Part VI: Summary of the risk management plan

Summary of risk management plan for Udenyca (pegfilgrastim)

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

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

This summary of the RMP for Udenyca 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 Udenyca's RMP.

I. The medicine and what it is used for

Udenyca 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 Udenyca's benefits can be found in Udenyca's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004413/human_med_002311.jsp.

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

Important risks of Udenyca together with measures to minimise such risks and the proposed studies for learning more about Udenyca'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*.

If important information that may affect the safe use of Udenyca is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Udenyca 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 Udenyca. 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 • Anaphylactic reaction and hypersensitivity reactions • 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 • Aortitis • Haemoptysis and Pulmonary haemorrhage
Important potential risks	• AML/MDS • Cytokine release syndrome • Medication errors including overdose • Drug interaction with lithium • Off-label use • Immunogenicity (incidence and clinical implications of anti-pegfilgrastim 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 risk: 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.
Risk factors and risk groups	Underlying conditions that can lead to an enlarged spleen include: diseases of the blood (haematologic diseases), high pressure in the venous system that drains blood from the intestines to the liver

	(portal hypertension), protein storage diseases (for example Gaucher's disease, Niemann-Pick disease, histiocytosis X), systemic diseases (for example sarcoidosis, amyloidosis, or collagen diseases like systemic lupus erythematosus and rheumatoid arthritis), and systemic infections (for example septicaemia, bacterial endocarditis, typhoid, infectious mononucleosis, tuberculosis, brucellosis, syphilis, malaria, leishmaniasis, and schistosomiasis).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: 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.
Risk factors and risk groups	Cutaneous vasculitis may be a primary disorder or another disease becoming visible on the skin (such as systemic necrotising vasculitis, other connective tissue diseases, systemic bacterial infections, or cancers).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • Package leaflet Section 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: Sweet's Syndrome	
Evidence for linking the risk to the medicine	Sweet's Syndrome, which is a skin disease presenting with plum-coloured, raised, painful sores on the limbs and sometimes the face and neck as well as fever, has been identified as an important identified risk in Neulasta post-marketing adverse event reporting.
Risk factors and risk groups	Approximately 20% to 25% of all patients diagnosed with Sweet's syndrome have cancer, the most common being AML (a form of leukaemia). Other associated conditions include infections, inflammatory diseases, and pregnancy.

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • Package leaflet Section 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: Anaphylactic Reaction and Hypersensitivity Reactions	
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 and Udenyca clinical studies and in post-marketing adverse event reporting in Neulasta.
Risk factors and risk groups	Patients with a history of allergic or anaphylactic reactions (severe allergic reactions) may be considered to be at risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.3, 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: Capillary Leak Syndrome	
Evidence for linking the risk to the medicine	Capillary leak syndrome (a syndrome in which the plasma portion of blood leaks from vessels into surrounding tissue causing swelling, difficulty in breathing and in some cases low blood pressure) has been identified as an important identified risk in Neulasta clinical studies and post-marketing adverse event reporting.
Risk factors and risk groups	Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins, chemotherapeutic agents like gemcitabine and doxorubicin, granulocyte-macrophage colony-stimulating factor, and interferon. Capillary leak syndrome has also been reported in relation to different conditions such as carbon monoxide poisoning, after having a baby (postpartum state), and some skin diseases (e.g.pustular psoriasis).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction.

Important identified risk: Serious Pulmonary Adverse Events (Including Interstitial Pneumonia and Acute Respiratory Distress Syndrome)	
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 and post-marketing adverse event reporting.
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have shown that an elevated risk for developing interstitial pneumonia is associated with use of rituximab in NHL (a cancer of the white blood cells). 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: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None.

Important identified risk: 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.
Risk factors and risk groups	Patients with sickle cell disease are at risk for sickle cell crisis which presents with symptoms such as severe pain in the bones, chest, gut, or joints. Factors such as infections, dehydration, low levels of oxygen, acidosis (the blood containing more acid than normal), extreme physical exercise, physical or psychologic stress, alcohol, pregnancy, cold weather, and concomitant medical conditions (for example sarcoidosis, diabetes mellitus, herpes) have been identified as a cause of sickle cell crisis.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Section 2 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: 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.
Risk factors and risk groups	No specific risk group or risk factor have been defined in cancer patients receiving pegfilgrastim.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • Package leaflet Section 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: 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.
Risk factors and risk groups	No risk groups or risk factors for leukocytosis are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: 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.
Risk factors and risk groups	Many drugs, including chemotherapeutic agents, can cause thrombocytopenia.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine

Additional pharmacovigilance activities	None

Important identified risk: 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 and literature.
Risk factors and risk groups	Infections, autoimmune diseases, diabetes, cancer, as well dysfunctions in part of the immune system (the complement system), and genetic susceptibility can play a role in the aetiology of glomerulonephritis. Certain chemotherapeutics can cause glomerular injury.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: Aortitis	
Evidence for linking the risk to the medicine	Aortitis (inflammation of the large blood vessel which transports blood from the heart to the body) has been identified as an important identified risk in G-CSF and Neulasta post-marketing adverse event reporting and literature.
Risk factors and risk groups	Only limited information is available on how and why aortitis develops under treatment with G-CSF, but chemotherapeutic treatment as well as radiation may be risk factors in cancer patients. Long-term administration of filgrastim could also pose a risk, as 4.1% of patients in a severe and longstanding low neutrophil counts who had their information collected in aa registry developed some form of vasculitis (mainly cutaneous).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • Package leaflet Sections 2 and 4 • Prescription only medicine
Additional pharmacovigilance activities	None

Important identified risk: Haemoptysis and Pulmonary haemorrhage	
Evidence for linking the risk to the medicine	Haemoptysis and Pulmonary haemorrhage (coughing up blood and bleeding from the lung) have been identified as an important identified risk in G-CSF and Neulasta post-marketing adverse event reporting and literature.
Risk factors and risk groups	Only limited information is available on how and why patients develop haemoptysis and pulmonary haemorrhage under treatment with G-CSF, but chemotherapeutic treatment as well as radiation may be risk factors in cancer patients.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.8 • Package leaflet Section 4 • Prescription only medicine
Additional pharmacovigilance activities	None.

Important potential risk: Acute Myeloid Leukaemia / Myelodysplastic Syndrome	
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.
Risk factors and risk groups	AML: Relatives of patients with leukaemia are at higher risk of developing this blood cancer (by approximately 2- to 7-fold). There is evidence that a sibling of an AML patient who becomes a bone marrow or blood stem cell 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 cancer is associated with risk of secondary AML. Alkylating agents and topoisomerase II inhibitors have been implicated as being leukaemogenic. Environmental risk factors for AML may include ionizing radiation, non-ionizing radiation, benzene, pesticides, smoking, diet, diagnostic radiology, medications (e.g. 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 anaemia, paroxysmal nocturnal haemoglobinuria, ionizing radiation, alkylating agents, occupational and environmental carcinogens (e.g. 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: • SmPC Section 4.4 • Package leaflet Section 2 • Prescription only medicine
Additional pharmacovigilance activities	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 and the scientific literature.
Risk factors and risk groups	The administration of monoclonal antibodies and other drugs can cause infusion reactions, but 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 white blood cells in the blood stream. During the first infusion of rituximab to patients with relapsed B-cell chronic lymphocytic leukaemia 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	No risk minimisation measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction.

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 the literature.
Risk factors and risk groups	No risk factors are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 1, 2, 4.2, 4.5 and 4.9 • Package leaflet Section 3

	• Prescription only medicine
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction.

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 the literature.
Risk factors and risk groups	Lithium can be used for haematologic conditions include: idiopathic neutropenia, Felty's Syndrome, several childhood neutropenic disorders, infectious and iatrogenic (treatment related) neutropenia, clozapine and carbamazepine-induced granulocytopenia, aplastic anaemia, and post chemo-/ radio-therapy. Although lithium use is frequently associated with a raised white blood cell (WBC) count (leucocytosis), "a WBC count > 100 x 10^9/l represents a clinical emergency because of the risk of cerebral infarction and haemorrhage" but that WBC induction "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: • SmPC Section 4.5 • Prescription only medicine
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction.

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.
Risk factors and risk groups	No risk factors are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.1 and 4.4 • Prescription only medicine
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction.

Important potential risk: Immunogenicity (Incidence and Clinical Implications of Anti-Pegfilgrastim 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 the literature.
Risk factors and risk groups	No risk factors are known.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • Package leaflet Section 2 • Prescription only medicine
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Testing for anti pegfilgrastim antibodies in patients who experience a potentially immune-based AE.

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 and the literature.
Risk factors and risk groups	Extramedullary haematopoiesis is a common complication of chronic blood-related disorders such as thalassaemia, leukaemia, lymphoma, and myelofibrosis.
Risk minimisation measures	No risk minimisation measures.

Additional pharmacovigilance activities	None.

Missing Information: Pregnant and Breastfeeding Women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2 and 4.8 • Prescription only medicine
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Pregnancy and lactation follow-up form - Pregnancy and lactation surveillance program

Missing Information: Paediatric Patients	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • Package leaflet Section 2 • Prescription only medicine
Additional pharmacovigilance activities	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 Udenyca.

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

There are no studies required for Udenyca.