PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Neulasta® (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Neulasta®. The RMP details important risks of Neulasta®, how these risks can be minimized, and how more information will be obtained about Neulasta's risks.

Neulasta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Neulasta® should be used.

This summary of the RMP for Neulasta® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Neulasta's RMP.

I. The medicine and what it is used for

Neulasta® is authorized for reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) in adult patients (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 Neulasta's benefits can be found in Neulasta's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/neulasta

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Neulasta®, together with measures to minimize such risks and the proposed studies for learning more about Neulasta's risks, are outlined below.

Measures to minimize 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, such as warnings, precautions, and advice on correct use;
- Important advice on the medicine's packaging;

- The authorized 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 public (eg, with or without prescription) can help to minimizes its risks.

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

In the case of medication errors including underdose – on-body injector, resulting in lack of efficacy, these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (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 Neulasta® are risks that need special risk management activities to further investigate or minimize 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 Neulasta®. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risk	• Capillary leak syndrome • Sickle cell crisis in patients with sickle cell disease • Medication errors – on body injector, resulting in lack of efficacy due to underdose (as a result of user error or device issue) • Glomerulonephritis • Acute respiratory distress syndrome
Important Potential Risk	• Cytokine release syndrome • Acute myeloid leukemia/myelodysplastic syndrome
Missing Information	• None

II.B. Summary of Important Risks

Important Identified risk: Capillary leak syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of capillary leak syndrome in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins (Kai-Feng et al, *BMC Cancer*, 2011;11:204), gemcitabine (Baron et al, *Clin Oncol (R Coll Radiol)*, 2006;18:90-91), doxorubicin (Krzesiński et al, *Cardiol J*, 2010;17:88-91), granulocyte-macrophage colony-stimulating (Al-Homaidhi et al, *Bone Marrow Transpl*, 1998;21(2):209-214), and interferon (Yamamoto et al, *Arch Intern Med*, 2002;25:481-482). 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, *BMC Cancer*, 2011;11:204).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None

Important identified risk: Sickle cell crisis in patients with sickle cell disease	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of sickle cell crisis in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Patients with sickle cell disease are at risk for sickle cell crisis (Rees et al, *Lancet,* 2010;376:2018-2031). 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, *Am Fam Physician*, 2000;61:1349-1356,1363-1344).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 Additional risk minimization measures: • None

Important identified risk: Medication errors – on body injector, resulting in lack of efficacy due to underdose (as a result of user error or device issue)	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. Medication errors have been reported in subjects receiving placebo via the OBI in placebo-controlled clinical studies.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.4, 4.8, and 5.1 • PL Section 3, 4, and 6 • Instructions for use (IFU) all sections Additional risk minimization measures: • Patient alert card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational Study 20170701 • Summary reports of medication error events reported with the on-body injector in the EU market See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Glomerulonephritis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies, postmarketing adverse event reporting and from the literature. There were no events of glomerulonephritis (GN) in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Other than the cancer itself, no specific risk factors were identified for this patient population.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None

Important identified risk: Acute respiratory distress syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. The placebo-controlled clinical study data show a higher rate of acute respiratory distress syndrome in subjects receiving pegfilgrastim compared to subjects receiving placebo.
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 non-Hodgkin's lymphoma (NHL) (Huang et al, *Ann Hematol*, 2011;90:1145-1151; Katsuya et al, *Leukemia & lymphoma*, 2009;50:1818-1823). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, *J Clin Onc*, 1984;2:396-405), particularly in Japan (Camus et al, *Br J Cancer,* 2004;91 Suppl 2:S18-23).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None

Important potential risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of cytokine release syndrome in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Patients receiving bi-specific antibodies and T cells engineered to express anti-CD19 chimeric antigen receptor are at particularly high risk for cytokine release syndrome (Frey, *Best Pract Res Clin Haematol*, 2017;30(4):336-340). The severity of the cytokine release syndrome mediating infusion reaction might be related to the number of circulating lymphocytes (Chung, *Oncologist*, 2008;13:725-732). Among patients with B-cell malignancies, risk factors for developing cytokine release syndrome included higher bone marrow tumor burden, higher chimeric antigen receptor T-cell (CAR-T) cell dose, bulk CD8+ T-cell selection, lymphodepletion using fludarabine/ cyclophosphamide, and presence of thrombocytopenia before lymphodepletion (Hay et al, *Blood*, 2017;130(21):2295-2306).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Important potential risk: Acute myeloid leukemia/myelodysplastic syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Chemotherapy only and radiotherapy and chemotherapy increases the risk of AML/MDS among elderly women diagnosed with breast cancer (Calip et al, *Breast Cancer Res Treat*, 2015;154(1):133-143). *AML* Increased risk of AML has been reported among relatives of patients with leukemia (Hemminki and Jiang, *Leuk Res*, 2002;26:611-613; Rauscher et al, *Am J Epidemiol*, 2002;156:517–526); patients receiving alkylating agents and topoisomerase II inhibitors (Leone et al, *Haematologica*, 2007;92:1389-1398); and exposure to environmental risk factors including radiation, benzene, pesticides, smoking, diagnostic radiology, chloramphenicol, and viruses (Bowen, *Sem Hematol*, 2006;43:82-88). *MDS* Risk factors for MDS include first degree relatives with history of MDS, aplastic anemia, paroxysmal nocturnal hemoglobinuria, ionizing radiation, alkylating agents, halogenated organics, copper, arc welding fumes, exhaust gases, pesticides, smoking, hair dye, benzene, and polyaromatic hydrocarbons in air pollution (Strom et al, *Semin Hematol,* 2008;45:8-13).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20160176 See Section II.C of this summary for an overview of the postauthorization development plan

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Neulasta®.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20170701	• To assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the patient alert card. Safety concerns addressed: Medication errors – on body injector, resulting in lack of efficacy due to underdose (as a result of user error or device issue)
Summary reports of medication error events reported with the on-body injector in the EU market	To provide an analysis of medication error events that were reported with the use of the on-body injector in the EU market Safety concerns addressed: Medication errors – on body injector, resulting in lack of efficacy due to underdose (as a result of user error or device issue)
Study 20160176	• Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, compare the risk of SEER-reported or Medicare-reported MDS/AML between those receiving G-CSF vs. not receiving G-CSF for each tumor type. • Among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer, describe the characteristics of patients overall, by tumor type, by use of G-CSF, and by occurrence of MDS/AML. • Calculate the pooled hazard ratio for MDS/AML following G-CSF use among patients aged 66 years and older, treated with chemotherapy for breast (stage I-III), lung (stage I-III) or prostate (stage I-IV) cancer. Safety concerns addressed: Acute myeloid leukemia/myelodysplastic syndrome