PART VI. SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for Summary Tables in the EPAR

VI.I.1. Summary Table of Safety Concerns

Table 93. Summary of Safety Concerns

Important identified risks	Severe splenomegaly/splenic rupture
	Cutaneous vasculitis
	Sweet syndrome
	Decreased bone density and osteoporosis in children with severe chronic neutropenia receiving chronic treatment
	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
	Transformation to myelodysplastic syndromes or leukemia in SCN patients
	GVHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant
Important potential risks	Cytogenetic Abnormalities and Development of Secondary Hematologic Malignancies
	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 hematopoiesis
Missing information	Risk during pregnancy and lactation

VI.1.2 Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3 Summary of Postauthorization Efficacy Development Plan

Not applicable.

VI.1.4 Summary Table of Risk Minimization Measures

Table 94. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Severe splenomegaly/ splenic rupture	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 2. What you need to know before you use Neupogen o Warnings and precautions 4. Possible side effects	None
Cutaneous vasculitis	Relevant text is provided in the following section of the SmPC • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Sweet syndrome	Relevant text is provided in the following section of the SmPC • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Decreased bone density and osteoporosis in children with SCN receiving chronic treatment	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen o Warnings and precautions 4. Possible side effects	None

Table 94. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks (continued)		
Anaphylactic reaction	Relevant text is provided in the following sections of the SmPC • Section 4.3, Contraindications • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen o Warnings and precautions 4. Possible side effects	None
Capillary leak syndrome	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Serious pulmonary adverse events (including interstitial pneumonia and ARDS)	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Sickle cell crisis in patients with sickle-cell disease	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen o Warnings and precautions 4. Possible side effects	None

Table 94. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks (continued)		
Musculoskeletal pain-related symptoms	Relevant text is provided in the following section of the SmPC • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Leukocytosis	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PL: 4. Possible side effects	None
Thrombocytopenia	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen • Warnings and precautions 4. Possible side effects	None
Transformation to MDS or leukemia in SCN patients	Relevant text is provided in the following sections of the SmPC • Section 4.1, Therapeutic indications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen o Loss of response 4. Possible side effects	None

Table 94. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks (continued)		
GVHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant	Relevant text is provided in the following sections of the SmPC • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properities Relevant text is provided in the following sections of the PL: 4. Possible side effects	None
Important Potential Risks		
Cytogenetic Abnormalities and Development of Secondary Hematologic Malignancies	Relevant text is provided in the following section of the SmPC • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following section of the PL: 2. What you need to know before you use Neupogen 4. Warnings and precautions	None
Cytokine release syndrome	None	None
Medication Errors Including Overdose	Relevant text is provided in the following sections of the SmPC • Section 1, Name of medicinal product • Section 2, Qualitative and quantitative composition • Section 4.2, Posology and method of administration • Section 4.9, Overdose • Section 6.6, Special precautions for disposal and handling Relevant text is provided in the following sections of the PL: 3. How to use Neupogen 6. Contents of the pack and other information	None
Drug interaction with lithium	Relevant text is provided in the following section of the SmPC • Section 4.5, Interaction with other medicinal products and other forms of interaction	None

Table 94. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks (continued)		
Off-label use	Relevant text is provided in the following section of the SmPC • Section 4.1, Therapeutic indications • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the PL: 1. What Neupogen is and what it is used for 2. What you need to know before you use Neupogen Warnings and precautions	None
Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen • Warnings and precautions	None
Extramedullary hematopoiesis	None	None
Risks during pregnancy and lactation	Relevant text is provided in the following sections of the SmPC • Section 4.6, Pregnancy and lactation Relevant text is provided in the following sections of the PL: 2. What you need to know before you use Neupogen • Pregnancy and breastfeeding	None

Page 5 of 5

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Filgrastim can be used

- to increase the number of white blood cells (WBCs) after treatment with chemotherapy to help prevent infections
- to increase the number of WBCs after a BMT to help prevent infections
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to the patient after chemotherapy treatment. These can be taken from the patient or from a donor. The stem cells will then go back into the bone marrow and produce blood cells.

- to increase the number of white blood cells for patients who suffer from SCN
- to help prevent infections in patients with advanced infection with HIV, which will help reduce the risk of infections

Chemotherapy-induced neutropenia (CIN)

Chemotherapy-induced neutropenia (lowered number of WBCs) occurs in patients receiving chemotherapy. CIN can result in infection, illness, and sometimes death. Neutropenia is very common in this setting. The worse the neutropenia is and the longer it lasts, the greater the risk of infection. Filgrastim is used to increase white blood cell counts and to shorten the duration of neutropenia.

Patients undergoing treatment that lowers the number of blood stem cells (myeloablative therapy) followed by BMT

After treatment with very high-dose chemotherapy, patients are given stem cells either harvested from bone marrow or collected from peripheral blood (PBPCs) using an apheresis (a machine that separates blood components). Since the WBCs are low, the patient is at high risk of infection until the new stem cells begin to produce new white blood cells. Filgrastim is used to stimulate the stem cells to produce white blood cells so that the patient white blood cell count recovers more rapidly.

Stimulation of blood stem cell production in bone marrow before chemotherapy

Filgrastim can also be used to increase the number of blood stem cells that can be harvested from the patient or from a normal donor prior to high-dose chemotherapy (see above).

Severe chronic neutropenia

Some patients have chronic low white blood cell counts and so are at risk for severe infection. SCN can occur due to a variety of causes and can occur in adults and children. Filgrastim is used to increase white blood cell counts in these patients and reduce the risk of infection.

Neutropenia in patients with HIV

Neutropenia following antiretroviral therapy (medication to treat HIV) in patients with HIV infection may increase the risk of potentially life-threatening infections. Filgrastim is used to increase neutrophil counts (a neutrophil is a special kind of white blood cell) in these patients.

VI.2.2 Summary of Treatment Benefits

Filgrastim

Filgrastim is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of medicines called cytokines. Growth factors are proteins that are produced naturally in the body but they can also be made using biotechnology for use as a medicine. Filgrastim works by encouraging the bone marrow to produce more white blood cells.

Studies to demonstrate that filgrastim is effective

The benefits of filgrastim for treating low white blood cells caused by chemotherapy were studied in 340 patients with lung cancer. Patients who received filgrastim had fewer, shorter, and less severe episodes of low white blood cells. Another study of 521 patients with AML showed that filgrastim reduced the length of time that patients had low white blood cells and fevers.

The main study of filgrastim as a treatment for low white blood cells after BMT involved 54 patients with high-risk blood cancers (lymphomas). Patients who received filgrastim recovered their white blood cell count more quickly compared to patients who received placebo.

There were 2 main studies using filgrastim to increase the number of stem cells for collection for a stem cell transplant. These stem cells can either be given back to the same patient after chemotherapy treatment, or can be collected from a donor. In the first study, 72 patients with HD or NHL either had a BMT, or had a blood stem cell transplant after filgrastim treatment. Patients who received a blood stem cell transplant after filgrastim treatment had a more rapid recovery of white blood cells and another type of blood cell, known as platelets. They also had fewer platelet transfusions and spent fewer days in the hospital. In the second study, filgrastim was very effective at increasing the number of stem cells for collection in 20 normal donors.

The main study for SCN involved 123 subjects with recurrent infections. Filgrastim increased white blood cell counts and reduced the number of infections.

In the main study in 258 patients with HIV, patients who received filgrastim had fewer infections than patients who did not receive treatment for low white blood cells.

VI.2.3 Unknowns Relating to Treatment Benefits

Filgrastim has not been studied in women who are pregnancy or breastfeeding.

Filgrastim could affect a woman's ability to become pregnant or stay pregnant. Women who are breastfeeding should not take filgrastim.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What Is Known	Preventability
Severe enlarged spleen or rupture of spleen (severe splenomegaly/splenic rupture)	Enlarged spleen occurs very commonly in patients with SCN, commonly in patients with HIV, and uncommonly in normal stem cell donors. Enlarged spleen can increase the risk of splenic rupture, which could result in a fatal outcome if not detected and treated in a timely manner.	Patient should contact their doctor if they experience left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of the shoulder, which could indicate an enlarged spleen.
Inflammation of the blood vessels in the skin (cutaneous vasculitis)	Inflammation of the blood vessels in the skin occurs commonly in patients with SCN. Cutaneous vasculitis, when limited to small blood vessels in the skin, generally recovery is good.	Patients should contact their doctor if they experience changes to their skin such as skin changes, purple or red spots or bumps, clusters of small dots, splotches, bruises, or hives.
Plum-colored, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweet syndrome)	Sweet syndrome is an uncommon side effect is patients with cancer treated with filgrastim.	Treatment of conditions that increase the risk of Sweet syndrome, such as cancer and infection, can help prevent Sweet syndrome.
Bone disease (decreased bone density and osteoporosis) in children with SCN receiving long-term (chronic) treatment	Decreased density of the bone has been reported in children with SCN and appears to be primary due to the disease itself; however, filgrastim treatment may speed up the process of bone loss in children with SCN.	Care givers and children with SCN should discuss with their doctor if they are at risk of developing bone health problems and should discuss the potential benefits of monitoring if they are at risk.
Rapidly progressing, life-threatening allergic reaction (anaphylactic reaction)	Allergic reactions, including rapidly progression, life-threatening allergic reaction (anaphylaxis); skin rash; and/or hives (urticaria), occur rarely in patients receiving filgrastim.	Patients should stop taking filgrastim and tell their doctor immediately if they experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face, skin rash, itchy rash (urticaria), swelling of the face lips, mouth, tongue or throat (angioedema) or shortness of breath (dyspnea).

Important Identified Risks (continued)

Risk	What Is Known	Preventability
Leakage of fluid from small blood vessels (capillary leak syndrome)	Leakage of fluids from small blood vessels can result in low blood pressure (hypotension), overly concentrated blood (hemoconcentration), and low levels of the protein albumin in the blood (hypoalbuminemia). This condition, which can be life-threatening if treatment is delayed, has been reported uncommonly with filgrastim treatment in patients with cancer undergoing chemotherapy who have infections.	Patients should contact their doctor if they have puffiness, swelling, fullness in the abdomen, light-headedness, nausea, dryness in mouth and throat, decreased urination, weakness, fatigue, cool skin temperature in hands or feet, or change in mental activity. No information is currently available on how to prevent this event.
Severe lung inflammation causing difficulty in breathing (serious pulmonary events [including interstitial pneumonia and acute respiratory distress syndrome {ARDS}])	Patients should tell their doctor if they experience cough, fever and difficulty breathing while taking filgrastim, as there is a theoretical risk that this may worsen.	Patients should see their doctor if they have symptoms such as cough fever, and shortness of breath that could be preliminary signs of ARDS.
Severe pain in the bones, chest, gut or joints in patients with sickle cell anemia (sickle cell crisis in patients with sickle-cell disease)	Sickle cell crises have occurred in patients with sickle cell receiving filgrastim. Patients should tell their doctor if they have sickle cell anemia or related conditions that cause red blood cells to form a sickle shape.	Patients with sickle cell disease should receive filgrastim only after careful evaluation of both risks and benefits of treatment.
Pain in muscle and/or bone (musculoskeletal pain-related symptoms)	Bone pain occurs very commonly in patients with cancer and patients with SCN receiving filgrastim. In cancer patients, the pain is most often mild or moderate in severity and last for 1 to 2 days.	No information is currently available on how to prevent this event.
Increase in white blood cells (leukocytosis)	Filgrastim is administered in order to increase the level of white blood cells; thus, there is a potential for an excessive increase in white blood cells, and regular monitoring of white blood cell count is recommended while taking filgrastim.	Dose reduction or interruption may correct leukocytosis.

Important Identified Risks (continued)

Risk	What Is Known	Preventability
Decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)	Low platelet levels have been reported in clinical trials with filgrastim. In patients with cancer, the thrombocytopenia may have been related to chemotherapy. In normal donors of blood stem cells, the thrombocytopenia may have been related to the process used to extract white blood cells.	The patient's platelet count should be checked regularly during filgrastim treatment.
Blood cell abnormalities and cancer of the blood (transformation to MDS or leukemia in SCN patients)	Since filgrastim stimulates the production of white blood cells, there is a theoretical possibility that filgrastim could be associated with the development of cancer of the blood (acute myelogenous leukemia) or disorders that occur when the blood-forming cells in the bone marrow are damaged (MDS in patients treated with filgrastim). It is not known whether filgrastim is associated with this risk.	No information is currently available on how to prevent this event.
Reaction of the donor cells against the recipient of the transplant (GVHD) in patients receiving bone marrow from another person or a blood stem cell transplant	In patients undergoing an allogenic (from a donor) stem cell or BMT, graft-versus-host disease may occur. This is a reaction of the donor cells against the recipient of the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina, and joints. In company-sponsored clinical trials, graft-versus-host disease was not more common in subjects receiving filgrastim compared with placebo.	No effective therapy has been developed to prevent GVHD. Graft manipulation has been associated with decreased risk (T cell depletion for example), which has not been translated into improved survival due to increased risk of rejection, relapse, and infection.

Important Potential Risks

Risk	What Is Known
Blood cell abnormalities and cancer of the blood (cytogenetic abnormalities and development of secondary hematologic malignancies)	Since filgrastim stimulates the production of white blood cells, there is a theoretical possibility that filgrastim could be associated with the development of cancer of the blood (acute myelogenous leukemia or disorders that occur when the blood-forming cells in the bone marrow are damaged (MDS in patients treated with filgrastim. It is not known whether filgrastim is associated with this risk.
Release of immune-stimulating cells (cytokines) by cells targeted by medicines that are antibody form (cytokine release syndrome)	Cytokine release syndrome is characterized by symptoms such as nausea, headache, rapid heart rate (tachycardia), low blood pressure (hypotension), rash, and shortness of breath. Most reactions are mild-to-moderate; however, the reaction may be severe, life-threatening, or fatal.
Medication errors including overdose	The effects of overdose of filgrastim are not known. Patients should tell their doctor if they receive more filgrastim that the doctor prescribed.
Drug interaction with lithium	A drug interaction with lithium could increase the production of white blood cells beyond that expected with filgrastim treatment alone, but there is no evidence that such an interaction is harmful.
Off-label use	Filgrastim should only be used within its approved indication. No specific safety concerns have currently been identified when filgrastim has been used outside of its approved indication (off-label use)
Immune response (immunogenicity [incidence and clinical implications of anti-G-CSF antibodies])	There is a potential for the body to react to filgrastim as though it were a disease-causing organism. While a small number of patients have shown an immune response to filgrastim, the response did not impact the activity of the protein, so that filgrastim was still effective, and the patients did not experience any adverse effects.
Formation and development of blood cells occurring outside of the inner space of the bone (extramedullary hematopoiesis)	Blood cells are normally produced in the inner space of bones (medullary cavity). When blood cells begin to form outside the medullary cavity, this can lead to blood disorders. It is possible that filgrastim could increase this effect.

Missing Information

Risk	What Is Known
Risks during pregnancy and lactation	Filgrastim has not been studied in pregnant women. Filgrastim could affect a woman's ability to become pregnant or stay pregnant. Filgrastim has not been studied in breastfeeding women. Women who are breastfeeding should not take filgrastim.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the PL. The measures in these documents are known as routine risk minimization measures.

The SmPC and the PL for filgrastim can be found in filgrastim's EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned Postauthorization Development Plan

Filgrastim has been authorized since 1991. No further efficacy studies are planned. No study is a condition of the marketing authorization.

VI.2.7 Summary of Major Changes to the Risk Management Plan Over Time

Table 95. Major Changes to the Risk Management Plan Over Time

Version Number	Date	Safety Concerns	Comment
2	16 December 2013	Transformation to MDS or leukemia in SCN patients and GVHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant were added as identified risks. The identified risk "splenomegaly/splenic rupture" was amended to "severe splenomegaly/splenic rupture" The identified risk "ARDS" was amended to "serious pulmonary adverse events (including interstitial pneumonia and ARDS)" The identified risk "sickle cell crisis" was amended to "sickle cell crisis in patients with sickle cell disease" The identified risk "bone pain" was amended to "musculoskeletal pain-related symptoms" Medication errors including overdose, drug interaction with lithium, off-label use, immunogenicity (incidence and clinical implications of anti-G-CSF antibodies), and extramedullary hematopoiesis were added as potential risks Missing information of Children (stem cell mobilization [patients < 16 years of age], post-transplant, HIV, and neonates), patients with renal impairment, patients with hepatic impairment, patients with pulmonary impairment, and patients with cardiac impairment were removed. Missing information of was amended to "risks during pregnancy and lactation".	

Table 95. Major Changes to the Risk Management Plan Over Time

Version Number	Date	Safety Concerns	Comment
3	02 June 2014	Updated the following sections: SVI.4; III.1 and III.4 to include PV actitivies; Part VI.2; Updated Part V to include key elements, and not the exact wording of the SmPC	
4	04 August 2017	Preclinical data updated to align to template requirements. Clinical exposure data updated Category 4 studies 20101192, 20110146, and 20110191 deleted as completed. Pregnancy and Lactation Surveillance language removed. SCNIR 20 year data updated. Healthy donor report updated.	

Page 2 of 2