BIMERVAX

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/0018/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for	27/03/2025	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).

	biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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				
II/0017	Update of sections 4.2, 4.4, and 5.1 of the SmPC in order to update information for immunocompromised individuals, based on final results from study HIPRA-HH-4 listed as a category 3 study in the RMP; this is a Phase IIb/III, open label, single arm, multi-centre trial to assess the immunogenicity and safety of an additional dose vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-CoV-2, in adults with pre-existing immunosuppressive conditions vaccinated against COVID-19. The Package Leaflet is updated accordingly. The RMP is also updated to version 1.5. In addition, the MAH took the opportunity to include editorial changes in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/03/2025		SmPC and PL	
X/0014/G	This was an application for a group of variations. Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure B.I.a.6.a - Changes to the active substance of a	17/10/2024	12/12/2024	SmPC, Labelling and PL	

	vaccine against human coronavirus - Replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method				
PSUSA/11045 /202403	Periodic Safety Update EU Single assessment - COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax)	31/10/2024	n/a		PRAC Recommendation - maintenance
II/0013	Update of section 4.8 of the SmPC in order to delete insomnia and back pain from the list of adverse drug reactions (ADRs), change frequency of odynophagia, abdominal pain and injection site hypersensitivity from Uncommon to Rare based on the updated pooled safety analysis from clinical studies HIPRA-HH-2, HIPRA-HH-5 and HIPRA-HH-10. Update of section 5.1 of the SmPC to update immunogenicity information based on final results from study HIPRA-HH-2 (PART A and PART B) listed as a category 3 study in the RMP; HIPRA-HH-2 was a Phase IIb, double-blind, randomised, active-	18/07/2024	12/12/2024	SmPC and PL	SmPC new text Study HIPRA-HH-2 is a double-blind, randomized (2:1), active controlled (comparator Comirnaty), multi-centre, non-inferiority trial to evaluate immunogenicity and safety of a single PHH-1V dose as a booster vaccination in in adults. This study was extended with a Part B, an open label extension study to determine the immunogenicity, reactogenicity, safety, and tolerability of a fourth dose of PHH-1V (also referred to as Bimervax) (HIPRA-HH-2 – Part B). This procedure relates to the submission of the interim data of part B of the mentioned study. The immunogenicity and safety of Bimervax as a fourth dose of COVID vaccine

	controlled, multi-centre, non-inferiority trial in adults fully vaccinated against COVID-19. The objective was to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion heterodimer vaccine candidate (PHH-1V) against SARS-CoV-2 (Part A). An extension to the study was introduced to add a fourth dose (Part B). The package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				was evaluated between 6 and 12 months after a 3rd dose of PHH-1V or after a 3rd dose of Comirnaty. Priming was performed with Comirnaty in both cohorts. Superiority has been shown for GMTs against Omicron BA.1 and BA. 4/5 as well as for former variants of concerns (VoCs) Beta and Delta after 4th doses in Cohort 1 and Cohort 2 when compared to GMT after 3rd dose in Cohort 2. These results allow the use of Bimervax as an additional booster not only after a booster of Comirnaty but also after a booster with Bimervax (refer to procedure II/004). In this submission, the MAH updated section 5.1 of the SmPC with immunogenicity data from the final report. New immunogenicity data from Day 98 and Day 182 post vaccination confirmed the previous shorter term (14-day) results in both Cohort 1 and Cohort 2. The MAH also provided an updated pooled safety analysis which includes the available safety data of the completed HIPRA-HH-2 HIPRA-HH-5 and the ongoing HIPRA-HH-10 clinical studies. Based on this pooled safety analysis, some updates have been made in the SmPC 4.8: back pain and insomnia AEs have been removed from the ADR table, since all these AEs in this safety data pool were assessed as not related to vaccination. In addition, the MAH updated the frequency of the AEs odynophagia, abdominal pain and injection site hypersensitivity from uncommon to rare, which is acceptable. For more information, please refer to the Summary of Product Characteristics.
PSUSA/11045 /202309	Periodic Safety Update EU Single assessment - COVID-19 Vaccine (recombinant, adjuvanted) (Bimervax)	16/05/2024	n/a		PRAC Recommendation - maintenance

II/0010	Submission of the final report from study HIPRA-HH-5, "A phase III, open label, single arm, multi-center, trial to assess the safety and immunogenicity of a booster vaccination with a recombinant protein RBD fusion heterodimer candidate (PHH-1V) against SARS-COV-2, in adults vaccinated against COVID-19". The RMP version 1.4 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	11/04/2024	n/a		
II/0004	Update of section 4.2 of the SmPC to introduce an homologous booster of Bimervax (PHH-1V) following a previous booster dose of PHH-1V based on interim results from clinical study HIPRA HH-2. Update of sections 4.4, 4.8 and 5.1 of the SmPC to add safety and immunogenicity information after a fourth dose based on interim results from study HIPRA-HH-2. Study HIPRA-HH2 is a Phase IIb, double-blind, randomised, active -controlled, multicentre, non-inferiority trial followed by a Phase III, single-arm, open-label trial to assess immunogenicity and safety of a booster vaccination with a PHH-1V against SARS-COV-2 in adults fully vaccinated against Covid-19 followed by an extension period to study a fourth dose administration of PHH-1V. The study is listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly. In addition, the MAH submitted the full user consultation with target patient groups.	22/02/2024	21/03/2024	SmPC and PL	SmPC new text Study HIPRA-HH-2 is a double-blind, randomized (2:1), active controlled (comparator Comirnaty), multi-centre, non-inferiority trial to evaluate immunogenicity and safety of a single PHH-1V dose as a booster vaccination in in adults. This study was extended with a Part B, an open-label extension study to determine the immunogenicity, reactogenicity, safety, and tolerability of a fourth dose of PHH-1V (also referred to as Bimervax) (HIPRA-HH-2 – Part B). This procedure relates to the submission of the interim data of part B of the mentioned study. The immunogenicity and safety of Bimervax as a fourth dose of COVID vaccine was evaluated between 6 and 12 months after a 3rd dose of PHH-1V or after a 3rd dose of Comirnaty. Priming was performed with Comirnaty in both cohorts. Superiority has been shown for GMTs against Omicron BA.1 and BA. 4/5 as well as for former variants of concerns (VoCs) Beta and Delta after 4th doses in Cohort 1 and

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Cohort 2 when compared to GMT after 3rd dose in Cohort 2. These results allow the use of Bimervax as an additional booster not only after a booster of Comirnaty but also after a booster with Bimervax. Therefore, sections 4.2 and 5.1 of the SmPC has been amended accordingly. The safety data of PHH-1V as a fourth dose administered either after a third dose with PHH-1V or a third dose with Comirnaty is consistent with the known safety profile of the vaccine. Section 4.8 of the SmPC has been updated accordingly. Section 4.4 of the SmPC has been amended to recommend not to administer a further dose of PHH-1V to those who have experienced anaphylaxis after a prior dose of PHH-1V. For more information, please refer to the Summary of Product Characteristics.
II/0007/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.b.1.c - Replacement or addition of a	07/03/2024	12/12/2024	SmPC, Labelling and PL	Section 2, 6.3, 6.4, 6.5 and 6.6 of the SmPC have been updated. The Labelling and PL have also been updated accordingly.

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes				
II/0006	Submission of the final report from study HAN-01 listed as a category 3 study in the EU-RMP. This is a phase IIb, randomised, controlled, observer-blinded study to evaluate safety and immunogenicity of a recombinant protein RBD fusion dimer candidate vaccine (PHH-1V) against SARS-CoV-2 in adult healthy volunteers. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/01/2024	n/a		
IB/0011/G	This was an application for a group of variations. 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 A.3 - Administrative change - Change in name of the AS or of an excipient	20/12/2023	21/03/2024	SmPC, Labelling and PL	
II/0005/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting	23/11/2023	n/a		

	material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
II/0002	Submission of the final study report HIPRA-HH-1 listed as a category 3 study in the RMP. This is a phase I/IIa study to evaluate safety and immunogenicity of PHH-1V against SARS-COV-2 in adult healthy volunteers. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2023	n/a		Not applicable For more information, please refer to the Summary of Product Characteristics.
II/0008	Submission of the final report from study HIPRA-HH-10 listed as a category 3 study in the RMP. This is a phase 2b, double-blind, randomised, active-controlled, multi-centre, non-inferiority trial to assess immunogenicity and safety of a booster vaccination with a recombinant protein RBD fusion dimer candidate (PHH-1V) against SARS-CoV-2, in adults fully vaccinated with adenovirus vaccine against COVID-19. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/10/2023	n/a		
IB/0003	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	18/08/2023	n/a		

	authorisation, including the RMP - Other variation				
IB/0001	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	29/06/2023	21/03/2024	SmPC and PL	To extend the shelf-life of the biological finished product, in accordance with the approved stability protocol, from 1 year to 15 months when stored at 2 ºC – 8 ºC.