Defitelio

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0063	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	19/12/2023		SmPC, Labelling and PL	
R/0061	Renewal of the marketing authorisation.	30/03/2023	26/05/2023	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

					Defitelio in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
S/0060	Annual re-assessment.	30/03/2023	n/a		
II/0059	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	12/01/2023	n/a		
II/0058/G	This was an application for a group of variations. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/07/2022	n/a		
S/0057	Annual re-assessment.	22/04/2022	24/06/2022	Annex II	
II/0056	Submission of the final report from study 15-007 listed as a specific obligation in the Annex II of the Product Information. This is a phase 3, randomised, adaptive study (15-007) of Defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP version 9 has also been submitted. The MAH has also taken the opportunity to align the	19/05/2022	24/06/2022	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Defitelio-II-56' For more information, please refer to the Summary of Product Characteristics.

	PI to the latest QRD template 10.2 which replaces the United Kingdom with United Kingdom (Northern Ireland) in the PIL. In addition, the MAH is correcting the following errata during the linguistic review of the PI: correction of the paragraph number for Regulation (EC) No 726.2004 which was cited incorrectly in Annex II of the French PI and formatting updates to Norwegian and Swedish language PIs. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/10086 /202010	Periodic Safety Update EU Single assessment - defibrotide	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0055	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/04/2021	n/a		
IB/0054	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/03/2021	n/a		
S/0051	Annual re-assessment.	25/02/2021	n/a		
IB/0052	B.I.a.2.z - Changes in the manufacturing process of	29/01/2021	n/a		

	the AS - Other variation				
IB/0050	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/12/2020	22/09/2021	Annex II	
IB/0049	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/10/2020	22/09/2021	SmPC and PL	
II/0048	Update the RMP version 8.0 in line with PRAC recommendations, following approval of PBRER 12 (EMEA/H/C/PSUSA/00010086/201910), to update section SVII 2, Safety Concerns and Reclassification for removal of the Important Potential Risks and Missing Information from the RMP: Injection site reactions/infections, including septicaemia as a serious complication of these reactions/infections; Immunogenicity (generation of anti-nuclear antibodies); Use in patients with grade B-D GvHD; Use in patients with ethnic background other than Caucasian; use in patients >65 years of age and off-label use; the RMP has been also updated with the results of study (DF VOD 2013 03 REG). Furthermore, the Marketing Authorisation Holder took the opportunity to: · Update Sub-section Cardiac Electrophysiology in section 5.1 of Annex I (SmPC) to correct a typographical error; · Introduce other minor editorial and QRD updates throughout Annexes I-III; · Change Annex IIIB in line with the excipients	17/09/2020	22/09/2021	SmPC, Annex II, Labelling and PL	

	warning for medicinal products containing Sodium. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2020	22/09/2021	PL	
PSUSA/10086 /201910	Periodic Safety Update EU Single assessment - defibrotide	14/05/2020	n/a		PRAC Recommendation - maintenance
S/0045	6th annual re-assessment	27/02/2020	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Defitelio should be maintained.
PSUSA/10086 /201904	Periodic Safety Update EU Single assessment - defibrotide	31/10/2019	n/a		PRAC Recommendation - maintenance
IB/0044	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	07/10/2019	n/a		
II/0043	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/09/2019	01/04/2020	Annex II	

S/0038	Annual re-assessment.	28/03/2019	11/07/2019	Annex II	
PSUSA/10086 /201810	Periodic Safety Update EU Single assessment - defibrotide	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0039	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/05/2019	01/04/2020	SmPC	
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/03/2019	11/07/2019	PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2018	11/07/2019	Labelling	
PSUSA/10086 /201804	Periodic Safety Update EU Single assessment - defibrotide	31/10/2018	n/a		PRAC Recommendation - maintenance
IA/0035/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/09/2018	n/a		
R/0032	Renewal of the marketing authorisation.	26/04/2018	26/07/2018	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing authorisation, the CHMP considers that the benefit-risk balance of Defitelio remains positive, but considers that its safety profile is to be closely

					monitored for the following reasons: The specific obligation to set up a patient registry to investigate long-term safety, health outcomes and patterns of utilisation of defibrotide under normal use has not been fulfilled and post-marketing experience remains limited, particularly with respect to long-term safety. Therefore, the CHMP decided that the MAH should continue to collect long-term safety information about Defitelio, as described in annex II. Therefore, based upon the safety profile of Defitelio, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0027	Submission of an update RMP version 4.3 in order to replace the remaining imposed non-interventional PASS (an observational registry, study DF-VOD2013-03-REG, which aims to record safety and outcome data in patients diagnosed with severe VOD following hematopoietic stem cell transplant (HSCT) treated or not with Defitelio) listed as a category 2 study in the RMP (specific obligation 001) by two new specific obligations: one to provide comparative safety data based on the final results of study 15-007 (a phase 3, randomised, adaptive study of defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing HSCT); the other to provide comparative data on efficacy based on a systematic literature reviews and analyses, and on data analysis from Center for International Blood and Marrow Transplant Research (CIBMTR) for patients treated and not treated with defibrotide. The Annex II.E of	28/06/2018	11/07/2019	Annex II	Following the MAH's request to consider SOB 001as fulfilled as this non-interventional PASS was considered by the MAH as no longer feasible in its current form due to ethical concerns in recruiting patients to the control arm, the CHMP concluded that based on the data provided, the currently available clinical study and post-marketing data cannot be considered as having adequately address the outstanding specific obligation for Defitelio. Therefore the current SOB 001 is being replaced by two new SOBs: an ongoing randomised phase 3 trial of Defitelio against best supportive care for prevention of VOD in patients (adults and paediatrics) undergoing HSCT (study 15-007) in order to collect comparative safety data and a systematic literature review, in conjunction with a data analyses from international blood and marrow transplantation registries, to collect comparative efficacy data.

	the product information is updated accordingly. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/10086 /201710	Periodic Safety Update EU Single assessment - defibrotide	17/05/2018	n/a		PRAC Recommendation - maintenance
IB/0033	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	24/04/2018	n/a		
II/0026	Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 listed as category 3 in the risk management plan (RMP). This is a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The final study report has been submitted. The RMP (version 3.4) and package leaflet are updated accordingly. In addition, the MAH took the opportunity to bring the	12/04/2018	26/07/2018	SmPC, Labelling and PL	Based on the results of the open label treatment IND study, the complete response by Day+100 has been revised to 39.3% (201/512) and the survival has been revised to 49.5% (*Kaplan Meier estimates for time-to-event analysis by Day+100) in section 5.1 of the SmPC. In addition, the frequencies of the adverse drug reactions have been revised. In section 4.8 of the SmPC, the tabulated list of adverse reactions incorporates the adverse drug reactions (ADRs) observed in study 2005-01 [ADR = any event reported as possibly related on at least two occasions] and treatment emergent adverse events (TEAEs) observed in T-IND 2006-05 study [TEAE = any AE that started or worsened in severity after the first dose of

	SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian languages. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				defibrotide]. For adverse reactions reported in both studies, the highest frequency was used in the tabulated list of adverse reactions. The safety data from the pivotal study are supported and confirmed with data from the completed Treatment-IND study.
S/0029	4th annual re-assessment	22/03/2018	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that the marketing authorisation of Defitelio should be maintained under exceptional circumstances.
IA/0031/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	24/01/2018	n/a		

PSUSA/10086 /201704	Periodic Safety Update EU Single assessment - defibrotide	26/10/2017	n/a		PRAC Recommendation - maintenance
IB/0028	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	04/10/2017	n/a		
IB/0025/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/09/2017	n/a		
PSUSA/10086 /201610	Periodic Safety Update EU Single assessment - defibrotide	05/05/2017	n/a		PRAC Recommendation - maintenance
N/0023	Minor change in labelling or package leaflet not	21/04/2017	26/07/2018	PL	

	connected with the SPC (Art. 61.3 Notification)				
S/0020	Annual re-assessment.	21/04/2017	n/a		
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/03/2017	n/a		
PSUSA/10086 /201604	Periodic Safety Update EU Single assessment - defibrotide	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0019	Submission of a revised RMP in order to include information regarding the additional risk minimisation measures (i.e. Healthcare professional material that highlights the existence of the Registry as well as the means to enter patients into the registry) as outlined in Annex II. In addition, the MAH took the opportunity to add administrative changes to the protocol of the registry study, to add information about the renal pharmacokinetics study, to add updated information about off-label use during post-marketing experience and to include further administrative changes to the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	13/10/2016	n/a		

IB/0017/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	11/08/2016	n/a		
II/0012	Update of sections 4.2, 4.9 and 5.2 of the SmPC based on information from a pharmacokinetic study in patients with renal impairment. Further, corrections to existing information on plasma protein binding and excretion of defibrotide are introduced in section 5.2 of the SmPC. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the SmPC and Annex II in line with the latest QRD template version 9.1. Moreover, section 6.4 of the SmPC has been amended to comply with QRD template and CHMP guideline on declaration of storage conditions. C.I.4 - Change(s) in the SPC, Labelling or PL due to	26/05/2016	11/01/2017	SmPC and Annex II	In vitro studies demonstrate that 93% of Defitelio is bound to plasma proteins. After administration of the therapeutic dose (6.25 mg/kg) to healthy subjects, an average of 9.48% of the total dose administered is excreted in urine as unchanged defibrotide in 24 hours, with the majority excreted during the first collection interval of 0-4 hours (approximately 98%). Accumulation of defibrotide over 4 doses was not found. Difference in exposure is not considered clinically relevant and so dose adjustment is not required for patients with renal impairment or who are on intermittent haemodialysis. Defibrotide is not removed by dialysis. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10086 /201510	Periodic Safety Update EU Single assessment - defibrotide	13/05/2016	n/a		PRAC Recommendation - maintenance
S/0013	2nd Annual Re-assessment	28/04/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Defitelio should be maintained.
IB/0016	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	18/03/2016	11/01/2017	SmPC and PL	
IAIN/0015/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the	05/02/2016	11/01/2017	SmPC, Annex II, Labelling and PL	

	PSMF location				
PSUSA/10086 /201504	Periodic Safety Update EU Single assessment - defibrotide	06/11/2015	n/a		PRAC Recommendation - maintenance
IAIN/0011	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/07/2015	n/a		
IA/0009/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	06/07/2015	n/a		
PSUSA/10086 /201410	Periodic Safety Update EU Single assessment - defibrotide	07/05/2015	n/a		PRAC Recommendation - maintenance
S/0005	1st Annual Re-assessment.	23/04/2015	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Defitelio should be maintained.
IAIN/0008/G	This was an application for a group of variations.	10/04/2015	n/a		

	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities				
IA/0007/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.6 - Administrative change - Change in ATC Code/ATC Vet Code	11/03/2015	28/01/2016	SmPC	

II/0002/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.II.f.1.e - Stability of FP - Change to an approved stability protocol	22/01/2015	28/01/2016	SmPC and Annex II	
PSUV/0003	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IAIN/0004	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities	17/09/2014	n/a		
II/0001	Update of section D of Annex II of the Product Information in order to fulfil a post-authorisation measure to submit additional information from the CIBMTR registry database concerning baseline	20/03/2014	12/01/2015	Annex II	The company has submitted data from the Centre for International Blood and Marrow Transplant registry database in order to fulfil a post-approval measure.There were some imbalances that have been noted in the

	characteristics from treated patients. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				baseline characteristics. The most notable imbalances appear to be age where 61% of the defibrotide group were under 16yrs old and 20% of the control group were 16yrs old and over and gender where 46% of the defibrotide group were male and 72% of the control group were female.