2 June 2022
EMA/648435/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

HBVAXPRO

Common name: hepatitis B vaccine (rDNA)

Procedure No. EMEA/H/C/000373/II/0076

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, MSD Vaccins submitted to the European Medicines Agency on 18 February 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.z	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	Type II	I, IIIA and IIIB

Update of section 5.1 of the SmPC in relation to the duration of protection over 9 years (re-challenge) in healthy subjects following procedure EMEA/H/C/000373/P46/061.
In addition, the MAH took the opportunity to implement editorial changes in the SmPC, Labelling and the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

HBVAXPRO is a monovalent hepatitis B vaccine that was approved in the EU for active immunization against hepatitis B virus infection in individuals from birth to 15 years of age considered at risk of exposure to hepatitis B virus.

HBVAXPRO is administered as a 0.5 mL intramuscular injection in a 3- (0, 1, 6 months) or 4-dose (0, 1, 2, 12 months) infant vaccination primary series, depending on local recommendations. One dose (0.5 mL) contains Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg).

To date, the duration of protective immune responses has not been established for primary series of HBVAXPRO.

During EMEA/H/C/000373/P46/061 procedure the CHMP recommended that, based on the data of V419-013 submitted, section 5.1 of the SmPC of HBVAXPRO be amended to incorporate the duration of protection over 9 years (re-challenge) in healthy subjects.

Since study V419-013 concerns the primary dose series of Vaxelis® rather than HBVAXPRO, the MAH proposed to revise the sentence from "As with other hepatitis B vaccines, the duration of the protective effect in healthy vaccinees is unknown at present" to "The duration of the protective effect in healthy vaccinees is unknown".

Overall, the proposed changes to the Product Information (section 5.1) are considered scientifically justified. The difference between HBVAXPRO and Vaxelis (a vaccine for DTaP-HB-IPV-Hib, received 8-9 years before), in terms of HBsAg contents and dose schedules, supports the MAH proposal not to incorporate the 9-year persistence data of V419-013 study in the HBVAXPRO SmPC 5.1.

The benefit-risk balance of HBVAXPRO remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation approved		**Type**	**Annexes affected**
C.I.3.z	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	Type II	I, IIIA and IIIB

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 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.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB are recommended.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Background on the product:

HBVAXPRO is a monovalent hepatitis B vaccine that was approved in EU for active immunization against hepatitis B virus infection in individuals from birth through 15 years of age considered at risk of exposure to hepatitis B virus.

HBVAXPRO is administered as a 0.5 mL intramuscular injection in a 3- (0, 1, 6 months) or 4-dose (0, 1, 2, 12 months) infant vaccination primary series, depending on local recommendations. One dose (0.5 mL) contains Hepatitis B virus surface antigen, recombinant (HBsAg) 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg).

The duration of protective effect of HBVAXPRO primary dose series has not yet been established.

- **Background on the study V419-013**

V419-013 was a single-group, open-label, single-dose, and multi-site study to evaluate the long-term durability of the immune protection against HBV infection approximately 9 years after receipt of a primary Vaxelis® immunization series. Participants had previously participated in studies V419-007 or V419-008 and received Vaxelis® according to a 3 + 1 (at 2, 3, 4 and 12 months of age) or a 2 + 1 (at 2, 4, and 11 to 12 months of age) schedule, respectively. They were 8 to 10 years of age at Protocol V419-013 enrollment and received a single intramuscular dose (5 µg dose) of HBVAXPRO. The trial was conducted under GCP.

V419-013 was assessed during EMEA/H/C/000373/P46/061 procedure.

- **Purpose of the Variation and Proposed changes to the Product Information:**

The submission of this variation was triggered by the outcome of EMEA/H/C/000373/P46/061 procedure, that related to the paediatric study V419-013.

CHMP comment:

Based on the data submitted, section 5.1 of the SmPC needs to be amended to incorporate the duration of protection over 9 years (re-challenge) in healthy subjects as part of this procedure.

MAH's response:

The proposed sentence in the SmPC is:

~~As with other hepatitis B vaccines, t~~The duration of the protective effect in healthy vaccinees is unknown ~~at present~~.

The MAH argued that duration of protection has been assessed in some hepatitis B vaccines, but it has not been assessed specifically for HBVAXPRO. The V419-013 study utilizes a HBVAXPRO challenge to demonstrate the durability of protection against hepatitis B virus infection in healthy children vaccinated about 9 years previously with Vaxelis. The HBsAg content and administrations schedules differ significantly between Vaxelis and HBVAXPRO and data generated by the V419-013 study does not inform the duration of the immune memory conferred by HBVAXPRO when administered as a primary series. The sentence above has therefore been adjusted to more accurately reflect what is known for HBVAXPRO which is that the duration of the protective effect of HBVAXPRO is unknown.

Assessor's comments:

The proposed changes to the Product Information (section 5.1) are scientifically justified.

The difference between HBVAXPRO and Vaxelis, in terms of HBsAg contents and dose schedules, supports the MAH approach to not incorporating the 9-year persistence data of V419-013 study in the HBVAXPRO SmPC 5.1.

5. Changes to the Product Information

Update of section 5.1 of the SmPC in relation to duration of protection following EMEA/H/C/000373/P46/061 procedure.

In addition, persistence of vaccine-induced immunologic memory for hepatitis B virus surface antigen (HBsAg) has been demonstrated through an anamnestic antibody response to a booster dose of a previous formulation of Merck's recombinant hepatitis B vaccine. ~~As with other hepatitis B vaccines, t~~The duration of the protective effect in healthy vaccinees is unknown ~~at present~~. The need for a booster dose of HBVAXPRO is not yet defined beyond the 12 month booster dose required for the 0, 1, 2 compressed schedule.

The MAH also took the opportunity to update some other sections of the product information:

- Editorial changes such as a change from ml to mL (Annex I, Annex IIIA, Annex IIIB) (alignment with Compilation of QRD decisions on stylistic matters in product information)

Please refer to Attachment 1 which includes all agreed changes to the Product Information.