivotal clinical trials.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Table 8: Reclassification of safety concern in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Sickle cell crisis in patients with sickle cell disease	Sickle cell crisis in patients with sickle cell disease, previously classified as an important identified risk, is removed from the list of safety concerns	To in line with the RMP of Reference product, Neulasta (version 11.0, date: 20 May 2025, published at EMA site on 08 Dec 2025).
Glomerulonephritis	Glomerulonephritis, previously classified as an important identified risk, is removed from the list of safety concerns.	

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Table 9: Details of important identified risks

Important identified risk: Capillary leak syndrome	
MedDRA terms (Preferred Terms)	Capillary leak syndrome, capillary permeability increased.
Potential mechanisms	The exact mechanism remains unclear. The potential mechanism is damage to the endothelial cells, resulting in extravasation of plasma proteins and fluid from the capillaries into the extravascular space or an increase of the neutrophil count and their phagocytic and cytotoxic functions and their expression of adhesion molecules.
Evidence source(s) and strength of evidence	This safety concern was identified in the post-marketing setting with Neulasta®. Ristempa® (pegfilgrastim): EPAR - Public assessment report (EMA/187414/2015) dated, 26 Feb 2015.
Characterisation of the risk	Capillary leak syndrome is characterized by episodes of severe hypotension, hypoalbuminemia, edema, and hemoconcentration. In cancer patients, due to preexisting anemia, hemoconcentration may be variable (Druey and Greipp, 2010 ²). During "attacks" of capillary leak syndrome, profound derangement of the vascular endothelium results in leakage of plasma and proteins into the interstitial compartment resulting in edema. Episodes vary in severity and frequency and may be fatal (Clarkson et al, 1960 ³ ; Marks et al, 1973 ⁴).
Risk factors and risk groups	Cancer patients undergoing chemotherapy (patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications). High white cell count might be contributory. Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins (Kai-Feng et al, 2011 ⁵), gemcitabine (Baron et al, 2006 ⁶), doxorubicin (Krziesinski et al, 2010 ⁷), granulocyte-macrophage colony-stimulating (Al-Homaidhi et al, 1998 ⁸), and interferon (Yamamoto et al, 2002 ⁹). Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis (Kai-Feng et al, 2011 ⁵).
Preventability	Close monitoring for Capillary leak syndrome symptoms in patients receiving pegfilgrastim. Immediate standard symptomatic treatment if symptoms occur.
Impact on the risk-benefit balance of the product	Capillary leak syndrome is a serious, potentially life-threatening event that requires immediate treatment (might include intensive care), and it might have significant adverse impact on individual patient.
Public health impact	Not expected to have a significant public health impact.

Important identified risk: Acute Respiratory Distress Syndrome	
MedDRA terms (Preferred Terms)	Interstitial pneumonia: Idiopathic pulmonary fibrosis, Influenza like illness, Interstitial lung disease, Interstitial pneumonia, Pulmonary fibrosis ARDS: Acute respiratory distress syndrome, Acute interstitial pneumonitis, Acute lung injury, Acute pulmonary oedema, Lung infiltration, Noncardiogenic pulmonary oedema, Pulmonary function test decreased
Potential mechanisms	The pathogenesis of ARDS is complex and probably involves multiple mechanisms, including prostaglandin release and complement activation, that lead to the sequestration of neutrophils in areas of inflammation in the pulmonary microvasculature, with resultant pulmonary dysfunction.
Evidence source(s) and strength of evidence	PEGF/USV/P3/003 Clinical Study Report. This safety concern was identified in the post-marketing setting with Neulasta®. Ristempa® (pegfilgrastim): EPAR - Public assessment report (EMA/187414/2015) dated, 26 Feb 2015.
Characterisation of the risk	ARDS is a clinical syndrome of severe dyspnoea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. There have been several reports of acute respiratory failure during G-CSF-induced neutropenia recovery (Takatsuka et al, 2002 ¹⁰ ; Azoulay et al, 2001 ¹¹). G-CSF is believed to enhance cytokine production and to activate the oxidative burst within circulating or resident alveolar neutrophils and macrophages (Karlin et al, 2005 ¹²).
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in NHL (Katsuya et al, 2009 ¹³ ; Huang et al, 2011 ¹⁴). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, 1984 ¹⁵), particularly in Japan (Camus et al, 2004 ¹⁶).
Preventability	Monitor for pulmonary signs such as cough, fever, and dyspnoea. For ARDS, association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs. Pegfilgrastim should be discontinued at the discretion of the physician and appropriate treatment is administered.
Impact on the risk-benefit balance of the product	Complications such as respiratory failure or ARDS are serious in nature with potential impact on the patient and therefore require immediate attention. ARDS may also be potentially fatal.
Public health impact	Mortality rates of approximately 40% were reported for patients with acute respiratory failure, with similar or slightly lower rates reported for patients with acute lung injury and ARDS (Lewandowski, 2003 ¹⁷).

Table 10: Details of important potential risks

Important potential risk: Cytokine release syndrome	
MedDRA terms (Preferred Terms)	Cytokine release syndrome, cytokine storm, infusion related reaction.
Potential mechanisms	Some monocyte / macrophages populations are reported to express G-CSF-R and may be able to respond to G-CSF through cytokine upregulation (Boneberg et al, 2000 ¹⁷). However, several studies evaluating monocyte cytokine release report that G-CSF treatment resulted in a decrease in proinflammatory cytokine production (Boneberg et al, 2000 ¹⁸ ; Pajkrt et al, 1997 ¹⁹ ; Hartung et al, 1995 ²⁰). Authors of one study (Boneberg et al, 2000 ¹⁸) proposed that attenuation of the inflammatory response would be protective against fatal over activation of the immune system.
Evidence source(s) and strength of evidence	This safety concern was identified in the post-marketing setting with Neulasta®. Ristempa® (pegfilgrastim): EPAR - Public assessment report (EMA/187414/2015) dated, 26 February 2015 and literature as cited above under potential mechanism.
Characterisation of the risk	Cytokine release syndrome is a rapid, uncontrolled hypercytokinaemia that results in a range of clinical effects from pyrexia and fatigue to multiple organ failure in association with therapeutic infusion of antibodies (e.g., rituximab, trastuzumab). Mechanism of action involves targeted activation of immune cells and elevation of both proinflammatory (e.g., tumor necrosis factor-α) and antiinflammatory (e.g., interleukin-10) cytokines (O'Neil, 2010²¹; Chung, 2008²²; Dillman, 1999²³; Winkler et al, 1999²⁴). The syndrome is typified by the appearance of plasma cytokines within a few hours of infusion of the antibody (Wing, 2008²⁵). Signs and symptoms of cytokine release syndrome generally occur acutely, within minutes to a few hours after first dose administration of the drug, and the events are mostly clinically indistinguishable from an acute IgE mediated anaphylactic or non-IgE mediated anaphylactoid reaction (O'Neil et al., 2010²¹; Kang and Saif, 2007²⁶). Monoclonal antibodies used in the treatment of cancers are commonly associated with infusion-related reactions secondary to the release of inflammatory cytokines, or the occurrence of tumour lysis syndrome, that involve cytokine release from malignant cells targeted by these monoclonal antibodies (Howard et al, 2011²⁷; Kang and Saif, 2007²⁶). However, Pegfilgrastim is not a monoclonal antibody and has no receptors to T-cells or B-cells.

Important potential risk: Cytokine release syndrome	
Risk factors and risk groups	The administration of monoclonal antibodies and other drugs elicit infusion reactions, and the risk factors for cytokine release syndrome-mediated infusion reactions remain unclear. The severity of the infusion reaction might be related to the number of circulating lymphocytes (Chung, 2008 ²¹). During the first infusion of rituximab to patients with relapsed B-cell chronic lymphocytic leukemia or low grade B-cell lymphoma, patients with lymphocyte counts $>50 \times 10^9/L$ were significantly more likely to have severe symptoms than those having lower baseline lymphocyte counts ($p = 0.0017$) (Winkler et al, 1999 ²⁴). A person's risk for an infusion reaction to a monoclonal antibody is influenced by the route and rate of administration, drug form, whether the drug is given in combination or as a single agent, and concomitant medications (Vogel, 2010 ²⁸). Geographic location may elevate the risk for an infusion reaction from cetuximab (O'Neil et al., 2007 ²⁹).
Preventability	Monitoring for Cytokine release syndrome symptoms and immediate treatment if symptoms occur.
Impact on the risk-benefit balance of the product	Most patients experience a mild to moderate reaction; however, the reaction may be severe and life-threatening.
Public health impact	Not expected to have a significant public health impact.

SVII.3.2. Presentation of missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table 11: Summary of safety concerns

Important identified risks	• Capillary leak syndrome • Acute respiratory distress syndrome
Important potential risks	• Cytokine release syndrome
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine PV activities including collection and reporting of adverse reactions and signal detection as stated in the PV System Master File are conducted by the MAH.

Routine PV activities beyond adverse reactions reporting and signal detection:

Specific follow-up questionnaires have been developed for Capillary leak syndrome and Cytokine release syndrome.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table 12: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Capillary leak syndrome	Section 4.4 and 4.8 of Pegfilgrastim SmPC
Acute respiratory distress syndrome	Section 2 and 4 of Pegfilgrastim PIL
	Other routine risk minimisation measures: Prescription only status
Important Potential Risks	
Cytokine release syndrome	Routine risk minimisation measures: Prescription only status
Missing information: None	

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures**Table 13: Summary table of PV activities and risk minimisation activities by safety concern**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Capillary leak syndrome	<u>Routine risk minimisation measures:</u> Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status <u>Additional risk minimisation measures:</u> None	<u>Routine PV activities beyond adverse reactions reporting and signal detection :</u> AE follow-up form <u>Additional PV activities:</u> None
Acute Respiratory Distress Syndrome	<u>Routine risk minimisation measures:</u> Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status <u>Additional risk minimisation measures:</u> None	<u>Routine PV activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional PV activities:</u> None
Important Potential Risks		
Cytokine release syndrome	Prescription only status <u>Additional risk minimisation measures:</u> None	<u>Routine PV activities beyond adverse reactions reporting and signal detection:</u> AE follow-up form <u>Additional PV activities:</u> None

Part VI: Summary of the risk management plan

Summary of risk management plan for Grasustek 6 mg solution for injection in pre-filled syringe (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Grasustek 6 mg solution for injection in pre-filled syringe. The RMP details important risks of Grasustek 6 mg solution for injection in pre-filled syringe, how these risks can be minimised, and how more information will be obtained about Grasustek 6 mg solution for injection in pre-filled syringe's risks and uncertainties (missing information).

Grasustek 6 mg solution for injection in pre-filled syringe's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Grasustek 6 mg solution for injection in pre-filled syringe should be used.

This summary of the RMP for Grasustek 6 mg solution for injection in pre-filled syringe should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Grasustek 6 mg solution for injection in pre-filled syringe's RMP.

I. The medicine and what it is used for

Grasustek 6 mg solution for injection in pre-filled syringe is authorised for 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) (see SmPC for the full indication).

It contains Pegfilgrastim as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Grasustek 6 mg solution for injection in pre-filled syringe's benefits can be found in Grasustek 6 mg solution for injection in pre-filled syringe's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. <https://www.ema.europa.eu/en/medicines/human/EPAR/grasustek>

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Grasustek 6 mg solution for injection in pre-filled syringe, together with measures to minimise such risks and the proposed studies for learning more about Grasustek 6 mg solution for injection in pre-filled syringe's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Grasustek 6 mg solution for injection in pre-filled syringe are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Grasustek 6 mg solution for injection in pre-filled syringe. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Capillary leak syndrome • Acute Respiratory Distress Syndrome (ARDS)
Important potential risks	• Cytokine release syndrome
Missing information	• None

II.B Summary of important risks

Important Identified Risks: Capillary leak syndrome	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with Neulasta®. Ristempa® (pegfilgrastim) : EPAR - Public assessment report (EMA/187414/2015) dated, 26 Feb 2015
Risk factors and risk groups	Cancer patients undergoing chemotherapy (patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications). High white cell count might be contributory. Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins, gemcitabine, doxorubicin, granulocyte-macrophage colony-stimulating, and interferon. Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis.

Risk minimisation measures	<u>Routine risk minimisation measures:</u> Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL <u>Additional risk minimisation measures:</u> None
Important Identified Risks: Acute Respiratory Distress Syndrome (ARDS)	
Evidence for linking the risk to the medicine	Serious and severe complications affecting the lung (including acute respiratory distress syndrome) have been identified as an important identified risk in Neulasta® clinical studies, post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in NHL. Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer, particularly in Japan.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL Prescription only status <u>Additional risk minimisation measures:</u> None
Important Potential Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Cytokine release syndrome (a severe inflammatory response caused by the release of immune-stimulating proteins) can be associated with a collection of symptoms including fever, pain, low blood pressure, rapid heart rate, headache, delirium, seizures and tremors. It has been identified as an important potential risk in Neulasta® post-marketing adverse event reporting following PRAC review of case reports in EudraVigilance, Ristempa® (pegfilgrastim) public assessment report and literature.
Risk factors and risk groups	The administration of monoclonal antibodies and other drugs elicit infusion reactions, and the risk factors for cytokine release syndrome-mediated infusion reactions remain unclear. The severity of the infusion reaction might be related to the number of circulating lymphocytes. During the first infusion of rituximab to patients with relapsed B-cell chronic lymphocytic leukemia or low grade B-cell lymphoma, patients with lymphocyte counts $>50 \times 10^9/L$ were significantly more likely to have severe symptoms than those having lower baseline lymphocyte counts ($p = 0.0017$). A person's risk for an infusion reaction to a monoclonal antibody is influenced by the route and rate of administration, drug form, whether the drug is given in combination or as a single agent, and concomitant medications. Geographic location may elevate the risk for an infusion reaction from cetuximab.

Risk minimisation measures	Prescription only status Additional risk minimisation measures: None
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II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which conditions of the marketing authorisation or specific obligation of Grasustek 6 mg solution for injection in pre-filled syringe.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Grasustek 6 mg solution for injection in pre-filled syringe as post-authorisation development plan.

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Annex 4 - Specific adverse drug reaction follow-up forms

JUTA has developed targeted follow-up questionnaires for following risks: Capillary leak syndrome; Cytokine release syndrome

Targeted Follow-up Questionnaire for Capillary leak syndrome

ADVERSE DRUG REACTION REPORT for Capillary leak syndrome					
Please forward to _____					
1. REPORTER INFORMATION					
Name: _____ Address: _____ Email: _____ Phone number: _____ Date: _____ Sign: _____	☐ Health Professional ☐ MD ☐ Pharmacist ☐ Other ☐ Patient ☐ Other (please specify) _____ ☐ Literature author In particular, please complete sections 3 (sex), 4 (date of birth), 10/11 (drug information), 12 (event information), and 13 (other information)				
PATIENT INFORMATION					
2. Patient Initials	3. Sex ☐ M ☐ F ☐ D	4. Date of Birth (dd/mmm/yyyy) or Age	5. Weight	6. If female, pregnant at time of event(s)? ☐ Yes ☐ No ☐ NA ☐ Don't know	7. Initial Report ☐ Follow-up Report ☐
8. Patient history (including allergies, concomitant medical conditions and other risk factors)					
DRUG INFORMATION					
9. Previous use of other G-CSF/Filgrastim or pegfilgrastim products (including biosimilars):					
Trade Name: _____	Start date: _____	Stop date: _____	Dosage: _____	Lot No: _____	
Trade Name: _____	Start date: _____	Stop date: _____	Dosage: _____	Lot No: _____	
10. Most current use of other G-CSF/Filgrastim or pegfilgrastim products (including biosimilars):					
Trade Name: _____	Start date: _____	Stop date: _____	Dosage: _____	Lot No: _____	
Indication: _____ Frequency of administration: _____ Treatment discontinued: ☐ Yes ☐ No					
11. Concomitant drugs:					
Trade Name (or INN): _____	Start date: _____	Stop date: _____	Dosage: _____	Indication: _____	
Trade Name (or INN): _____	Start date: _____	Stop date: _____	Dosage: _____	Indication: _____	
Trade Name (or INN): _____	Start date: _____	Stop date: _____	Dosage: _____	Indication: _____	

12. EVENT INFORMATION					
Adverse event	Onset date	End date	Recovered / Rec. with sequelae / Recovering / Ongoing / Unknown		
	(dd/mm/yyyy)				
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

Please provide a summary of the observed **clinical signs and symptoms**, in particular presence and sites of oedema, recorded blood pressure, and results of relevant tests / lab data (e.g., full blood count, differentials, haematocrite, blood albumin). Please attach relevant documents:

Did the patient receive any **ADR treatment**? If so, please provide details:

13. OTHER INFORMATION	
Check all appropriate tick boxes: ☐ Patient died (date of death (dd/mm/yyyy): _____) ☐ Hospitalization (from: _____ to: _____) ☐ Involved significant disability or incapacity ☐ Immediately life-threatening ☐ None of the above	If Grasustek was discontinued: Did reaction abate after stopping drug: ☐ yes ☐ no Was Grasustek restarted: ☐ yes ☐ no Did reaction reappear after restart: ☐ yes ☐ no ☐ Grasustek was not discontinued

Targeted Follow-up Questionnaire for Cytokine Release Syndrome

ADVERSE DRUG REACTION REPORT for Cytokine Release Syndrome					
Please forward to _____					
1. REPORTER INFORMATION					
Name:		☐ Health Professional		☐ Patient	
Address:		☐ MD		☐ Other (please specify)	
		☐ Pharmacist		_____	
Email:		☐ Other			
Phone number:		☐ Literature author			
Date:		Sign: _____		In particular, please complete sections 3 (sex), 4 (date of birth), 10/11 (drug information), 12 (event information), and 13 (other information)	
PATIENT INFORMATION					
2. Patient Initials	3. Sex ☐ M ☐ F ☐ D	4. Date of Birth (dd/mm/yyyy) or Age	5. Weight	6. If female, pregnant at time of event(s)? ☐ Yes ☐ No ☐ NA ☐ Don't know	7. Initial Report ☐ Follow-up Report ☐
8. Patient history (including allergies, concomitant medical conditions and other risk factors)					
DRUG INFORMATION					
9. Previous use of other G-CSF/Filgrastim or pegfilgrastim products (including biosimilars):					
Trade Name: _____		Start date: _____		Stop date: _____	
Dosage: _____		Lot No: _____			
Trade Name: _____		Start date: _____		Stop date: _____	
Dosage: _____		Lot No: _____			
10. Most current use of other G-CSF/Filgrastim or pegfilgrastim products (including biosimilars):					
Trade Name: _____		Start date: _____		Stop date: _____	
Dosage: _____		Lot No: _____			
Indication: _____		Frequency of administration: _____		Treatment discontinued: ☐ Yes ☐ No	
11. Concomitant drugs:					
Trade Name (or INN): _____		Start date: _____		Stop date: _____	
Dosage: _____		Indication: _____			
Trade Name (or INN): _____		Start date: _____		Stop date: _____	
Dosage: _____		Indication: _____			
Trade Name (or INN): _____		Start date: _____		Stop date: _____	
Dosage: _____		Indication: _____			

12. EVENT INFORMATION					
Adverse event	Onset date	End date	Recovered / Rec. with sequelae / Recovering / Ongoing / Unknown		
	(dd/mm/yyyy)				
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

Please provide a summary of the observed **clinical signs and symptoms** (including, but not limited to nausea, chills, fever, dyspnoea, hypotension, tachycardia) and results of relevant tests / lab data (e.g., blood uric acid, potassium, calcium, phosphate and lactate dehydrogenase, chest X-ray). Please attach relevant documents:

Did the patient receive any **ADR treatment**? If so, please provide details:

13. OTHER INFORMATION	
Check all appropriate tick boxes: ☐ Patient died (date of death (dd/mm/yyyy): _____) ☐ Hospitalization (from: _____ to: _____) ☐ Involved significant disability or incapacity ☐ Immediately life-threatening ☐ None of the above	If Grasustek was discontinued: Did reaction abate after stopping drug: ☐ yes ☐ no Was Grasustek restarted: ☐ yes ☐ no Did reaction reappear after restart: ☐ yes ☐ no ☐ Grasustek was not discontinued

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 - Other supporting data (including referenced material)

1. Pedersen-Bjergaard J, Andersen MK, Christiansen DH, Nerlov C. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. *Blood*. 2002 Mar 15;99(6):1909-12.
2. Druey KM and Greipp PR. Narrative Review: Clarkson Disease-Systemic Capillary Leak Syndrome. *Annals of Internal Medicine*. 2010; 153(2):90–8.
3. Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. *Am J Med*. 1960 Aug;29:193-216.
4. Marks J and Shuster S. Disorders of capillary permeability. *Br J Dermatol*. 1973 Jun;88(6):619-21.
5. Kai-Feng W, Hong-Ming P, Hai-Zhou L, Li-Rong S, Xi-Yan Z. Interleukin-11-induced capillary leak syndrome in primary hepatic carcinoma patients with thrombocytopenia. *BMC Cancer*. 2011 May 27;11:204. doi: 10.1186/1471-2407-11-204.
6. Baron D, Mayo A, Kluger Y. Gemcitabine-induced chronic systemic capillary leak syndrome: a lifethreatening disease. *Clin Oncol (R Coll Radiol)*. 2006 Feb;18(1):90-1.
7. Krzesinski P, Wierzbowski R, Gielerak G, Hałka J, Matysiak O, Smurzyński P. Impedance cardiography in the diagnosis of capillary leak syndrome caused by doxorubicin therapy in a patient with myeloma multiplex. *Cardiol J*. 2010;17(1):88-91.
8. Al-Homaidhi A, Prince HM, Al-Zahrani H, Doucette D, Keating A. Granulocyte-macrophage colonystimulating factor-associated histiocytosis and capillary-leak syndrome following autologous bone marrow transplantation: two case reports and a review of the literature. *Bone Marrow Transplant*. 1998 Jan;21(2):209-14.
9. Yamamoto K, Mizuno M, Tsuji T, Amano T. Capillary leak syndrome after interferon treatment for chronic hepatitis C. *Arch Intern Med*. 2002 Feb 25;162(4):481-2.
10. Takatsuka H, Takemoto Y, Mori A, Okamoto T, Kanamaru A, Kakishita E. Common features in the onset of ARDS after administration of granulocyte colony-stimulating factor. *Chest*. 2002 May;121(5):1716-20.
11. Azoulay E, Attalah H, Harf A, Schlemmer B, Delclaux C. Granulocyte Colony-Stimulating Factor or Neutrophil-Induced Pulmonary Toxicity: Myth or Reality? *Chest*. 2001; 120(5):1695–701.
12. Karlin L, Darmon M, Thiéry G, Cirolldi M, Miranda SD, Lefebvre A, et al. Respiratory status deterioration during G-CSF-induced neutropenia recovery. *Bone Marrow Transplantation*. 2005; 36(3):245–50.
13. Katsuya H, Suzumiya J, Sasaki H, Ishitsuka K, Shibata T, Takamatsu Y, Tamura K. Addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy has a high risk of developing interstitial pneumonia in patients with non-Hodgkin lymphoma. *Leuk Lymphoma*. 2009 Nov;50(11):1818-23.
14. Huang YC, Liu CJ, Liu CY, Pai JT, Hong YC, Teng HW, et al. Low absolute lymphocyte count and addition of rituximab confer high risk for interstitial pneumonia in patients with diffuse large B-cell lymphoma. *Ann Hematol*. 2011 Oct;90(10):1145-51.
15. Zimmerman MS, Ruckdeschel JC, Hussain M. Chemotherapy-induced interstitial pneumonitis during treatment of small cell anaplastic lung cancer. *J Clin Oncol*. 1984 May;2(5):396-405.
16. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *British Journal of Cancer*. 2004; 91.
17. Lewandowski K. Contributions to the epidemiology of acute respiratory failure. *Critical Care*. 2003; 7(4): 288-290.
18. Boneberg EM, Hareng L, Gantner F, Wendel A, Hartung T. Human monocytes express functional receptors for granulocyte colony-stimulating factor that mediate suppression of monokines and interferongamma. *Blood*. 2000 Jan 1;95(1):270-6.
19. Pajkrt D, Manten A, van der Poll T, Tiel-van Buul MM, Jansen J, Wouter ten Cate J, van Deventer SJ. Modulation of cytokine release and neutrophil function by granulocyte colonystimulating factor during endotoxemia in

- humans. *Blood*. 1997 Aug 15;90(4):1415-24.
20. Hartung T, Döcke WD, Gantner F, Krieger G, Sauer A, Stevens P, Volk HD, Wendel A. Effect of granulocyte colony-stimulating factor treatment on ex vivo blood cytokine response in human volunteers. *Blood*. 1995 May 1;85(9):2482-9.
21. O'Neil BH, Raftery L, Calvo BF, Chakravarthy AB, Ivanova A, Myers MO et al. A phase I study of bortezomib in combination with standard 5-fluorouracil and external-beam radiation therapy for the treatment of locally advanced or metastatic rectal cancer. *Clin Colorectal Cancer*. 2010 Apr;9(2):119-25.
22. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *Oncologist*. 2008 Jun;13(6):725-32.
23. Dillman RO. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. *Cancer Metastasis*. 1999; 18(4): 465-71.
24. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood*. 1999 Oct 1;94(7):2217-24.
25. Wing M. Monoclonal antibody first dose cytokine release syndromes-mechanisms and prediction. *J Immunotoxicol*. 2008 Jan;5(1):11-5.
26. Kang SP, Saif MW. Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer--identification, prevention, and management. *J Support Oncol*. 2007 Oct;5(9):451-7.
27. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med*. 2011 May 12;364(19):1844-54.
28. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs*. 2010 Apr;14(2):E10-21.
29. O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol*. 2007 Aug 20;25(24):3644-8.
30. Summary of Product Characteristic (SmPC) and Package Information Leaflet (PIL) of Grasustek 6 mg solution for injection in pre-filled syringe.
31. Ristempa® (pegfilgrastim): EPAR - Public assessment report (EMA/187414/2015) dated, 26 February 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/003910/WC500185707.pdf
32. Neulasta® (Pegfilgrastim) injection, Efficacy. Help protect your patients at risk of febrile neutropenia (FN) with Neulasta® FIRST and EVERY cycle. Available from: <http://www.neulastahcp.com/efficacy-neutrophils-studies/>
33. PRAC PSUR assessment report of Pegfilgrastim (EMEA/H/C/PSUSA/00002326/202201) dated 29 Sep 2022
34. Grasustek : EPAR - Risk management plan, https://www.ema.europa.eu/en/documents/rmp-summary/grasustek-epar-risk-management-plan_en.pdf as accessed on 22 Dec 25