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	2.0
Data lock point for this RMP	27 June 2023
Date of final sign off	16 Aug 2023

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: To update the RMP as per PRAC PSUR assessment report of Pegfilgrastim (EMEA/H/C/PSUSA/00002326/202201) dated 29 Sep 2022.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part I, Part II (SVII, SVIII), Part III, Part V, Part VI, Part VII (annex 4, annex 7, annex 8)

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version	**Procedure**	**Date of approval**
1.2	EMEA/H/C/004556/0000 (MA. No. EU/1/19/1375/001)	20 June 2019

QPPV name: Dr. med. Renald Hennig

QPPV signature: [redacted]

TABLE OF CONTENTS

LIST OF TABLES

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	EMEA/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. *Excipient(s) with known effect:* 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. Posology One 6 mg dose (a single pre-filled syringe) of Pegfilgrastim is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. Method of administration 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
In vivo comparative studies in neutropenic and non-neutropenic rats 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.
A comparative 4-week sub-chronic toxicity study by repeated subcutaneous administration once weekly to CD rats 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.
The local tolerance study in rabbits was conducted by five routes (intraarterial, intramuscular, intravenous, paravenous and subcutaneous administration 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 with 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).
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	**Test product:** Grasustek 0.2 mL Solution for Subcutaneous Injection (10 mg/mL); to give a single dose of 2 mg **Reference product:** 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. **Safety Conclusion**: 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

Clinical Study Design	Study treatment	Comment
		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	**Test product**: Grasustek (6 mg) by s.c. injection: 60 subjects **Reference product:** 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.
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 Myelosuppressive Chemotherapy	**Test product**: Grasustek (6 mg) by s.c. injection: 170 subjects **Reference product:** 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®). **Efficacy and safety Conclusions**: In conclusion, the data based on the primary and the secondary efficacy endpoints, demonstrate the

Clinical Study Design	Study treatment	Comment
		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	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)
per the clinical judgment of the investigator precluding informed consent		
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
Known hypersensitivity to any of the chemotherapy drugs used in TAC regime or *E. coli* 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

Exclusion criteria	Missing information	Rational for being an exclusion criteria (if not missing information)
		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
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 1: 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 5: 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
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 19 Apr 2023, and the defined daily dose (DDD) provided by the WHO collaborating Centre for Drug Statistics, 0.3 mg.

Cumulative sales indicate a total of 1,553,160 DDDs or 4,255 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 (≥ 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 (≥ 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 (≥ 1/10). These are listed event in SmPC section 4.8.
- Reversible, mild to moderate bone pain (very common [≥ 1/10]) and musculoskeletal pain (common [≥ 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 (≥ 1/1000 to < 1/100). These are listed event in SmPC section 4.8.
- Injection site reactions, including injection site erythema (uncommon (≥ 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 PV namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- 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 6: Risks considered important for inclusion in the RMP list of safety concerns

Risks considered important for inclusion in the RMP list of safety concerns	Risk-benefit impact
Important Identified Risks	
Capillary leak syndrome	This risk was not reported in clinical trials with USV Pegfilgrastim. Capillary Leak Syndrome has been reported as uncommon (≥ 1/1,000 to < 1/100) in cancer patients undergoing chemotherapy following administration of G-CSF. Cases of capillary leak syndrome have been reported in the post marketing setting with G-CSF 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. No additional PV or risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Acute Respiratory Distress Syndrome (ARDS)	This risk was reported in clinical trials with USV Pegfilgrastim (PEGF/USV/P3/003) with following frequency: – ARDS: 1 subject from USV Pegfilgrastim treatment arm (0.6%). – During treatment period, one fatal SAE was reported in the USV Pegfilgrastim treatment arm due to ARDS. – ARDS is severe and assessed as unlikely related to the USV Pegfilgrastim. Uncommon (≥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 ARDS. In such circumstances pegfilgrastim should be discontinued at the discretion of the physician and the appropriate treatment given. No additional PV or risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
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. The frequency category was estimated from a statistical calculation based upon 1,576 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 for patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status, and be

Risks considered important for inclusion in the RMP list of safety concerns	Risk-benefit impact
	attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis. No additional PV or 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. No additional PV or risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.
Important Potential Risks	
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. No additional PV or risk minimisation activities are deemed necessary till data-lock point of this RMP in-line with reference product.

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

Below mentioned changes made to the safety concerns are in line with the reference product Neulasta, as per PRAC PSUR assessment report of Pegfilgrastim (EMEA/H/C/ PSUSA/00002326/202201) dated 29 Sep 2022.

Anaphylactic reaction, Cutaneous vasculitis, Leukocytosis, Musculoskeletal pain-related symptoms, Severe splenomegaly/splenic rupture, Sweet's syndrome (Acute Febrile Dermatosis) and Thrombocytopenia, previously classified as important identified risks, are removed from the list of safety concerns.

Acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS], Drug interaction with lithium, Extramedullary haematopoiesis, Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies), Medication errors including overdose and Off-label use, previously classified as important potential risks, are removed from the list of safety concerns.

'Risks in children <18 years of age' and 'Risks during pregnancy and lactation', previously classified as missing information, are 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 7: 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[1]). 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[2]; Marks et al, 1973[3]).
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[4]), gemcitabine (Baron et al, 2006[5]), doxorubicin (Krzesinski et al, 2010[6]), granulocyte-macrophage colony-stimulating (Al-Homaidhi et al, 1998[7]), and interferon (Yamamoto et al, 2002[8]). 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[4]).
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[9]; Azoulay et al, 2001[10]). 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[11]).
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[12]; Huang et al, 2011[13]). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, 1984[14]), particularly in Japan (Camus et al, 2004[34]).
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[16]).

Important identified risk: Sickle cell crisis in patients with sickle cell disease	
MedDRA terms (Preferred Terms)	Haemoglobinopathy; Sickle cell anaemia; Sickle cell anaemia with crisis; Sickle cell trait; Red blood cell sickled cells present.
Potential mechanisms	Sickle cell disease is characterized by sickling of the red blood cells that leads to hypoxia. In addition, there is a chronic inflammatory state, with elevated leukocyte counts, increased serum levels of C-reactive protein and cytokines, and a propensity for erythrocyte and platelet activation, all processes that might be exacerbated by G-CSF usage. Leukocytosis induced by G-CSF, the propensity of sickle red cells for vaso-occlusion, and the chronic inflammatory state of patients with sickle cell disease, could explain the potentially hazardous role for G-CSF administration in patients with sickle cell disease (Fitzhugh et al, 2009[17]).
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	Sickle cell crisis is a complication of sickle cell disease. Onset of sickle cell crisis has been associated with the use of G-CSF in patients with sickle cell disease (Fitzhugh et al, 2009[17]).
Risk factors and risk groups	Patients with sickle cell disease are at a risk for sickle cell crisis (Rees et al, 2010[18]). Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (eg, sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis (Yale et al, 2000[19]).
Preventability	Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Physicians should exercise caution when administering pegfilgrastim to these patients, monitor appropriate clinical parameters and laboratory status, and be attentive to the possible association of pegfilgrastim with splenic enlargement and vaso-occlusive crisis.
Impact on the risk-benefit balance of the product	Sickle cell anemia with crisis impacts quality of life. These patients should be carefully treated, and precipitant agent avoided if possible after careful consideration by the treating physician.
Public health impact	Significant morbidity and mortality in individuals with sickle cell disease are well documented. Patients with sickle cell disease develop chronic anemia, acute chest syndrome, stroke, splenic and renal dysfunction, pain crises, and susceptibility to bacterial infections. The primary causes of pediatric mortality are bacterial infection and stroke. In adults, there are multiple causes of mortality, and more symptomatic disease is associated with early mortality (Ashley-Koch et al, 2000[20]).

Important identified risk: Glomerulonephritis	
MedDRA terms (Preferred Terms)	Glomerulonephritis, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Glomerulonephropathy, Azotemia, Haematuria, Proteinuria.
Potential mechanisms	Glomerular lesions in acute glomerulonephritis are the result of glomerular deposition or in situ formation of immune complexes. On gross appearance, the kidneys may be enlarged up to 50%. Histopathologic changes include swelling of the glomerular tufts and infiltration with polymorphonucleocytes. Except in poststreptococcal glomerulonephritis (PSGN), the exact triggers for the formation of the immune complexes are unclear. In PSGN, involvement of derivatives of streptococcal proteins has been reported. A streptococcal neuraminidase may alter host immunoglobulin G (IgG). IgG combines with host antibodies. IgG/anti-IgG immune complexes are formed and then collect in the glomeruli. In addition, elevations of antibody titers to other antigens, such as antistreptolysin O or antihyaluronidase, DNAase-B, and streptokinase, provide evidence of a recent streptococcal infection (Parmar et al, 2017[21]). Glomerulonephritis has occurred in patients receiving Neulasta. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy (Neulasta USPI).
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	Not reported in clinical trials with USV pegfilgrastim.
Risk factors and risk groups	No risk groups or risk factors for glomerulonephritis are known.
Preventability	Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.
Impact on the risk-benefit balance of the product	Not expected to have a significant impact on individual patient.
Public health impact	Not expected to have a significant public health impact.

Table 8: 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[22]). However, several studies evaluating monocyte cytokine release report that G-CSF treatment resulted in a decrease in proinflammatory cytokine production (Boneberg et al, 2000[22]; Pajkrt et al, 1997[23]; Hartung et al, 1995[24]). Authors of one study (Boneberg et al, 2000[22]) 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, 2010[25]; Chung, 2008[26]; Dillman, 1999[27]; Winkler et al, 1999[28]). The syndrome is typified by the appearance of plasma cytokines within a few hours of infusion of the antibody (Wing, 2008[29]). 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., 2010[25]; Kang and Saif, 2007[30]). 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, 2011[31]; Kang and Saif, 2007[30]). However, Pegfilgrastim is not a monoclonal antibody and has no receptors to T-cells or B-cells.
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[26]). 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 x 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[Fehler! Textmarke nicht definiert.]). 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[32]). Geographic location may elevate the risk for an infusion reaction from cetuximab (O'Neil et al., 2007[33]).
Preventability	Monitoring for Cytokine release syndrome symptoms and immediate treatment if symptoms occur.

Important potential risk: Cytokine release syndrome	
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 9: Summary of safety concerns

Important identified risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
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 20: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Capillary leak syndrome Acute respiratory distress syndrome Sickle cell crisis in patients with sickle cell disease Glomerulonephritis	Section 4.4 and 4.8 of Pegfilgrastim SmPC 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 31: 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	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None	Routine PV activities beyond adverse reactions reporting and signal detection : AE follow-up form Additional PV activities: None
Acute Respiratory Distress Syndrome	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activities: None
Sickle cell crisis in patients with sickle cell disease	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activities: None
Glomerulo-nephritis	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC Section 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activities: None
Important Potential Risks		
Cytokine release syndrome	Prescription only status	Routine PV activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	AE follow-up form Additional PV activities: 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) • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
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	Routine risk minimisation measures: Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL Additional risk minimisation measures: 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	Routine risk minimisation measures: Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None
Important Identified Risks: **Sickle cell crisis in patients with sickle cell disease**	
Evidence for linking the risk to the medicine	Sickle cell crisis in patients with sickle cell disease has been identified as an important identified risk in Neulasta® post-marketing adverse event reporting, Ristempa® (pegfilgrastim) public assessment report and literature.
Risk factors and risk groups	Patients with sickle cell disease are at risk for sickle cell crisis. Factors such as infections, dehydration, low oxygen tension, acidosis, extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (e.g., sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: None
Important Identified Risks: Glomerulonephritis	
Evidence for linking the risk to the medicine	Glomerulonephritis (damage to the tiny filters inside the kidneys) has been identified as an important identified risk in Neulasta® post-marketing adverse event reporting, Ristempa® (pegfilgrastim) public assessment report and literature.

Risk factors and risk groups	No risk groups or risk factors for glomerulonephritis are known.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.4 and 4.8 of Pegfilgrastim SmPC Sections 2 and 4 of Pegfilgrastim PIL Prescription only status Additional risk minimisation measures: 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 x 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

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.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

MAH 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 safety-juta@scratch-pv.com

1. REPORTER INFORMATION

Name:

Address:

Email:

Phone number:

Date: Sign:_____

☐ Health Professional ☐ Patient

☐ MD ☐ Other (please specify)

☐ Pharmacist _____

☐ Other

☐ 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 (dd/mmm/yyyy)	End date (dd/mmm/yyyy)	Recovered / Rec. with sequelae / Recovering / Ongoing / Unknown
			☐ ☐ ☐ ☐ ☐
			☐ ☐ ☐ ☐ ☐
			☐ ☐ ☐ ☐ ☐

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/mmm/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 safety-juta@scratch-pv.com

1. REPORTER INFORMATION

Name:

Address:

Email:

Phone number:

Date: Sign:_____

☐ Health Professional ☐ Patient

☐ MD ☐ Other (please specify)

☐ Pharmacist _____

☐ Other

☐ 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 (dd/mmm/yyyy)	End date (dd/mmm/yyyy)	Recovered / Rec. with sequelae / Recovering / Ongoing / Unknown
			☐ ☐ ☐ ☐ ☐
			☐ ☐ ☐ ☐ ☐
			☐ ☐ ☐ ☐ ☐

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/mmm/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 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

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

Not applicable