PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR DEFITELIO (DEFIBROTIDE)

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

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

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

I THE MEDICINE AND WHAT IT IS USED FOR

Defitelio is authorised for the treatment of severe hepatic veno-occlusive disease (VOD) in haematopoietic stem-cell transplantation (HSCT) therapy (see SmPC for the full indication). It contains defibrotide as the active substance and it is given by intravenous infusion, over two hours.

Further information about the evaluation of Defitelio’s benefits can be found in Defitelio’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

II.A List of Important Risks and Missing Information

Important risks of Defitelio 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 Defitelio. 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 II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Haemorrhage (including, but not limited to, gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis) Hypotension Coagulopathy Immunogenicity (Allergic/Hypersensitivity reactions)
Important potential risks	Thromboembolic events Reproductive toxicity
Missing information	Safety in pregnant or lactating women Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage (including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors) Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD) Patients with intrinsic lung disease

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Haemorrhage (including, but not limited to, gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis)	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Concomitant therapies: Concomitant use with other medications known to cause bleeding (i.e. anticoagulants, antiplatelets, thrombolitics) would theoretically increase the risk of haemorrhage. Age: In T-IND study, the overall incidence of haemorrhagic events was slightly higher in adults compared to paediatrics (32.4% vs. 27.4% respectively). However, the incidence of pulmonary haemorrhage events was higher in paediatric patients compared to adults (10.0% vs. 4.3%, respectively), with the highest incidence observed in the youngest paediatric subgroup (Infants/Toddlers [<2 years]: 14.8%); Children [2-11 years]: 7.3%; Adolescents [12-16 years]: 11.2%). The results of multivariate analysis examining potential confounding factors or risk factors for pulmonary haemorrhage (i.e. age, primary disease, HSCT form, conditioning regimen for current HSCT, pulmonary dysfunction presence at study entry, including ventilator dependency, as well as severity of the VOD) concluded that after adjusting for other confounding factors, young age itself was a significant risk factor for pulmonary haemorrhage in patients who develop VOD after HSCT or chemotherapy, with the highest risk observed in the 0-2 years (OR=3.62) [95%Wald CI 1.951 – 6.701], 2-<12 years (OR=1.78) [95% Wald CI 0.971 – 3.251] and 12-16 years (OR=2.60) [95%Wald CI 1.262 – 5.362], compared to adults (> 16 years). The underlying mechanism for this observation is not fully elucidated.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Important identified risk: Hypotension	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	No special risk factors for hypotension related to defibrotide treatment have been identified.

Important identified risk: Hypotension	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Important identified risk: Coagulopathy	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	No clear-cut risk factors for the development of coagulopathy during defibrotide treatment were identified although use of other medications with the potential to produce coagulopathy would increase risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Important identified risk: Immunogenicity (Allergic/Hypersensitivity Reactions)	
Evidence for linking the risk to the medicine	Literature (Artesani et al., 2006; Ferrari et al., 1990); clinical trial data
Risk factors and risk groups	Prior hypersensitivity to defibrotide would be expected to predispose to further hypersensitivity on re-exposure.
Risk minimisation measures	Routine risk minimisation measures:

Important identified risk: Immunogenicity (Allergic/Hypersensitivity Reactions)	
	SmPC Section 4.3 SmPC Section 4.8 <u>Additional risk minimisation measures</u>: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities</u>: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Non-clinical study data.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: No routine risk minimisation measures proposed. <u>Additional risk minimisation measures</u>: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities</u>: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Important potential risk: Reproductive toxicity	
Evidence for linking the risk to the medicine	Non-clinical study data.
Risk factors and risk groups	Any patient becoming pregnant with exposure to defibrotide.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: SmPC Section 4.6 <u>Additional risk minimisation measures</u>: No additional risk minimisation measures proposed.

Missing information: Safety in pregnant or lactating women	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: No additional risk minimisation measures proposed.

Missing information: Patients treated concomitantly with defibrotide and medications that increase the risk of haemorrhage (including the newer oral anti-coagulants direct thrombin and factor Xa inhibitors)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Missing information: Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.9 SmPC Section 5.2 Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

Missing information: Patients with intrinsic lung disease	
Risk minimisation measures	Routine risk minimisation measures:

Missing information: Patients with intrinsic lung disease	
	No routine risk minimisation measures proposed. Additional risk minimisation measures: No additional risk minimisation measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Data analysis from CIBMTR for patients treated and not treated with defibrotide - Observational registry (DEFIFrance)

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorisation:

Study 15-007

Purpose of the study: To obtain comparative safety data

Data analysis from CIBMTR for patients treated and not treated with defibrotide

Purpose of the study: To obtain comparative efficacy data

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

DEFIFrance

Purpose of the study: To investigate the safety and outcome of patients treated with defibrotide in France from 15 Jul 2014 (labelled indication as well as off-label use)