Summary of Risk Management Plan for Defitelio (Defibrotide)

Based on version 8.3 of the Risk Management Plan

Gentium S.r.l

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 minimize them.

The RMP summary of Defitelio 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 Defitelio in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Clinipace AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Defitelio.

1. Summary of Risk Management Plan for Defitelio

1.1 The Medicine and What It Is Used for

Defitelio is authorized 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: https://www.ema.europa.eu/en/medicines/human/EPAR/Defitelio.

1.2 Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Defitelio, together with measures to minimize such risks and the proposed studies for learning more about Defitelio's risks, are outlined below. Measures to minimize 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 authorized 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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.

1.2.1 List of Important Risks and Missing Information

Important risks of Defitelio are risks that need special risk management activities to further investigate or minimize 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).

Summary of safety concerns:

Important identified risk	Haemorrhage (including, but not limited to, gastrointestinal haemorrhage, pulmonary haemorrhage and epistaxis) Hypotension Coagulopathy Immunogenicity (Allergic/ Hypersensitivity reactions)
Important potential risk	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

1.2.2 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 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 minimization measures	Routine risk minimization measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8

	Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Important Identified risk: Hypotension	
Evidence for linking the risk to medicine	Clinical trial data.
Risk factors and risk groups	No special risk factors for hypotension related to defibrotide treatment have been identified.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 SmPC Section 4.8 Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Important Identified risk: Coagulopathy	
Evidence for linking the risk to 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 minimization measures	Routine risk minimization measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Important Identified risk: Immunogenicity (Allergic/ Hypersensitivity reactions)	
Evidence for linking the risk to 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 minimization measures	Routine risk minimization measures: SmPC Section 4.3 SmPC Section 4.8 Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Important Potential risk: Thromboembolic events	
Evidence for linking the risk to medicine	Non- clinical study data.
Risk factors and risk groups	No risk factors have been identified.
Risk minimization measures	Routine risk minimization measures: No routine risk minimization measures proposed. Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Important Potential risk: Reproductive toxicity	
Evidence for linking the risk to medicine	Non- clinical study data.
Risk factors and risk groups	Any patient becoming pregnant with exposure to defibrotide.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 Additional risk minimization measures:

	No additional risk minimization measures proposed.

Missing information: Safety in pregnant or lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 Additional risk minimization measures: No additional risk minimization 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 minimization measures	Routine risk minimization measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.5 Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

Missing information: Patients with pre-existing liver or severe renal insufficiency (aetiologies other than VOD)	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 SmPC Section 4.9 SmPC Section 5.2 Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007)

	- Observational registry (DEFIFrance)

Missing information: Patients with intrinsic lung disease	
Risk minimization measures	Routine risk minimization measures: No routine risk minimization measures proposed. Additional risk minimization measures: No additional risk minimization measures proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - Prevention of VOD study (15-007) - Observational registry (DEFIFrance)

1.2.3 Post- authorization development plan

1.2.3.1 Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

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.

1.2.3.2 Other Studies in Post-Authorization 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).