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.

This summary of the RMP for Fulphila® should be read in the context of all the 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 Fulphila®'s RMP.

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.

Further information about the evaluation of Fulphila®'s benefits can be found in Fulphila®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/fulphila-0.

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 regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

List of Important Risks and Missing Information

Important risks of Fulphila® are risks that need special risk management activities to further investigate or minimise the risk, 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 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/use in special patient populations etc.).

Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Capillary leak syndrome • Acute respiratory distress syndrome • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis
Important Potential Risks	• Cytokine release syndrome
Missing Information	• None

Summary of Important Risks

Important Identified Risk: Capillary leak syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference product, 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.[1]
Risk Minimisation Measures	Routine risk minimization measures

[1] MHRA. Filgrastim and pegfilgrastim: risk of capillary leak syndrome. Drug Safety Update [Internet]. 2014. Available from: https://www.gov.uk/drug-safety-update/filgrastim-and-pegfilgrastim-risk-of-capillaryleak-syndrome.

	SmPC sections: 4.2, 4.4 and 4.8. Specific follow-up questionnaire for capillary leak syndrome Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Important Identified Risk: Acute respiratory distress syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important identified risk.
Risk Factors and Risk Groups	Combination with chemotherapeutic agents known to induce pulmonary toxicity. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.[2]
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Important Identified Risk: Sickle cell crisis in patients with sickle cell disease

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference product, 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. 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)

[2] Azoulay E, Attalah H, Harf A, Schlemmer B, Delclaux C. Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. Chest. 2001;120(5):1695-701.

	have been identified as the cause of sickle cell crisis. [3]
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Important Identified Risk: Glomerulonephritis

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference product, 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. According to the SmPC of the reference product, dosing adjustment is not recommended in patients with renal impairment, including those with end stage renal disease. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim.
Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Important Potential Risk: Cytokine release syndrome

Evidence for Linking the Risk to the Medicine	Based on the published literature data and in line with the RMP for the reference product, this safety concern has been classified as an important potential risk.
Risk Factors and Risk Groups	According to some published data, conditions such as stress, obesity, diabetes, and hypertension exacerbate inflammation and may constitute risk factors for CRS. [4]

[3] Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. Am Fam Physician. 2000;61(5):1349-56, 63-4.

[4] Xing X, Hu X. Risk factors of cytokine release syndrome: stress, catecholamines, and beyond. Trends in Immunology. 2023;44(2):93-100.

Risk Minimisation Measures	Routine risk minimization measures SmPC sections: 4.2, 4.4 and 4.8. Specific follow-up questionnaire for cytokine release syndrome Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Post-Authorisation Development Plan

Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Fulphila®.

Other Studies in Post-Authorisation Development Plan

There are no studies required for Fulphila®.