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

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

Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector Summary of Product Characteristics (SmPC) and Package Leaflet give essential information to Healthcare Professionals and patients on how Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector should be used.

This summary of the RMP for Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector 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 Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector's RMP.

I. The medicine and what it is used for

Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector 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). It contains pegfilgrastim as the active substance and is given by subcutaneous injection.

Further information about the evaluation of Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector's benefits can be found in the Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector'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/pelgraz.

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

Important risks of Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector, together with measures to minimise such risks and the proposed studies for learning more about Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector'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*.

II.A List of important risks and missing information

Important risks of Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector 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 Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector. 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).

Important identified risks	• Acute Respiratory Distress Syndrome (ARDS) • Capillary leak syndrome • 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: **Acute Respiratory Distress Syndrome (ARDS)**	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with Neulasta.
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 minimization measures	<u>Routine risk minimisation measures</u>: Sections 4.4 and 4.8 of Pelgraz SmPC have information on this safety concern. Section 2 of Pelgraz PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. <u>Additional risk minimization measures</u>: None
Important Identified Risks: **Capillary leak syndrome**	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta.
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 Pelgraz SmPC have information on this safety concern. Sections 2 and 4 of Pelgraz PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. 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	This safety concern was identified in the post-marketing setting with Neulasta.
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: Sections 4.4 and 4.8 of Pelgraz SmPC have information on this safety concern. Section 2 of Pelgraz PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: None
Important Identified Risks: Glomerulonephritis	

Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta.
Risk factors and risk groups	Not Specified
Risk minimisation measures	Routine risk minimisation measures: Sections 4.4 and 4.8 of Pelgraz SmPC have information on this safety concern. Sections 2 and 4 of Pelgraz PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: None
Important Potential Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	PRAC review of case reports in EudraVigilance and the scientific 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

II.C Post-authorisation development plan

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

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

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

There are no studies required for Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector.