Part VI: Summary of the risk management plan

Summary of risk management plan for Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe. The RMP details important risks of Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe, how these risks can be minimised, and how more information will be obtained about Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe risks and uncertainties (missing information).

Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe Summary of Product Characteristics (SmPC) and Package Leaflet give essential information to Healthcare Professionals and patients on how Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe should be used.

This summary of the RMP for Pelgraz 6 mg/0.6 mL 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 Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe RMP.

I. The medicine and what it is used for

Pelgraz 6 mg/0.6 mL 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 is given by subcutaneous injection.

Further information about the evaluation of Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe's benefits can be found the Pelgraz EPAR, including in its plain-language summary, available on the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/003961/human_med_002308.jsp

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

Important risks of Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe, together with measures to minimise such risks and the proposed studies for learning more about Pelgraz 6 mg/0.6 mL 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 Pelgraz 6 mg/0.6 mL 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 Pelgraz 6 mg/0.6 mL 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 Pelgraz 6 mg/0.6 mL 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	• Acute febrile neutrophilic dermatosis (Sweet's syndrome) • Serious Pulmonary Adverse Events including interstitial pneumonia and Acute Respiratory Distress Syndrome (ARDS) • Capillary leak syndrome • Cutaneous Vasculitis • Severe allergic reaction (anaphylactic reaction) • Sickle Cell Crisis in Patients with Sickle Cell Disease • Severe splenomegaly/splenic rupture • Musculoskeletal pain-related symptoms • Thrombocytopenia • Leukocytosis • Glomerulonephritis

List of important risks and missing information	
Important potential risks	• Cytokine release syndrome • Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies) • Drug Interaction with lithium • Malignant Cell Growth (myeloid malignancies such as acute myelogenous leukaemia [AML] and myelodysplastic syndrome [MDS]) • Off label use • Extramedullary hematopoiesis • Medication errors including overdose
Missing information	• Risks in children <18 years of age • Risks during pregnancy and lactation

II.B Summary of important risks

Important Identified Risks: **Acute febrile neutrophilic dermatosis (Sweet's syndrome)**	
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	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 minimization measures	Routine risk minimisation measures: Section 4.8 of Pelgraz SmPC has information on this safety concern Section 4 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: **Serious Pulmonary Adverse Events including interstitial pneumonia and 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	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 minimization measures: 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: **Cutaneous vasculitis**	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta.
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 Pelgraz SmPC has information on this safety concern Section 4 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: **Severe allergic reaction (anaphylactic reaction)**	
Evidence for linking the risk to the medicine	APO-Peg-02 CSR, 154-14 CSR (Module 5.3.4.1) and APO-Peg-03 CSR (Module 5.3.5.1).
Risk factors and risk groups	History of drug allergy, history of hypersensitivity to pegfilgrastim.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.3, 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 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. 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: **Severe splenomegaly/splenic rupture**	
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	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 infections [septicemia, bacterial endocarditis, typhoid, infectious mononucleosis, tuberculosis, brucellosis, syphilis, malaria, leishmaniasis, and schistosomiasis]).
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: **Musculoskeletal pain-related symptoms**	
Evidence for linking the risk to the medicine	APO-Peg-02 CSR, 154-14 CSR (Module 5.3.4.1), APO-Peg-03 CSR (Module 5.3.5.1) and postmarketing adverse event reporting for Neulasta.
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 Pelgraz SmPC has information on this safety concern.

	Section 4 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: Thrombocytopenia	
Evidence for linking the risk to the medicine	154-14 CSR (Module 5.3.4.1), APO-Peg-03 CSR (Module 5.3.5.1) and postmarketing adverse event reporting for Neulasta.
Risk factors and risk groups	Many drugs, including chemotherapeutic agents, can cause thrombocytopenia.
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: Leukocytosis	
Evidence for linking the risk to the medicine	APO-Peg-03 CSR (Module 5.3.5.1) and this safety concern was identified in the postmarketing setting for Neulasta.
Risk factors and risk groups	No risk groups or risk factors for leukocytosis are known.
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: 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

Important Potential Risk: Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	
Evidence for linking the risk to the medicine	APO-Peg-02 CSR, 154-14 CSR (Module 5.3.4.1) and APO-Peg-03 (Module 5.3.5.1), postmarketing adverse event reporting for Neulasta and scientific literature.
Risk factors and risk groups	Risk factors are not known
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of Pelgraz SmPC has 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 Potential Risk: Drug interaction with lithium	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting with Neulasta and scientific literature.
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, a white blood cell count (WCC) ">100 L-9 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 Pelgraz SmPC 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 Potential Risk: Malignant Cell Growth (myeloid malignancies such as acute myelogenous leukaemia [AML] and myelodysplastic syndrome [MDS])	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta.
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	Routine risk minimisation measures: Section 4.4 of Pelgraz SmPC has 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 Potential Risk: Off label use	
Evidence for linking the risk to the medicine	Postmarketing adverse event reports for Neulasta.
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: Sections 4.1 and 4.4 of Pelgraz SmPC 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: Extramedullary haematopoiesis	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta and scientific 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 Pelgraz SmPC 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 Potential Risk: Medication errors including overdose	
Evidence for linking the risk to the medicine	Post-marketing adverse event reports for Neulasta and scientific literature.

Risk factors and risk groups	No clear risk group or risk factor has been defined in cancer patients receiving pegfilgrastim.
Risk minimisation measures	Sections 4.2, 4.5 and 4.9 of Pelgraz SmPC 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.
Missing information: Risks in children <18 years of age	
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 and 4.8 of Pelgraz SmPC 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
Missing information: Risks during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Sections 4.6 and 5.3 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

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/0.6 mL solution for injection in pre-filled syringe.

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

There are no studies required for Pelgraz 6 mg/0.6 mL solution for injection in pre-filled syringe.