HBVAXPRO

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
N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2024		Labelling and PL	
WS/2361	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/01/2023	n/a		

[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).

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/2360	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	01/12/2022	n/a		
IG/1524/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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	15/08/2022	19/06/2023	Annex II	
II/0076	Update of section 5.1 of the SmPC in relation to study V419-013, following procedure EMEA/H/C/000373/P46/061. The sentence "As with other hepatitis B vaccines, the duration of the protective effect in healthy vaccinees is unknown at	02/06/2022	19/06/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion Procedure No. EMEA/H/C/000373/II/0076. For more information, please refer to the Summary of

	present" was revised to "The duration of the protective effect in healthy vaccinees is unknown". In addition, the MAH took the opportunity to implement editorial changes in the SmPC, Labelling and the Package Leaflet. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				Product Characteristics.
T/0075	Transfer of Marketing Authorisation	14/03/2022	04/04/2022	SmPC, Labelling and PL	
IB/0074/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	14/02/2022	04/04/2022	SmPC, Labelling and PL	To delete the pack size HBVAXPRO 5 micrograms, suspension for injection, 1 vial with syringe and needle (EU/1/01/183/019). To improve the readability of the artwork (outer packaging).
WS/2173	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	13/01/2022	n/a		
WS/2143	This was an application for a variation following a worksharing procedure according to Article 20 of	11/11/2021	n/a		

	Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
II/0071/G	This was an application for a group of variations. IA (B.II.e.7.b) To add Schott Schweiz AG, St Gallen, as alternative supplier of the primary packaging material, pre-filled syringe barrel assembly components. IB (B.II.d.2.d) To add the syringeability test to the finished product specifications. II (B.II.e.1.b.2) To change the immediate packaging of the sterile suspension for injection 5 microgram/0.5mL and 10 microgram/1.0mL pre-filled syringe presentations, to add alternative syringe components to those currently authorised. In addition, the applicant made a correction to the Company name and email address as stated in the package leaflet. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	29/04/2021	04/04/2022	SmPC and PL	The SmPC section 6.5 has been updated as follows: 6. PHARMACEUTICAL PARTICULARS 6.5 Nature and contents of container 0.5 ml of suspension in pre-filled syringe (glass) without needle with a plunger stopper (gray chlorobutyl or bromobutyl). Pack size of 1, 10, 20, 50. 0.5 ml of suspension in pre-filled syringe (glass) with 1 separate needle with a plunger stopper (gray chlorobutyl or bromobutyl). Pack size of 1, 10. 0.5 ml of suspension in pre-filled syringe (glass) with 2 separate needles with a plunger stopper (gray chlorobutyl or bromobutyl). Pack size of 1, 10, 20, 50.

	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
PSUSA/1597/202002	Periodic Safety Update EU Single assessment - hepatitis B vaccine (rDNA)	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0070/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.I.z - Quality change - Active substance - Other variation	12/08/2020	n/a		
WS/1804/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	30/04/2020	n/a		

IB/0067	C.I.5.z - Change in the legal status of a medicinal product for centrally authorised products - Other variation	13/01/2020	11/01/2021	SmPC, Annex II, Labelling and PL	
IB/0066	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/11/2019	n/a		
IB/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.z - Quality change - Finished product - Other variation	07/08/2019	n/a		
II/0064	B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	17/01/2019	18/12/2019	SmPC, Labelling and PL	
PSUSA/1597/ 201802	Periodic Safety Update EU Single assessment - hepatitis B vaccine (rDNA)	31/10/2018	n/a		PRAC Recommendation - maintenance
IA/0062	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	26/04/2018	n/a		
IB/0061/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or	10/01/2018	n/a		

	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				
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2017	18/12/2017	Labelling	
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	18/12/2017	PL	
IG/0777	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2017	18/12/2017	SmPC, Labelling and PL	
II/0055	B.II.d.2.z - Change in test procedure for the finished product - Other variation	02/02/2017	n/a		
IG/0758	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2017	18/12/2017	SmPC, Labelling and PL	
N/0056	Update of the package leaflet with revised contact details of the local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2016	18/12/2017	PL	
PSUSA/1597/ 201602	Periodic Safety Update EU Single assessment - hepatitis B vaccine (rDNA)	27/10/2016	n/a		PRAC Recommendation - maintenance

IAIN/0053	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/04/2016	n/a		
IG/0625	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	16/11/2015	n/a		
II/0051	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	08/10/2015	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/05/2015	18/12/2017	PL	
IB/0049	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	12/05/2015	n/a		
II/0048/G	This was an application for a group of variations. Change in test procedure for the active substance and the finished product B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/03/2015	n/a		Change in test procedure for the active substance and the finished product

	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
PSUSA/1597/201402	Periodic Safety Update EU Single assessment - hepatitis B vaccine (rDNA)	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0047/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	12/09/2014	n/a		
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2014	11/02/2015	PL	
II/0044	B.I.d.1.a.3 - Stability of AS - Change in the re-test period/storage period - Extension of storage period of a biological/immunological AS not in accordance with an approved stability protocol	24/07/2014	n/a		
IG/0435	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2014	11/02/2015	SmPC, Labelling and PL	
IG/0434	C.I.8.a - Introduction of or changes to a summary of	09/04/2014	n/a		

	Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location				
IB/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/03/2014	11/02/2015	SmPC, Annex II, Labelling and PL	The product information was updated according to the new pharmacovigilance guidances and QRD requirements. In addition, in order to harmonise each pharmaceutical form and dosage, some minor inaccuracies had been noticed during a quality check of the PI and updates have also been implemented.
IB/0041	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/02/2014	n/a		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/07/2013	11/02/2015	PL	
IG/0312	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/06/2013	n/a		
IB/0036	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/07/2012	n/a		
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/07/2012	11/02/2015	PL	
IG/0156	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	24/02/2012	n/a		

II/0033	To include the term uveitis in section 4.8 of the SmPC based on post authorisation spontaneous reporting. The PL is updated accordingly. The MAH took further the opportunity to correct some typing errors in the SmPC and PL, to include the date of the last renewal in the SmPC and to update the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	26/08/2011	SmPC and PL	Section 4.8 was updated to include uveitis under the System Organ Class (SOC) "Eye Disorders" based on apost-marketing reports received from healthcare providers from market introduction through 14 September 2010 containing one or more of the following preferred terms: chorioretinitis, intermediate uveitis, iridocyclitis, iritis, and uveitis. This search retrieved a total of 47 reports, some of which with a positive rechallenge after a further dose of the vaccine. Based on a calculation using data from clinical studies the frequency classification of "Very rare" was included in section 4.8 of the SmPC and the statement "Inflammation of the eye which causes pain and redness has also been reported" in Section 4 Possible side effects of the PL.
II/0032/G	This was an application for a group of variations. Change in the manufacturing process of the FP Change to in-process tests or limits applied during the manufacture of the FP B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	21/07/2011	21/07/2011		

II/0031	Change in rubber stopper formulation. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	14/04/2011	29/04/2011		
IG/0059/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	15/04/2011	n/a		
II/0030	Update of section 4.9 of the SmPC on the adverse events profile reported with overdose. The MAH took the opportunity to add a warning on the presence of latex in the stopper of the vials. The PL was updated accordingly. Furthermore, information on contact details for the local representatives in Bulgaria and Cyprus was updated in the PL. The SmPC, Labelling and PL were updated with further minor corrections. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	17/02/2011	24/03/2011	SmPC, Labelling and PL	Following a review of reports of overdose for HBVAXPRO, the CHMP agreed that the adverse event profile reported with an overdose was comparable with that observed with the recommended dose. The PI was updated to include the information.

	clinical, clinical or pharmacovigilance data				
R/0029	Renewal of the marketing authorisation.	20/01/2011	17/03/2011	Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of HBVAXPRO continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. The marketing authorisation holder will continue to submit periodic safety update reports on a 1-year cycle.
IA/0028/G	This was an application for a group of variations. To change in the name of the Drug substance and drug product manufacturer. Following the merger between Merck & Co., Inc. and Schering-Plough Corporation, the name of the company has changed from Merck & Co., Inc. to Merck Sharp & Dohme Corp. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	30/03/2010	n/a	Annex II	

II/0027	Update of the detailed description of pharmacovigilance system (DDPS) including the change of the Qualified Person Responsible for Pharmacovigilance (QPPV). The version number of the DDPS in Annex II has been updated accordingly. In addition, the MAH made minor amendments to the list of representatives of Austria, Czech Republic, Denmark, Latvia and Malta in the Package Leaflet (PL). Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II and PL	The DDPS has been updated to version 2.0 in order to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0026	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	24/04/2008	29/04/2008		
II/0021	Change(s) to shelf-life or storage conditions	24/01/2008	31/01/2008		
II/0022	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics to implement the class labelling text on the risk of apnoea following vaccination of very prematurely born infants agreed by the CHMP in July 2007. The MAH took the opportunity to update the list of local rapresentatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	15/11/2007	21/12/2007	SmPC and PL	Following a review on the risk of apnoea in very premature infants after immunisation the CHMP recommended a class labelling on apnoea for all vaccines in very premature infants. The SPC was updated to include information about the potential risk of apnoea and the need for respiratory monitoring for 48-72h, when the primary immunisation series is administered to very premature infants (born ? 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. Nonetheless, preterm infants should not be withdrawn from the immunisation scheme because the benefit of vaccination

					outweighs the risk of apnoea.
IA/0025	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	17/12/2007	17/12/2007	SmPC, Labelling and PL	
IA/0024	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	17/12/2007	17/12/2007	SmPC, Labelling and PL	
IA/0023	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	17/12/2007	17/12/2007	SmPC, Labelling and PL	
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2007	n/a	Labelling and PL	
IB/0019	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	29/08/2006	n/a		
II/0016	To add "Polyarteritis nodosa" and "Eczema" in the section 4.8 of the SPC and to add "Eczema" in the Packet Leaflet in the section 4 following the CHMP assessment of the Periodic Safety Update Report covering the period 27 April 2005 and 26 October 2005. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	21/08/2006	SmPC and PL	Following the assessment of the Periodic Safety Update Report covering the period 27 April 2005 to 26 October 2005, the adverse reactions "Polyarteritis nodosa" and "Eczema" have been included in section 4.8 "Undesirable Effects" of the SPC. A review of safety reports from the US Vaccine Adverse Events Reporting System, (VAERS), from the MAH's Worldwide Adverse Experience System database, (WAES) and from literature has shown that the onset of "Polyarteritis nodosa" and "Eczema" occurred in a close temporal relationship to the date of vaccination. Due to the seriousness of the events, their frequency and the temporal relationship with administration of the vaccine, the CHMP considered to include both adverse reactions in section 4.8

					"Undesirable Effects" of the SPC, as very rare events (1/10.000). The PL was updated in section 4 to include "Eczema".
R/0014	Renewal of the marketing authorisation.	27/04/2006	04/08/2006	SmPC, Annex II, Labelling and PL	
IB/0018	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	04/08/2006	n/a		
A20/0015	On 13 February 2006, the European Commission (EC) triggered the procedure under Article 20 of Regulation (EC) No726/2004, after the CHMP expressed concerns on the low immunogenicity of the HepB vaccine component. The CHMP was requested to give an opinion as to whether the MA for HBVAXPRO should be maintained, varied, suspended or withdrawn.	27/04/2006	04/08/2006	SmPC, Annex II, Labelling and PL	Please refer to the scientific conclusions: HBVAXPRO-H-373-A20-15-SC
IA/0017	To update section 4.8 (Undesirable effects) of the SPC with the addition of "Pain in extremity" as requested by the CHMP following the assessment of the Periodic Safety Update Reports (PSURs) covering the period 27 April 2003 to 26 April 2004. Also, the SPC has been updated according to the current QRD/ EMEA templates IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	30/06/2006	n/a		Following the CHMP assessment of the Periodic Safety Update Reports (PSURs) covering the period 27 April 2003 to 26 April 2004, the adverse event "Pain in extremity" was added to section 4.8 (Undesirable effects) of the SPC. Based on the reporting rate and the number of reports received, the CHMP considered this reaction as a very rare event.

II/0010	Change(s) to the manufacturing process for the finished product	17/11/2005	24/11/2005		
II/0011	Change(s) to the test method(s) and/or specifications for the finished product	15/09/2005	29/09/2005		
IB/0009	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	19/07/2005	19/07/2005	SmPC, Labelling and PL	
IA/0013	IA_47_a_Deletion of a pharmaceutical form	19/07/2005	n/a	SmPC, Labelling and PL	
IA/0012	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	19/07/2005	19/07/2005	SmPC, Labelling and PL	
II/0007	To update section 4.8 (Undesirable effects) of the SPC with the addition of "Pain in extremity" as requested by the CHMP following the assessment of the Periodic Safety Update Reports (PSURs) covering the period 27 April 2003 to 26 April 2004. Also, the SPC has been updated according to the current QRD/ EMEA templates Update of Summary of Product Characteristics	16/03/2005	25/04/2005	SmPC	Following the CHMP assessment of the Periodic Safety Update Reports (PSURs) covering the period 27 April 2003 to 26 April 2004, the adverse event "Pain in extremity" was added to section 4.8 (Undesirable effects) of the SPC. Based on the reporting rate and the number of reports received, the CHMP considered this reaction as a very rare event.
IA/0008	IA_01_Change in the name and/or address of the marketing authorisation holder	10/03/2005	n/a	SmPC, Labelling and PL	
II/0005	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	03/08/2004		

	Change(s) to the test method(s) and/or specifications for the finished product				
IA/0006	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	05/07/2004	05/07/2004	SmPC, Labelling and PL	
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/09/2002	23/10/2002	PL	
I/0002	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	30/11/2001	10/12/2001		
I/0003	01_Change following modification(s) of the manufacturing authorisation(s)	22/11/2001	27/11/2001		
I/0001	30_Change in pack size for a medicinal product	30/08/2001	15/11/2001	SmPC, Labelling and PL	