HEPLISAV B

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
II/0037	Update of section 4.9 of the SmPC in order to revise information regarding overdose to indicate "Not Applicable" following review of overall safety data. In addition, the MAH took the opportunity to make some editorial updates to the PI and bring it in line with the latest QRD template.	27/02/2025		SmPC and Annex II	The MAH has submitted a Type II variation application to update the section 4.9 Overdose of the SmPC for a change from "no cases of overdose have been reported" to "not applicable". In addition, minor editorial changes are proposed to the PI to aid in readability. No changes to the risk management plan are proposed with this variation,

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				since the proposed changes have no impact on the safety profile, risk minimisation measures or additional pharmacovigilance requirements. A review of the overall safety dataset as well as all adverse events reported in the Global Safety Database performed by the MAH did not identify any trends in safety events resulting from the administration of an extra dose of HEPLISAV B given per administration or cumulatively; there is no evidence to support the inclusion of information concerning both observed and theoretical signs and symptoms of overdose. Additionally, no recommendations are required for clinical management including the provision of antidotes and proper supportive therapy concerning an overdose of HEPLISAV B. As a result, the following revised wording of section 4.9 of the SmPC was endorsed by the CHMP, aligning with other SmPC texts for vaccines: 4.9 Overdose "Cases of overdose have been reported during post-marketing surveillance. In general, the adverse event profile reported with overdose was comparable to that observed with the recommended dose of Heplisav B." The overall benefit-risk balance of Heplisav B remains positive. For more information, please refer to the Summary of Product Characteristics.
IB/0036/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same	02/09/2024	n/a		

	pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
IB/0035	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	31/07/2024	n/a		
IB/0034/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.z - Quality change - Active substance - Other variation A.7 - Administrative change - Deletion of manufacturing sites	26/06/2024	n/a		
PSUSA/10919 /202311	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	13/06/2024	n/a		PRAC Recommendation - maintenance

II/0031	Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from study DV2-HBV-28 - Post-marketing observational surveillance study to evaluate pregnancy outcomes among women who receive HEPLISAV-B or Engerix-B; HBV-28 was conducted using the same patient population as two observational post-marketing surveillance studies designed to evaluate the incidence of AMI (HBV-25) or new-onset immunemediated diseases, herpes zoster, and anaphylaxis (HBV-26) in recipients of HEPLISAV-B compared with recipients of Engerix-B. The primary objective of this study was to describe and compare pregnancy outcomes in recipients of HEPLISAV-B and recipients of Engerix-B.The Package Leaflet is updated accordingly. The RMP version 2.2 has also been submitted. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2024	26/02/2025	SmPC and PL	This procedure entails amendments to the product information (PI) and the risk management plan (RMP) of HEPLISAV-B regarding the use of the product during pregnancy based on the results of the completed pregnancy registry HBV-28. The primary objective of study HBV-28 was to describe and compare the risk of pregnancy outcomes among women exposed to HEPLISAV-B with pregnant patients exposed to Engerix-B during the 28 days prior to conception or during pregnancy. Therefore, pregnancy outcomes and outcomes among live births were compared. In the analysis of the safety of administration of HEPLISAV-B compared to Engerix-B no different safety profile between both vaccine groups could be observed. A comparison of the number of events, the percentages or event rates in both groups, as well as the adjusted relative risk showed a comparable profile between both vaccine groups. Even if the data in pregnant women are very limited, no safety concern could be identified, neither from clinical nor non-clinical data. Besides, in general, no enhanced risk for the vaccination of pregnant women with non-live vaccines is known. In this light, the MAH proposed to delete the sentence “As a precautionary measure, it is preferable to avoid the use of HEPLISAV B during pregnancy.” in the section 4.6 of the SmPC whilst the current wording regarding pregnancy remains with a statement that vaccination should only be performed if the benefit for the mother clearly outweighs the risk. This is acceptable to the PRAC. The MAH also proposed amendments to the RMP by removing (1) “Safety in pregnancy and lactation” as missing information in the summary of safety concerns,

					and (2) "Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder" as an important potential risk in the summary of safety concerns. The version 2.2 of the RMP was endorsed accordingly by the PRAC. For more information, please refer to the Summary of Product Characteristics.
IAIN/0032	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/01/2024	n/a		
PSUSA/10919 /202305	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	30/11/2023	n/a		PRAC Recommendation - maintenance
IB/0030/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/10/2023	n/a		
II/0026	Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add a 4-dose regimen posology for patients with renal insufficiency including those undergoing haemodialysis and to update safety and pharmacodynamic information based on final results from study HBV-24 "An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of	14/09/2023	19/10/2023	SmPC and PL	In this submission the MAH proposed a modified schedule of HEPLISAV B for individuals with CKD (chronic kidney disease) who are initiating or receiving HD (haemodialysis). The company submitted the final results from study HBV-24 "An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B in Adults With End-Stage Renal Disease Undergoing Hemodialysis". In this

	HEPLISAV-B in Adults With End-Stage Renal Disease Undergoing Hemodialysis". The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make some editorial updates to the PI mainly to align the wording with the QRD guidance and templates. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				trial, four doses of HEPLISAV B were given to CKD patients one month apart: the proposed schedule for HD was 4 doses of the approved dose level (20 mcg rHBsAg/3000 mcg CpG 1018 [20/3000]), one IM injection given at 0, 1, 2, and 4 months. Anti-HBs were measured at baseline and then at Weeks 4, 8, 16, and 20. Seroprotection was defined as anti-HBs ≥ 10 mIU/mL. The primary immunogenicity objective was to evaluate the immunogenicity induced by HEPLISAV B at Week 20 as measured by the seroprotection rate (SPR). In the 75 subjects in the PP population, the SPR at each visit through Week 20 was 20.3% after the first vaccine dose at Week 4, 56.8% after the second vaccine dose at Week 8, 78.7% after the third vaccine dose at Week 16, and 89.3% at Week 20 (with 95% confidence interval [CI]: 80.1%, 95.3%). The CHMP noted that high seroprotection rate after four doses of HEPLISAV B in this patient group, as well as the increase of responses after each subsequent dose, justifying the proposed posology. As regards to safety, the CHMP is of the view that the safety results did not cause further concern; the safety profile of four doses of HEPLISAV B in this population was considered acceptable by the CHMP. Based on the above, updates of sections 4.2, 4.8 and 5.1 of the SmPC were performed accordingly to add the above-mentioned 4-dose regimen posology for patients with renal insufficiency including those undergoing HD whilst updating safety and pharmacodynamic information. The Package Leaflet was updated consequently. In addition, the MAH took the opportunity to make some editorial updates to the PI mainly to align the wording with the QRD guidance and templates.

					For more information, please refer to the Summary of Product Characteristics.
IB/0028	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	06/07/2023	19/10/2023	SmPC, Labelling and PL	
IB/0027	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	06/07/2023	n/a		
PSUSA/10919 /202211	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	08/06/2023	n/a		PRAC Recommendation - maintenance
II/0024	B.II.g.4.a - Changes to an approved change management protocol - Major changes	25/05/2023	n/a		
IA/0025	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	12/05/2023	n/a		
II/0023	Update of section 4.8 of the SmPC in order to add 'injection site pruritus' to the list of adverse drug reactions (ADRs) with frequency 'uncommon', based on post-marketing surveillance. In addition, the MAH took the opportunity to introduce minor changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to	26/04/2023	19/10/2023	SmPC and PL	Based on clinical trial data, the addition of "injection site pruritus" to the list of adverse drug reactions in section 4.8. of the SmPC (with a frequency "uncommon") was performed during this procedure. In addition, "fever" was removed under section 4.8 - "undesirable effects" in the SmPC, under the section "summary of the safety profile" but not from the tabulated list of adverse reactions, based on the fact that fever occurred in considerably lower

	new quality, preclinical, clinical or pharmacovigilance data				frequencies than the other adverse reactions (such as injection site pain, headache, malaise, fatigue). In light of the above, the Product Information was amended accordingly. For more information, please refer to the Summary of Product Characteristics.
IA/0022	B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	13/02/2023	n/a		
IB/0020	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/01/2023	n/a		
PSUSA/10919 /202205	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0019	B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	07/11/2022	n/a		
II/0015	Submission of the final report from the study HBV-26: Post-Marketing Observational Surveillance Study to Evaluate the Incidence of New-Onset Immune-mediated Diseases, Herpes Zoster, and Anaphylaxis, listed as a category 3 post-authorisation safety study (PASS) in the RMP. This is a post-marketing observational surveillance study comparing the incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in recipients of HEPLISAV B with recipients of another hepatitis B vaccine.	29/09/2022	n/a		Potentially immune-mediated disorders is a known theoretical risk that requires no further characterisation and is followed up via routine pharmacovigilance. There is no known causality mechanism. The final study results of study HBV-26 (category 3 PASS study in the RMP) confirm that there is a similar safety profile for these disorders as for the comparator product. Based on the evidence in this study, the important potential risk 'Potentially immune-mediated disorders (including inflammatory disorders)' was removed from the RMP as a safety concern. In conclusion, this observational study did not identify

	The RMP version 1.3 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				safety concerns for HEPLISAV-B with respect to herpes zoster, anaphylaxis, or selected immune-mediated diseases. This study did not identify a potential safety signal that requires further investigation.
IB/0017	B.II.z - Quality change - Finished product - Other variation	12/07/2022	n/a		
PSUSA/10919 /202111	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0016/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/06/2022	n/a		
II/0014	Submission of the final report from study (HBV25) listed as a category 3 PASS study in the RMP. This is a post-marketing observational surveillance study comparing the occurrence of Acute Myocardial Infarction (AMI) in recipients of HEPLISAV-B with recipients of another hepatitis B vaccine. As a consequence, the RMP version 1.2 has also been submitted, in which the MAH proposed the removal of AMI as an important potential risk from the list of safety concerns.	05/05/2022	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0010	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	07/04/2022	n/a		
IB/0013	B.II.z - Quality change - Finished product - Other variation	28/02/2022	n/a		
PSUSA/10919 /202105	Periodic Safety Update EU Single assessment - hepatitis B surface antigen, CpG 1018 adjuvant	02/12/2021	n/a		PRAC Recommendation - maintenance
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2021	19/10/2023	Labelling and PL	
IB/0009	B.I.z - Quality change - Active substance - Other variation	18/08/2021	n/a		
IB/0007	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/08/2021	n/a		
IB/0005	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	10/08/2021	n/a		
IB/0006	B.II.z - Quality change - Finished product - Other variation	05/08/2021	n/a		
IB/0003	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure	14/07/2021	n/a		

	(including replacement or addition)				
IB/0004	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/07/2021	n/a		
IA/0002	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	09/06/2021	n/a		
IB/0001	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	07/06/2021	n/a		