Summary of risk management plan for Pegfilgrastim Mundipharma (pegfilgrastim)

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

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

This summary of the RMP for Pegfilgrastim Mundipharma 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 Pegfilgrastim Mundipharma's RMP.

I. The medicine and what it is used for

Pegfilgrastim Mundipharma is a biosimilar medicine authorised for reducing 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, which is already authorised in the European Union. It is given by subcutaneous injection.

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

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

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

II.A List of important risks and missing information

Important risks of Pegfilgrastim Mundipharma are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely used. 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 Pegfilgrastim Mundipharma. 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	Capillary leak syndrome Sickle cells crisis in patients with sickle cell disease Glomerulonephritis Acute respiratory distress syndrome
Important potential risks	AML/MDS Cytokine release syndrome
Missing information	Not applicable

II.B Summary of important risks

Important identified risks:

Capillary leak syndrome	
Evidence for linking the risk to the medicine	Product information for Neulasta/Ristempa EPAR and Summary of the RMP for Ristempa
Risk factors and risk groups	The risk factors for development of capillary leak syndrome attributed to G-CSF use are not fully elucidated. This syndrome was found independent on patients' age. The potential risk factors for development of capillary leak syndrome are underlying condition (e.g., acute graft-versus-host disease, bone marrow transplantation), use of certain medication (including G-CSF or cyclosporine A) or treatment strategies (e.g., intensive radio- and chemotherapy). However, the use of G-CSF was only a non-significant risk factor for the development of this syndrome if no other contributing factors were present. The risk factors for development of capillary leak syndrome, identified in a study in paediatric patients undergoing stem cell transplantation were severe infection (presented with fever, inflammation marker increase and eventual haemodynamic instability) and acute graft-versus-host disease. Other potential risk factors suggested in association with G-CSF-use include enhanced leukocytosis.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4. Prescription only medicine

Sickle cells crisis in patients with sickle cell disease	
Evidence for linking the risk to the medicine	Product information for Neulasta/Ristempa EPAR and Summary of the RMP for Ristempa
Risk factors and risk groups	Patients with sickle cell disease or trait No other more specific risk factors have yet been established
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine
Glomerulonephritis	
Evidence for linking the risk to the medicine	Product information for Neulasta
Risk factors and risk groups	Patients with pre-existing renal injury are more prone to pegfilgrastim-induced glomerulonephritis. More cases of glomerulonephritis were reported in patients with severe congenital neutropenia who require long-term treatment with G-CSF and other therapeutic agents, even though, the causal link to G-CSF is not always established.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine
Acute respiratory distress syndrome	
Evidence for linking the risk to the medicine	Product information for Neulasta
Risk factors and risk groups	Not yet fully established Patients receiving chemotherapy with known potential for pulmonary toxicity (e.g. bleomycin, cyclophosphamide, or doxorubicin) are at increased risk of (exaggerated) pulmonary toxicity associated with the activity of G-CSF. Same level of risk applies to patients receiving oxygen therapy or radiotherapy prior to treatment with G-CSF. A recent history of pulmonary infiltrates in neutropenic patients may represent a risk factor for the development of acute respiratory distress syndrome at neutropenia recovery. The risk of G-CSF- induced acute respiratory distress syndrome further increases in patients with human leukocyte antigens-B51/B52, presence of

	pulmonary fibrosis and pneumonia or other underlying lung disease, especially if pneumonia is associated with sepsis. Elderly and infants undergoing chemotherapy may be more prone to pulmonary toxicity associated with G-CSF.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Prescription only medicine

Important potential risks:

AML / MDS	
Evidence for linking the risk to the medicine	Product information for Neulasta/Ristempa EPAR and Summary of the RMP for Ristempa
Risk factors and risk groups	Not yet established
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1 and 4.4 PL section 2 Prescription only medicine
Cytokine release syndrome	
Evidence for linking the risk to the medicine	Product information for Neulasta/Ristempa EPAR and Summary of the RMP for Ristempa

Risk factors and risk groups	Not yet established
Risk minimisation measures	No specific text in the product information is deemed necessary at this point. If further characterisation of this risk results in need for special warnings or precautions, or if this potential risk is confirmed as associated with pegfilgrastim, all reference documents will be updated. Prescription only medicine

Missing information:

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies, which are conditions or specific obligations of the marketing authorisation for Pegfilgrastim Mundipharma.

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

There are no further studies required for Pegfilgrastim Mundipharma.