Summary of the Risk Management Plan

Summary of Risk Management Plan for RATIOGRASTIM/TEVAGRASTIM (FILGRASTIM)

This is a summary of the risk management plan (RMP) for Ratiograstim/Tevagrastim (Filgrastim) (herein after also referred to as Filgrastim). The RMP details important risks of Filgrastim, how these risks can be minimised, and how more information will be obtained about Filgrastim 's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Ratiograstim/Tevagrastim is authorised to stimulate the production of white blood cells in the following situations:

- to reduce the duration of neutropenia (low levels of neutrophils, a type of white blood cell) and the occurrence of febrile neutropenia (neutropenia with fever) in patients receiving chemotherapy (cancer treatment) that is cytotoxic (cell-killing);
- to reduce the duration of neutropenia in patients undergoing treatment to destroy the bone marrow cells before a bone marrow transplant (such as in some patients with leukaemia) if they are at a risk of long-term, severe neutropenia;
- to increase levels of neutrophils and reduce the risk of infections in patients with neutropenia who have a history of severe, repeated infections;
- to treat persistent neutropenia in patients with advanced human immunodeficiency virus (HIV) infection, to reduce the risk of bacterial infections when other treatments are not appropriate.

It can also be used in patients who are about to donate blood stem cells for transplant, to help release these cells from the bone marrow.

It contains filgrastim as the active substance and it is given by injection or infusion.

Further information about the evaluation of Ratiograstim/Tevagrastim’s benefits can be found in Ratiograstim/Tevagrastim’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpages:

https://www.ema.europa.eu/en/medicines/human/EPAR/ratiograstim

https://www.ema.europa.eu/en/medicines/human/EPAR/tevagrastim

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of filgrastim, together with measures to minimise such risks and the proposed studies for learning more about filgrastim'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 Ratiograstim/Tevagrastim is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of filgrastim 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 filgrastim. 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);

Table 1: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Splenic rupture • Cutaneous vasculitis • Pulmonary adverse events • Sweet's syndrome • Decreased bone density and osteoporosis in children with SCN receiving chronic treatment • Anaphylactic reaction • Capillary leak syndrome • Sickle cell crisis in patients with sickle cell disease • Musculoskeletal pain-related symptoms • Leukocytosis • Thrombocytopenia • Transformation to myelodysplastic syndrome or leukaemia in SCN patients • GVHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant
Important potential risks	• Treatment-related AML/MDS in patients with myeloid malignancies and chemotherapy-induced neutropenia • Acute myeloid leukemia (AML)/ myelodysplastic syndrome (MDS) in normal donors of peripheral blood progenitor cells (PBPCs) • 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

II.B Summary of Important Risks

Table 2: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Splenic rupture	
Evidence for linking the risk to the medicine	Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal.
Risk factors and risk groups	Splenic rupture: - Normal donors undergoing peripheral blood progenitor cell mobilisation. Splenomegaly: - Normal donors undergoing peripheral blood progenitor cell mobilisation. - Severe chronic neutropenia (SCN) patients. - Patients with HIV
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Cutaneous vasculitis	
Evidence for linking the risk to the medicine	Cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients
Risk factors and risk groups	- Cancer patients - Severe chronic neutropenia (SCN) patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.

Important identified risk: Pulmonary adverse events	
Evidence for linking the risk to the medicine	Pulmonary adverse reactions, in particular interstitial lung disease, have been reported after G-CSF administration.
Risk factors and risk groups	Cancer patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Sweet's syndrome	
Evidence for linking the risk to the medicine	Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patientstreated with filgrastim.
Risk factors and risk groups	Cancer patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Decreased bone density and osteoporosis in children with SCN receiving chronic treatment	
Evidence for linking the risk to the medicine	Cases of decreased bone density and osteoporosis have been reported in paediatric patients with SCN receiving chronic treatment with filgrastim.
Risk factors and risk groups	Severe chronic neutropenia patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.

Important identified risk: Anaphylactic reaction	
Evidence for linking the risk to the medicine	Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim.
Risk factors and risk groups	- Cancer patients: reports were more common after IV administration. - Normal donors undergoing peripheral blood progenitor cell mobilisation
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Capillary leak syndrome	
Evidence for linking the risk to the medicine	Capillary leak syndrome has been reported after G-CSF administration.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** 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 some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease.
Risk factors and risk groups	Cancer patients (with sickle cell disease)
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.

Important identified risk: Musculoskeletal pain-related symptoms	
Evidence for linking the risk to the medicine	Musculoskeletal pain is a commonly reported adverse reaction
Risk factors and risk groups	Bone pain with filgrastim is associated with younger age, tumor type (NSCLC > breast > NHL), and chemotherapy regimen (more common in patients receiving taxane).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Leukocytosis	
Evidence for linking the risk to the medicine	White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5 % of patients receiving filgrastim at doses above 0.3 MIU/kg/day (3 µg/kg/day).
Risk factors and risk groups	Unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: Thrombocytopenia	
Evidence for linking the risk to the medicine	Transient thrombocytopenia following filgrastim administration and leukapheresis was observed in 35 % of subjects studied.
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. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.

Important identified risk: Transformation to myelodysplastic syndrome or leukaemia in SCN patients	
Evidence for linking the risk to the medicine	There was a low frequency (approximately 3 %) of myelodysplastic syndromes or leukaemia in clinical trial patients with SCN treated with filgrastim.
Risk factors and risk groups	Patients with congenital neutropenia have an inordinately high predisposition to spontaneous development of myelodysplastic syndrome and/or acute myeloid leukaemia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 2. Prescription only medicine. **Additional risk minimisation measures:** None.
Important identified risk: GVHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant	
Evidence for linking the risk to the medicine	There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation.
Risk factors and risk groups	Recipients of allogeneic peripheral blood progenitor cells mobilised with Filgrastim
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.8 and 5.1. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important potential risk: Treatment-related AML/MDS in patients with myeloid malignancies and chemotherapy-induced neutropenia	
Evidence for linking the risk to the medicine	There was a low frequency of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with severe chronic neutropenia treated with filgrastim. However, this observation has only been made in patients with congenital neutropenia.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.

Important potential risk: Acute myeloid leukemia (AML)/ myelodysplastic syndrome (MDS) in normal donors of peripheral blood progenitor cells (PBPCs)	
Evidence for linking the risk to the medicine	Transient cytogenetic abnormalities have been observed in normal donors following G-CSF use. The significance of these changes is unknown. Nevertheless, a risk of promotion of a malignant myeloid clone can not be excluded.
Risk factors and risk groups	Normal donors undergoing peripheral blood progenitor cell mobilization.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** None.
Important potential risk: Cytogenetic abnormalities and development of secondary hematologic malignancies	
Evidence for linking the risk to the medicine	G-CSF exerts its biological activities through binding to G-CSF receptors, which are present on pluripotent and myeloid-committed progenitors, and on differentiated myeloid cells. G-CSFs can stimulate in vitro proliferation and maturation. Thus, there is a theoretical risk that G-CSF might potentially be involved in the development of AML or MDS.
Risk factors and risk groups	AML Relatives of patients with leukemia are at higher risk of contracting AML (by approximately 2- to 7-fold) (Hemminki and Jiang, 2002; Rauscher et al, 2002; Goldgar et al, 1994; Shpilberg et al, 1994; Pottern et al, 1991; Bortin et al, 1987; Gunz et al 1975). 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 (Pabst et al, 2001; Preudhomme et al, 2000). Chemotherapy and/or radiation treatment for a primary malignancy is associated with risk of secondary AML (Travis et al, 2008; Mauritzson et al, 2002). Alkylating agents and topoisomerase II inhibitors have been implicated as being leukemogenic (Travis et al, 2008; Leone et al, 2007; Pedersen-Bjergaard, 2005; Pedersen-Bjergaard et al, 2002b). 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 (Bowen, 2006; Pedersen-Bjergaard et al, 2002; Zeeb and Blettner, 1998). MDS First-degree relatives of adults with MDS have a 15-fold increased risk of MDS (Lucas et al, 1989). 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) (Strom et al, 2008; Pedersen-Bjergaard et al, 2002b; Aul et al, 1998).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures:** None.

Important potential risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	In clinical trials with filgrastim, 4 cases consistent with capillary leak syndrome were reported among 2460 subjects (0.16%) During routine signal detection activities, a signal of disproportionate reporting of systemic capillary leak syndrome (SCLS) and cytokine release syndrome (CRS) was identified by the EMA in 2012 based on 15 cases retrieved from EudraVigilance for filgrastim and pegfilgrastim.
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.
Important potential risk: Medication errors including overdose	
Evidence for linking the risk to the medicine	The majority of the medication error events that have been reported in the postmarketing setting were wrong dose (overdose, underdose, or wrong dose schedule events), wrong route of administration, or storage error events. There have also been reports of errors involving the use of the wrong medication, particularly the use of filgrastim instead of pegfilgrastim or vice versa.
Risk factors and risk groups	No risk factors are known.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.9 and 6.6. Prescription only medicine. **Additional risk minimisation measures:** None.
Important potential risk: Drug interaction with lithium	
Evidence for linking the risk to the medicine	Since lithium promotes the release of neutrophils, it is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.
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 (Focosi et al, 2009). 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 one to five times the upper limit of the normal range" and is "reversible on withdrawing the drug [lithium]" (Flanagan and Dunk, 2008).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.5. Prescription only medicine. **Additional risk minimisation measures:** None.

Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	A potential for off-label-use with Ratiograstim/Tevagrastim cannot be fully excluded.
Risk factors and risk groups	- Patients with stroke/cerebral ischemia - Patients with coronary artery disease/ myocardial infarction/chronic heart failure - Patients with Crohn's disease - Therapeutic use of Filgrastim - Fixed dose administration
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.1. Prescription only medicine. **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	As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low.
Risk factors and risk groups	No special risk groups identified
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.
Important potential risk: Extramedullary hematopoiesis	
Evidence for linking the risk to the medicine	Specific clinical conditions (tumor invasion of the marrow and myelosuppressive chemotherapy [Wang and Darvishian, 2006]) result in production of blood cells outside of the marrow without the stimulation of exogenous G-CSF, and it appears that the administration of G-CSF could increase this effect.
Risk factors and risk groups	Extramedullary hematopoiesis is a common complication of chronic hematologic disorders such as thalassaemia, leukemia, lymphoma, and myelofibrosis.
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine. **Additional risk minimisation measures:** None.

Missing information: Risk during pregnancy and lactation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2. Prescription only medicine. **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 Ratiograstim/Tevagrastim (Filgrastim).

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for filgrastim.