Summary of risk management plan for Fulphila® (Pegfilgrastim)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of "Fulphila®" is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Fulphila® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. "Mylan Pharma GmbH, Steinhausen" is fully responsible for the accuracy and correctness of the content of the published summary RMP of Fulphila®.

Mylan

Better Health for a Better World

Mylan Pharma GmbH, Turmstrasse 24, CH-6312 Steinhausen •
T +41 41 768 55 55 • F +41 41 768 55 50 • http://www.mylan.ch/

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Fulphila® (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Fulphila®. The RMP details important risks of pegfilgrastim, how these risks can be minimised, and how more information will be obtained about pegfilgrastim' s risks and uncertainties (missing information).
Fulphila® 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

I. The medicine and what it is used for

Fulphila® 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). It contains pegfilgrastim as the active substance and it is given by pre-filled syringes each containing 6 mg of pegfilgrastim in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only.
The concentration is 20 mg/ml if the PEG moiety is included.

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

Important risks of Fulphila®, together with measures to minimise such 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 public (e.g. with or without prescription) can help to minimises its risks.

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

In addition to these measures, information about adverse events is collected continuously and is regularly analysed, 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 Fulphila® is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Fulphila® are those risks that need special risk management activities to further investigate or minimise them, so that the medicinal product can be safely administered to patients.

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 Fulphila®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but the definite causal 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/use in special patient populations etc.).

Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Severe splenomegaly / splenic rupture • Cutaneous vasculitis • Sweet's syndrome • Anaphylactic reaction • Capillary leak syndrome • Serious pulmonary adverse events including interstitial pneumonia and acute respiratory distress syndrome) • Sickle cell crisis in patients with sickle cell disease • Musculoskeletal pain-related symptoms • Leukocytosis • Thrombocytopenia • Glomerulonephritis
Important potential risks	• Acute myelogenous leukaemia/ myelodysplastic syndrome • 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 haematopoiesis
Missing information	• Use in paediatric patients • Use during pregnancy and breastfeeding

II.B Summary of important risks

Important Identified Risk: Severe Splenomegaly/Splenic Rupture	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Several underlying conditions which have been associated with splenomegaly as hematologic diseases (chronic myelogenous leukaemia, chronic lymphocytic leukaemia, acute leukaemia, malignant lymphoma, chronic myelofibrosis, polycythaemia vera, hairy cell leukaemia, thalassemia major, thalassemia intermedia, sickle cell anaemia, haemolytic anaemias, and megaloblastic anaemia), portal hypertension (cirrhosis and hepatic, portal, and splenic vein thrombosis), storage diseases (Gaucher's disease, Niemann-Pick disease, histiocytosis X), and systemic diseases (including sarcoidosis, amyloidosis, systemic lupus erythematosus and rheumatoid arthritis, systemic infections [such as septicaemia, bacterial endocarditis, typhoid, infectious mononucleosis, tuberculosis, brucellosis, syphilis, malaria, leishmaniosis, and schistosomiasis])[2]. However, no particular risk groups or risk factors specific to patients treated with pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Cutaneous Vasculitis	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Sweet's Syndrome	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Anaphylactic Reaction	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No specific risk groups or risk factors for hypersensitivity reactions to pegfilgrastim are known. For drug hypersensitivity reactions in general the most important risk factor is a previous reaction to the same or a related compound.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Capillary Leak Syndrome	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	The cases of capillary leak syndrome reported in association with the reference product have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaire.

Important Identified Risk: Serious Pulmonary Adverse Events Including Interstitial Pneumonia and Acute Respiratory Distress Syndrome	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	In most case reports reporting of pulmonary toxicity, G-CSF was given in combination with chemotherapeutic agents known to induce pulmonary toxicity. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Sickle Cell Crisis in Patients with Sickle Cell Disease	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	This risk is confined to individuals with heterozygous sickle cell trait or homozygous sickle cell disease. No further risk groups or risk factors within this patient population are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Musculoskeletal Pain-Related Symptoms	
Evidence for linking the risk to the medicine	Based on published literature, clinical trials and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Younger children appear to be at higher risk for bone pain than older patients. Treatment with taxanes has also been reported to be a risk factors for bone pain and bone pain has been reported to decrease in frequency by tumour type: breast cancer > non-small-cell lung carcinoma > non-Hodgkin lymphoma > small-cell lung carcinoma, however, other researchers could not confirm these associations.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Leukocytosis	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Thrombocytopenia	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Glomerulonephritis	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Important Identified Risk: Acute Myelogenous Leukaemia / Myelodysplastic Syndrome	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Based on mechanistic considerations, patients with an underlying myeloid cell disorder such as acute myelogenous leukaemia or myelodysplastic syndrome could be at elevated risk. Whereas most protocols have failed to show a benefit of G-CSF in terms of disease-free or overall survival in such patients, clinical trials have not suggested an increased risk for progression of myelodysplasia into overt leukaemia or stimulation of myeloid leukaemia cells, respectively.
Risk minimization measures	Routine risk minimisation measures.

Important Potential Risk: Cytokine Release Syndrome	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaire

Important Potential Risk: Medication errors including overdose	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaire.

Important Potential Risk: Drug interaction with lithium	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaires.

Important Potential Risk: Off-label use	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaire.

Important Potential Risk: Immunogenicity (Incidence and Clinical Implications of Anti-G-CSF Antibodies)	
Evidence for linking the risk to the medicine	Based on published literature, clinical trials and reference product label, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	For biopharmaceuticals in general, genetic predisposition, concomitant kidney or liver illness and autoimmune diseases are considered factors that might contribute to immunogenicity. Whether this is applicable also to pegfilgrastim or whether there are other risk groups or risk factors specific to pegfilgrastim is currently unknown.
Risk minimization measures	Routine pharmacovigilance activities, including follow up questionnaire.

Important Potential Risk: Extramedullary Haematopoiesis	
Evidence for linking the risk to the medicine	Based on published literature and reference product label, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	No risk groups or risk factors specific to pegfilgrastim are known.
Risk minimization measures	Routine risk minimisation measures.

Missing information: Use during pregnancy and breast-feeding	
Risk minimization measures	Routine risk minimisation measures including follow up questionnaire.

Missing information: Use in paediatric patients	
Risk minimization measures	Routine risk minimisation measures.

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 Fulphila®/ pegfilgrastim. Not applicable, as no post-authorisation efficacy studies are planned or ongoing.

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

There are no studies required for Fulphila®.