Grasustek
(pegfilgrastim)

6 mg solution for injection
in pre-filled syringe

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Grasustek is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Grasustek in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. iQone Healthcare Switzerland SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Grasustek.

RMP summary: Version 1.0

Name of Marketing Authorisation Holder: iQone Healthcare Switzerland SA

Date: 7 April 2021

Reference RMP: EU RMP version 1.2

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 and signal management activity, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Grasustek 6 mg solution for injection in pre-filled syringe is not yet available, it is listed under 'missing information' below.

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	• Severe splenomegaly/splenic rupture • Cutaneous vasculitis • Sweet's syndrome (Acute Febrile Dermatosis) • Anaphylactic reaction • Capillary leak syndrome • Serious pulmonary adverse events (including Interstitial pneumonia and ARDS) • Sickle cell crisis in patients with sickle cell disease • Musculoskeletal pain-related symptoms • Leukocytosis • Thrombocytopenia • Glomerulonephritis
Important potential risks	• Acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS] • Cytokine release syndrome • Medication errors including overdose • Drug interaction with lithium • Off-label use • Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies) • Extramedullary haematopoiesis
Missing information	• Risks in children <18 years of age • Risks during pregnancy and lactation

II.B Summary of important risks

Important Identified Risks: **Severe splenomegaly/splenic rupture**	
Evidence for linking the risk to the medicine	A grossly enlarged spleen and rupture of the spleen have been identified as important identified risks in Neulasta® post-marketing adverse event reporting,

	Ristempa® (pegfilgrastim) public assessment report and literature.
Risk factors and risk groups	Severe splenomegaly predisposes patients to develop splenic rupture. The underlying conditions associated with splenomegaly include: hematologic diseases (CML, chronic lymphocytic leukemia, acute leukemia, malignant lymphoma, chronic myelofibrosis, polycythemia vera, hairy cell leukemia, thalassemia major or intermedia, sickle cell anemia, hemolytic anemias, and megaloblastic anemia), portal hypertension (cirrhosis and hepatic, portal, and splenic vein thrombosis), storage diseases (Gaucher's disease, Niemann-Pick disease, histiocytosis X), and systemic diseases (sarcoidosis, amyloidosis, collagen diseases [eg, systemic lupus erythematosus and rheumatoid arthritis], and systemic mastocytosis and infections [septicemia, bacterial endocarditis, typhoid, infectious mononucleosis, tuberculosis, brucellosis, syphilis, malaria, leishmaniasis, and schistosomiasis]).
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: **Cutaneous vasculitis**	
Evidence for linking the risk to the medicine	Inflammation of blood and lymph vessels in the skin (cutaneous vasculitis), which can be associated with pain, itching, swelling and reddening of the skin, has been identified as an important identified risk in Neulasta® clinical studies and post-marketing adverse event reporting, Ristempa® (pegfilgrastim) Public assessment report and literature.
Risk factors and risk groups	Cutaneous vasculitis may be a primary disorder or a cutaneous manifestation of other diseases such as systemic necrotizing vasculitis, other connective tissue diseases, systemic bacterial infections, or malignancies.

Risk minimisation measures	Routine risk minimisation measures: Section 4.8 of Pegfilgrastim SmPC has information on this safety concern Section 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: **Sweet's syndrome (Acute Febrile Dermatosis)**	
Evidence for linking the risk to the medicine	Sweet's syndrome (Acute Febrile Dermatosis), has been identified as an important identified risk in Neulasta® clinical studies and post-marketing adverse event reporting, Ristempa® (pegfilgrastim) Public assessment report and literature.
Risk factors and risk groups	Approximately 20% to 25% of all patients diagnosed with Sweet's syndrome have cancer, the most common being acute myelogenous leukemia. Other associated conditions include infections, inflammatory diseases, and pregnancy.
Risk minimisation measures	Routine risk minimisation measures: Section 4.8 of Pegfilgrastim SmPC has information on this safety concern Section 1 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: **Anaphylactic reaction**	
Evidence for linking the risk to the medicine	Anaphylactic reaction and hypersensitivity reactions (severe, rapidly progressing allergic reactions associated with wheezing, shortness of breath and low blood pressure) have been identified as an important identified risk in Neulasta® clinical studies, post-marketing adverse event reporting in Neulasta®, Ristempa® (pegfilgrastim) public assessment report.

Risk factors and risk groups	History of drug allergy, history of hypersensitivity to pegfilgrastim.
Risk minimisation measures	Routine risk minimisation measures: Section 4.3, 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include prescription only status of the product. Additional risk minimisation measures: None
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 February 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: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: **Serious pulmonary adverse events (including Interstitial pneumonia and ARDS)**	

Evidence for linking the risk to the medicine	Serious and severe complications affecting the lung (including interstitial pneumonia and 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: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. 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 (eg, sarcoidosis, diabetes mellitus, herpes) have been identified as the cause of sickle cell crisis.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern.

	Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: **Musculoskeletal pain-related symptoms**	
Evidence for linking the risk to the medicine	Muscle and bone pain-related symptoms have been identified as an important identified risk in Neulasta® clinical studies and post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	No clear risk group or risk factor has been defined in cancer patients receiving pegfilgrastim.
Risk minimisation measures	Routine risk minimisation measures: Section 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Identified Risks: Leukocytosis	
Evidence for linking the risk to the medicine	Leukocytosis (increased white blood cell counts above the normal range) has been identified as an important identified risk in Neulasta® post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	No risk groups or risk factors for leukocytosis are known.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures:

	None
Important Identified Risks: Thrombocytopenia	
Evidence for linking the risk to the medicine	Thrombocytopenia (low platelet counts below the normal range), which reduces the ability of blood to clot, has been identified as an important identified risk in Neulasta® clinical studies and post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	Many drugs, including chemotherapeutic agents, can cause thrombocytopenia.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. 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: Section 4.4 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Section 2 and 4 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Potential Risk: Acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS]	

Evidence for linking the risk to the medicine	Acute myeloid leukaemia/myelodysplastic syndrome (cancer of the blood and a disorder that can occur when the blood-forming cells of the bone marrow are damaged) has been identified as an important potential risk in Neulasta® post-marketing adverse event reporting, Ristempa® (pegfilgrastim) public assessment report and literature.
Risk factors and risk groups	AML: Relatives of patients with leukemia are at higher risk of contracting AML (by approximately 2- to 7-fold). There is evidence that a sibling of an AML patient who becomes a bone marrow or PBPC donor may develop AML later in life independent of drugs or techniques used to facilitate the donation. Chemotherapy and/or radiation treatment for a primary malignancy is associated with risk of secondary AML. Alkylating agents and topoisomerase II inhibitors have been implicated as being leukemogenic. Environmental risk factors for AML may include ionizing radiation, non-ionizing radiation, benzene, pesticides, smoking, diet, diagnostic radiology, medications (eg, chloramphenicol), viruses, and other occupational exposure such as from the leather and printing industry. MDS: First-degree relatives of adults with MDS have a 15-fold increased risk of MDS. Chemotherapy and/or radiation treatment for a primary malignancy is also a risk factor for MDS. Other risk factors include aplastic anemia, paroxysmal nocturnal hemoglobinuria, ionizing radiation, alkylating agents, occupational and environmental carcinogens (eg, halogenated organics, metals, copper, arc welding fumes, exhaust gases, pesticides, smoking, hair dye, benzene, polyaromatic hydrocarbons in air pollution).
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Section 4.4, 5.1 and 5.3 of Pegfilgrastim SmPC has information on this safety concern. Section 2 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product.

	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	Routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Potential Risk: Medication errors including overdose	
Evidence for linking the risk to the medicine	Medication errors including overdose have been identified as an important potential risk in Neulasta® clinical studies, post-marketing adverse event

	reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	No clear risk group or risk factor has been defined in cancer patients receiving pegfilgrastim.
Risk minimisation measures	Routine risk minimisation measures: Section 1, 2, 4.2, 4.5 and 4.9 of Pegfilgrastim SmPC has information on this safety concern. Section 1 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Potential Risk: Drug interaction with lithium	
Evidence for linking the risk to the medicine	Drug interaction with lithium has been identified as an important potential risk in Neulasta® clinical studies, post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	Therapeutic uses of lithium for hematologic conditions include: idiopathic neutropenia, Felty's Syndrome, several childhood neutropenic disorders, infectious and iatrogenic neutropenia, clozapine and carbamazepine-induced granulocytopenia, aplastic anemia, and post chemo-/ radio-therapy. Although lithium use is frequently associated with leukocytosis, (White blood Cell count [WCC] >100 X 10^9/L) represents a clinical emergency because of the risk of cerebral infarction and haemorrhage" but that "WCC induced does not exceed 1 to 5 times the upper limit of the normal range" and is "reversible on withdrawing the drug [lithium]".
Risk minimisation measures	Routine risk minimisation measures: Section 4.5 of Pegfilgrastim SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None

Important Potential Risk: Off-label use	
Evidence for linking the risk to the medicine	Off-label use (use outside of the approved indications) has been identified as an important potential risk in Neulasta® post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report. Ristempa® (pegfilgrastim) : EPAR - Public assessment report (EMA/187414/2015) dated, 26 February 2015
Risk factors and risk groups	It is known that pegfilgrastim has been used off-label to treat AML, MDS, peripheral blood stem cell apheresis/harvest, idiopathic neutropenia/ agranulocytosis, and unspecified leukaemia. Information on how well pegfilgrastim works in other conditions or what side effects could be seen is not available.
Risk minimisation measures	Routine risk minimisation measures: Section 4.1 and 4.4 of Pegfilgrastim SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Important Potential Risk: Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	
Evidence for linking the risk to the medicine	Immunogenicity (risk of the body producing an antibody against Pegfilgrastim, which may result in a lack of effect or an allergic reaction) has been identified as an important potential risk in Neulasta® clinical studies, post-marketing adverse event reporting and Ristempa® (pegfilgrastim) public assessment report.
Risk factors and risk groups	Risk factors are not known
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of Pegfilgrastim SmPC has information on this safety concern. Section 2 of Pegfilgrastim PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product.

	Additional risk minimisation measures: None
Important Potential Risk: Extramedullary haematopoiesis	
Evidence for linking the risk to the medicine	Extramedullary haematopoiesis (development of blood outside of the inner space of the bone) has been identified as an important potential risk in Neulasta® clinical studies, post-marketing adverse event reporting, Ristempa® (pegfilgrastim) public assessment report and literature.
Risk factors and risk groups	Extramedullary hematopoiesis is a common complication of chronic hematologic disorders such as thalassemia, leukemia, lymphoma, and myelofibrosis.
Risk minimisation measures	Routine risk minimisation measures: Section 5.3 of Pegfilgrastim SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Missing information: Risks in children <18 years of age	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 and 4.8 of Pegfilgrastim SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Missing information: Risks during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Section 4.6 of Pegfilgrastim SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. 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 authorization 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.