PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PREHEVBRIO™

3-antigen Hepatitis B Vaccine (recombinant)

Single dose vial, 10 micrograms/mL Hepatitis B surface antigens (S [83%], pre-S2 [11%] and pre-S1 [6%])
Adsorbed on 500 micrograms of Al3+ as aluminium hydroxide, hydrated

Intramuscular injection

Active Immunizing Agent

VBI Vaccines Inc.
310 Hunt Club Road East
Suite 201, Ottawa, ON
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Canada

Date of Initial Authorization:
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March 17, 2023

Imported and distributed by:
McKesson Specialized Distribution Inc.
8449 Lawson Road, Unit 102
Milton, ON
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Canada

Submission Control Number: 259302

RECENT MAJOR LABEL CHANGES

Not applicable.	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PREHEVBRIO (3-antigen, recombinant Hepatitis B vaccine) is indicated for active immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

It can be expected that hepatitis D will also be prevented by immunization with PREHEVBRIO as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

The National Advisory Committee of Immunization (NACI) provides additional guidance on the use of hepatitis B vaccines in Canada, including a list of recommended individuals for vaccination against hepatitis B. Please refer to the Canadian Immunization Guide.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): PREHEVBRIO has been studied in the geriatric population (see 7.1 Special Populations, 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

PREHEVBRIO is contraindicated in patients who are hypersensitive to this vaccine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container, and who have experienced the following:

- Hypersensitivity to the active substance or to any of the excipients listed in 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- History of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B antigen-containing vaccine.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The vaccination regimen of PREHEVBRIO consists of 3 doses (1.0 mL each) given according to the following schedule: first dose at an elected date; second dose 1 month after the first dose; third dose 6 months after the first dose.

Booster dose

The need for a booster dose has not been established. No data are available.

Geriatric population

No dose adjustments are required in persons aged 65 years and older.

4.4 Administration

For intramuscular use only.

PREHEVBRIO should be injected intramuscularly (IM) into the deltoid region using a sterile needle of appropriate length to ensure IM administration. Injection into the gluteal (buttocks) region should be avoided.

The vaccine should be used under aseptic conditions.

The suspension should be shaken well prior to administration.

The suspension is slightly white opaque when mixed. Upon settling, the solution is clear and colorless with a white deposit.

The suspension should be visually inspected prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.

4.5 Missed Dose

If a planned dose of PREHEVBRIO is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 OVERDOSAGE

No cases of overdose have been reported with PREHEVBRIO.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

PREHEVBRIO is an injectable suspension, for intramuscular use supplied as a single-dose vial. A single dose of PREHEVBRIO is 1.0 mL.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	One dose (1.0 mL) of sterile suspension for injection contains Hepatitis B surface antigens (S [83%], pre-S2 [11%] and pre-S1 [6%])[1, 2] 10 micrograms. Packaged in 10 x 1.0 mL single-dose vials	Aluminum hydroxide, disodium phosphate dodecahydrate, hydrochloric acid, potassium chloride, potassium di-hydrogen phosphate, sodium chloride, sodium hydroxide, water for injection

[1] Adsorbed on 500 micrograms of Al3+ as aluminum hydroxide, hydrated
[2] Produced in Chinese Hamster Ovary cells by recombinant DNA technology

Excipients with known effect

Sodium: This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

Potassium: This medicinal product contains less than 1 mmol of potassium (39 mg) per dose, i.e. is essentially potassium-free'.

7 WARNINGS AND PRECAUTIONS

General

Vaccination should be postponed in subjects suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paresthesia, and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury.

Hepatitis B has a long incubation period. PREHEVBRIO may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

Acute Allergic Reactions

As with all injectable vaccines, appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Driving and Operating Machinery

PREHEVBRIO has no or negligible influence on the ability to drive and use machinery. However, some of the effects mentioned in 8 ADVERSE REACTIONS (e.g. fatigue, headache, dizziness) may temporarily affect the ability to drive or operate machinery.

Hematologic

As with other intramuscular injections, the vaccine should be given with caution in subjects receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as hemophilia) because bleeding or bruising may occur following an intramuscular administration in these vaccinees.

Immune

Immunocompromised persons may have a diminished immune response to PREHEVBRIO. There are limited data available among immunocompromised population. Attention should be given to ensure that a protective antibody level is maintained as defined by national recommendations and guidelines.

Patients with chronic liver disease or with HIV infection or hepatitis C carriers should not be precluded from vaccination against hepatitis B. The vaccine could be advised since hepatitis B infection can be severe in these patients: the PREHEVBRIO vaccination should thus be considered on a case-by-case basis by the physician.

Renal Impairment

Pre-hemodialysis and hemodialysis patients are at risk of exposure to hepatitis B virus and have a higher risk of becoming chronically infected. Attention should be given to ensure that a protective antibody level is achieved and maintained as defined by national recommendations and guidelines.

Reproductive Health: Female and Male Potential

- **Fertility**

There are no data on fertility in humans from the use of PREHEVBRIO (see 7.1.1 Pregnant Women).

- **Teratogenic Risk**

There are no data on teratogenic risk in humans from the use of PREHEVBRIO.

Animal studies do not indicate direct or indirect harmful effects with respect to embryolethality, fetotoxicity, or teratogenicity (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of the vaccine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY).

Vaccination during pregnancy should only be performed if the risk-benefit ratio at the individual level outweighs possible risks for the fetus.

7.1.2 Breast-feeding

It is unknown whether PREHEVBRIO is excreted in human milk.

A risk to the breastfed newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to abstain from PREHEVBRIO vaccination taking into account the benefit of breast-feeding for the child and the benefit of vaccination for the woman.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of PREHEVBRIO in pediatric patients has not been established in Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥ 65 years of age)

Immunogenicity of PREHEVBRIO has been studied in clinical trials in population 65 years of age and older. Seroprotection Rate (95% Confidence Interval) was 83.6% (78.6, 87.8) in a group of 268 individuals who received PREHEVBRIO compared to 64.7% (58.6, 70.4) in a group of 266 individuals who received Engerix-B with a difference in SPR of 18.9% (11.6, 26.1) between PREHEVBRIO and Engerix-B. Safety data were consistent with other age groups (See 8.2 Clinical Trial Adverse Reactions

and 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The clinical trial safety profile of PREHEVBRIO is based on two Phase 3 controlled clinical trials (Sci-B-Vac-001 and Sci-B-Vac-002) in which 2920 adults received at least one dose of PREHEVBRIO.

Local and systemic post-injection reactions were monitored using diary cards for a 7-day period starting on the day of each vaccination. The most common solicited local reactions after three injections were injection-site pain (72.2%), tenderness (71.2%) and local pruritus/itching (12.2%). Most common solicited systemic reactions were myalgia (41.7%), fatigue (37.5%), and headache (36.3%).

The frequency and severity of solicited adverse events generally declined or remained similar with successive vaccinations.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

A total of 2920 individuals age ≥18 years received at least one dose of PREHEVBRIO in two phase 3 clinical trials conducted in the United States, Canada, Belgium, Finland, Germany, and United Kingdom. Enrolled subjects had no history of hepatitis B vaccination or infection. Vaccinations were administered at 0, 1 and 6 months.

Study Sci-B-Vac-001 in adults age ≥18 years

Study Sci-B-Vac-001 was a randomized, double-blind, active-controlled, multicenter study in which 796 subjects received at least 1 dose of PREHEVBRIO and 811 subjects received at least 1 dose of Engerix-B [Hepatitis B Vaccine (Recombinant)]. In the total study population at baseline the mean age was 57 years, 81% were age ≥45 years; 37.2% were age ≥65 years, 62% women, 90% White, 8% Black, 1% Asian, and 10% Hispanic/Latino; 37% obese (BMI >30 kg/m^2), 14% current smokers and 8% had Type 2 diabetes mellitus. Demographic and baseline characteristics were similar in both vaccine groups. Completion rate of 3-dose vaccination was 95.2% for PREHEVBRIO 96.8% for Engerix-B.

Study Sci-B-Vac-002 in adults age 18-45 years

Study Sci-B-Vac-002 was a randomized, double-blind, active-controlled, multicenter study in which 2124 subjects received at least 1 dose of PREHEVBRIO and 712 subjects received at least 1 dose of Engerix-B. In the total study population at baseline, the mean age was 34 years; 58% women, 92% White, 6% Black, 2% Asian, and 10% Hispanic/Latino; 18% obese (BMI >30 kg/m^2) and 19% current smokers. Demographic and baseline characteristics were similar in both vaccine groups. Completion rate of 3-dose vaccination was 92.6% for PREHEVBRIO and 94.2% for Engerix-B.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who reported local and systemic reactions in both studies are shown in Table 2 to Table 5.

Table 2: Solicited Local and Systemic Adverse Events after Any Vaccination by Treatment Group – Age Group 18-44 Years (Study 001)

	Engerix-B (N=154) %	PREHEVBRIO (N=145) %
Local (Injection Site)		
Pain	51.9	74.5
Tenderness	50.0	70.3
Itching	13.0	9.0
Redness*	1.9	2.1
Swelling*	2.6	3.4
Systemic		
Headache	40.9	51.0
Fatigue	41.6	43.4
Myalgia	29.2	43.4
Diarrhea	14.9	14.5
Nausea/ vomiting	15.6	12.4
Fever	1.9	1.4

* Redness and swelling ≥ 2.5 cm

Table 3: Solicited Local and Systemic Adverse Events after Any Vaccination by Treatment Group – Age Group 45-64 Years (Study 001)

	Engerix-B (N=361) %	PREHEVBRIO (N=355) %
Local (Injection Site)		
Pain	36.8	67.0
Tenderness	37.1	63.4
Itching	7.8	8.5
Redness*	2.5	2.5
Swelling*	0.8	2.3

	Engerix-B (N=361) %	PREHEVBRIO (N=355) %
Systemic		
Headache	32.4	34.6
Fatigue	30.2	30.1
Myalgia	25.8	37.2
Diarrhea	11.9	9.0
Nausea/ vomiting	10.2	7.0
Fever	1.1	0.6

* Redness and swelling ≥ 2.5 cm

Table 4: Solicited Local and Systemic Adverse Events after Any Vaccination by Treatment Group – Age Group ≥ 65 Years (Study 001)

	Engerix-B (N=296) %	PREHEVBRIO (N=296) %
Local (Injection Site)		
Pain	27.4	53.0
Tenderness	24.0	53.0
Itching	6.1	11.1
Redness*	1.0	2.0
Swelling*	1.7	1.7
Systemic		
Headache	19.6	17.6
Fatigue	25.7	24.3
Myalgia	19.9	27.4
Diarrhea	10.1	9.8
Nausea/ vomiting	4.1	4.4
Fever	0.7	0.7

* Redness and swelling ≥ 2.5 cm

Table 5: Solicited Local and Systemic Adverse Events after Any Vaccination by Treatment Group – Age Group 18-45 Years (Study 002)

	Engerix-B (N=712) %	PREHEVBRIO (N=2124) %
Local (Injection Site)		
Pain	53.9	75.6
Tenderness	54.9	75.1
Itching	12.4	13.2
Redness*	1.7	2.9
Swelling*	0.8	2.6
Systemic		
Headache	37.6	38.2
Fatigue	39.9	40.1
Myalgia	32.4	44.4
Diarrhea	14.7	13.0
Nausea/ vomiting	12.1	11.8
Fever	1.1	1.1

* Redness and swelling ≥ 2.5 cm

The majority of subjects who experienced local solicited AEs within 7 days of any vaccination reported the maximum severity as mild (50.2% and 44.2%) or moderate (28.3% and 10.0%) for PREHEVBRIO and Engerix-B, respectively. Similarly, the maximum severity of systemic solicited AEs was mild (40.7% and 32.6%) or moderate (21.1% and 18.9%) for PREHEVBRIO and Engerix-B, respectively. The frequency and severity of solicited AEs generally declined or remained similar with successive vaccinations.

Unsolicited Adverse Events (AEs)

In both studies, unsolicited adverse events, including serious and non-serious events, that occurred within 28 days following each vaccination were recorded on a diary card by all subjects.

In both studies combined, unsolicited AEs that occurred within 28 days of any vaccination were reported by 48.3% and 48.4% of subjects who received PREHEVBRIO or Engerix-B, respectively. The most common (≥ 1%) unsolicited AEs in subjects who received PREHEVBRIO for which available information suggests a causal relationship to vaccination include injection site bruising (1.4%), dizziness/vertigo (1.1%), abdominal pain (0.7%), and rash (0.3%).

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions have been reported in less than 1% of the patients in Study 001 and Study 002.

Gastrointestinal Disorders: Abdominal pain

General Disorders and Administration Site Conditions: General pruritus/itchiness

Immune system disorders: Lymphadenopathy/lymph node pain

Musculoskeletal and Connective Tissue Disorders: Arthralgia

Skin and Subcutaneous Tissue Disorders: Rash, urticaria/hives

Vascular Disorders: Flushing/hot flushes

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There were no clinically significant changes in laboratory findings related to PREHEVBRIO identified during clinical trials or post-marketing of PREHEVBRIO.

8.5 Post-Market Adverse Reactions

The safety profile observed post-marketing with PREHEVBRIO is consistent with that observed during clinical studies.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed.

There are no data to assess the concomitant use of PREHEVBRIO with immune globulin. When concomitant administration of PREHEVBRIO and immune globulin is required, they should be given with different syringes at different injection sites. If concomitant administration of other vaccines is required, these should be given with different syringes at separate injection sites.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of PREHEVBRIO.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PREHEVBRIO confers seroprotection against hepatitis B virus infection through the stimulation of a specific immune response, as measured by the induction of anti-HBs antibodies at a level ≥10 mIU/mL.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator at 2°C to 8°C. Store in original package in order to protect from light.

Do not freeze; discard if the vaccine has been frozen.

Do not use the vaccine after the expiration date shown on the vial label.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Hepatitis B surface antigens (S [83%], pre-S2 [11%] and pre-S1 [6%])

Product Characteristics

PREHEVBRIO is manufactured by recombinant DNA technology in CHO (Chinese Hamster Ovary) mammalian cells, and contains the full antigenic structure of the HBV surface antigen, including the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The immunogenicity of PREHEVBRIO was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in 2 randomized, active controlled, double-blinded, multi-center Phase 3 clinical trials in adults 18 years of age and older. PREHEVBRIO and Engerix-B were given as a 3-dose regimen at 0, 1, and 6 months.

A total of 2920 individuals age ≥18 years received at least one dose of PREHEVBRIO in two phase 3 clinical trials (Sci-B-Vac-001 and Sci-B-Vac-002) conducted in the United States, Canada, Belgium, Finland, Germany, and United Kingdom. Enrolled subjects had no history of hepatitis B vaccination or infection. Vaccinations were administered at 0, 1 and 6 months. Summary of patient demographics is provided in Table 6.

Table 6: Summary of patient demographics for clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Sci-B-Vac-001	Phase III Comparative Randomized, Two arm Double-blind Multi-center	PREHEVBRIO ($Al(OH)_3$ without thimerosal); single dose IM, 10 µg (n=796) Comparator: Engerix B: 20 µg (n=811)	1607	56.6	Male = 38.5% (n=618) Female = 61.5% (n=989)
Sci-B-Vac-002	Phase III Comparative Randomized, Four arm Double-blind Multi-center	PREHEVBRIO($Al(OH)_3$ without thimerosal) Single dose IM, 10 µg Lot A (n=711) Lot B (n=709), Lot C (n= 706) Comparator: Engerix B: 20 µg (n=712)	2838	33.5	Male = 42.2% (n=1198 Female = 57.8% (n=1638)

Sci-B-Vac-001

A total of 2472 subjects were screened for the study with 1607 subjects randomized, including 796 subjects to the PREHEVBRIO treatment arm and 811 subjects to the Engerix-B® treatment arm. All randomized subjects received their assigned treatment.

Most subjects in both treatment arms completed study treatment as planned, including 758 (95.2%) in the PREHEVBRIO arm and 785 (96.8%) subjects in the Engerix-B® arm. Early discontinuation from treatment was reported for 38 (4.8%) in the PREHEVBRIO arm and 26 (3.2%) subjects in the Engerix-B® arm. The most common reason for treatment discontinuation was lost to follow-up (1.1% PREHEVBRIO and 1.2% Engerix-B®) followed by withdrawal of consent by the subject (1.0% PREHEVBRIO and 0.6% Engerix-B®). Treatment discontinuation due to non-serious AEs or SAE was uncommon, reported in 5 (0.6%) subjects in each treatment arm.

Overall, 756 (95.0%) in the PREHEVBRIO arm and 769 (94.8%) subjects in the Engerix-B® arm completed the study. The number of subjects who discontinued from the study was low and well balanced across the 2 treatment arms. Early discontinuation from the study was reported for 40 (5.0%) in the PREHEVBRIO arm and 42 (5.2%) subjects in the Engerix-B® arm. The most common reasons for early discontinuation from the study were lost to follow-up and withdrawal of consent. Study discontinuation due to non-serious AEs or SAE was uncommon, reported in 1 (0.1%) subject in the PREHEVBRIO arm and 3 (0.4%) subjects in the Engerix-B® arm.

Sci-B-Vac-002

A total of 4452 subjects were screened for the study with 2838 subjects randomized, including 712 subjects to the Engerix-B® group, and 2126 to the 3 PREHEVBRIO groups (711 to Lot A group, 709 to Lot B group, and 706 to Lot C group). Of the 2838 subjects, 2836 (99.9%) subjects received their assigned treatment. Two subjects were randomized to receive PREHEVBRIO but did not receive vaccination: One subject withdrew consent before receiving any vaccination and the other subject was discontinued due to non-compliance with the study procedures.

Most subjects (93%) completed study treatment as planned. Early discontinuation from treatment was reported in 159 (7.5%) subjects who received PREHEVBRIO and in 41 (5.8%) subjects who received Engerix-B®. The most common reason for treatment discontinuation was lost to follow-up or withdrawal of consent by subject.

14.2 Study Results

Immunogenicity

Study Sci-B-Vac-001 in adults age ≥18 years

The primary immunogenicity endpoint of the study was the seroprotection rate (SPR), defined as the percentage of subjects with anti-HBs levels of ≥10 mIU/mL. The two co-primary analyses, tested hierarchically, were: (1) non-inferiority of PREHEVBRIO compared to Engerix-B at Day 196, 4 weeks after receiving the third dose in all adults age ≥18 years and (2) superiority of PREHEVBRIO compared to Engerix-B in subjects ≥45 years old at Day 196.

The study met both co-primary endpoints. The estimated difference in SPR was 14.9% (95% CI: 11.2, 18.6) meeting the non-inferiority margin of -5%. The estimated difference in SPR in subjects ≥45 years of age was 16.4% (95% CI: 12.2, 20.7%) meeting the superiority criteria. These results are shown in Table 7, as well as SPR per age group.

Table 7: Seroprotection Rate (SPR) 4 Weeks After Receiving the Third Dose of PREHEVBRIO or Engerix-B

Study Population	PREHEVBRIO N	PREHEVBRIO SPR (95% CI)	Engerix-B N	Engerix-B SPR (95% CI)	Difference in SPR; PREHEVBRIO – Engerix-B (95% CI)
All Adults (Age 18+) [a]	718	91.4 (89.1, 93.3)	723	76.5 (73.2, 79.5)	14.9 (11.2, 18.6) [c]
Age 45+ [b]	625	89.4 (86.8, 91.7)	627	73.1 (69.4, 76.5)	16.4 (12.2, 20.7) [d]
Age 18-44	125	99.2 (95.6, 100.0)	135	91.1 (85.0. 95.3)	- [e]
Age 45-64	325	94.8 (91.8, 96.6)	322	80.1 (75.3, 84.3)	- [e]
Age 65 +	268	83.6 (78.6, 87.8)	266	64.7 (58.6, 70.4)	- [e]

N=number of subjects in the Per-Protocol Set; SPR= Seroprotection Rate defined as % of subjects with anti-HBs titers ≥10 mIU/mL in serum
[a] Per-protocol set (PPS). PPS included all subjects in the full analysis set who received all 3 vaccinations, had an evaluable serum immunogenicity sample at baseline and at the time point of interest, were seronegative at baseline, and had no major protocol violations leading to exclusion.
[b] Full analysis set (FAS). FAS included all subjects who received at least 1 vaccination and provided at least 1 evaluable serum immunogenicity sample both at baseline and after baseline. Subjects were seronegative at baseline.
[c] Non-inferiority was met because the lower bound of the 95% CI of the difference in SPR (PREHEVBRIO - Engerix-B) was > -5%.
[d] Superiority was met if the lower bound of the 95% CI of the difference in SPR (PREHEVBRIO minus Engerix-B) was greater than 0%.
[e] Exploratory analysis

SPR (95% Confidence Interval) at 4 weeks after receiving the third dose was higher for PREHEVBRIO compared with Engerix-B in subjects with diabetes (83.3% vs. 58.3%) and in subjects with BMI over 30 (89.22% vs. 68.11%).

Study Sci-B-Vac-002 in adults aged 18-45 years

In the secondary analysis, the data from the three lots were combined (pooled) to demonstrate non-inferiority of PREHEVBRIO compared to Engerix-B based on SPR.

The non-inferiority of PREHEVBRIO compared to Engerix-B based on SPR was met, the estimated difference in SPR at day 196 was 4.49% (95% CI: 2.90, 6.63%). The results are shown in Table 8**.**

Table 89: Seroprotection Rate (SPR) 4 Weeks After Receiving the Third Dose of PREHEVBRIO or Engerix-B

	PREHEVBRIO Pooled		Engerix-B		Difference in SPR (PREHEVBRIO–Engerix-B)
Study Population	**N**	**SPR (95% CI)**	**N**	**SPR (95% CI)**	**Difference (95% CI)***
Age 18-45 years	1753	99.26% (98.74. 99.60)	592	94.76% (92.65, 96.41)	4.49 (2.90, 6.63)

N=number of subjects in the Per-Protocol Set 2 (received all 3 doses at months 0, 1 and 6); SPR= Seroprotection Rate defined as % of subjects with anti-HBs titers ≥10 mIU/mL in serum; Pooled PREHEVBRIO includes the PREHEVBRIO Lots A, B, and C
*Non-inferiority was met because the lower bound of the 95% CI of the difference in SPR (PREHEVBRIO - Engerix-B) was > -5%.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

PREHEVBRIO has not been evaluated for carcinogenicity, mutagenic potential, or male infertility in

animals.

Vaccination of female rats with a vaccine formulation containing 10 micrograms/dose had no effect on fertility and no evidence of embryolethality, fetotoxicity or teratogenicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PREHEVBRIO™

Hepatitis B vaccine (recombinant), 3-antigen, Suspension for Intramuscular Injection

Read this carefully before you start taking **PREHEVBRIO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PREHEVBRIO.

What is PREHEVBRIO used for?

- PREHEVBRIO is a vaccine which prevents infection caused by the hepatitis B virus. It is used in adults to protect from all known types of hepatitis B virus.
- PREHEVBRIO may also protect against hepatitis D which can only occur in people who have hepatitis B infection.

How does PREHEVBRIO work?

When a person is given the PREHEVBRIO vaccine, it helps the body's natural defence system (immune system) produce specific protection (antibodies) against the hepatitis B virus.

- PREHEVBRIO contains a substance (called an 'adjuvant') which improves the body's production of antibodies and makes the protection last for longer.
- A course of three injections of PREHEVBRIO is required to provide full protection against hepatitis B.
- PREHEVBRIO is not used to treat a person who is already infected with the hepatitis B virus including anyone who has previously been infected and who is now a carrier of the virus.

What are the ingredients in PREHEVBRIO?

Medicinal ingredients: Hepatitis B surface antigens (S, pre-S1 and pre-S2).

Non-medicinal ingredients: aluminium hydroxide, disodium phosphate dodecahydrate, hydrochloric acid, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium hydroxide, water for injection

PREHEVBRIO contains sodium and potassium. This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. is essentially 'sodium-free', and less than 1 mmol of potassium (39 mg) per dose, i.e. is essentially 'potassium-free'.

PREHEVBRIO comes in the following dosage forms:

Sterile suspension for intramuscular injection supplied as a single-dose vial. A single dose vial of PREHEVBRIO contains 10 micrograms of non-infectious, recombinant Hepatitis B surface antigens (pre-S1, pre-S2 and S) in 1.0 mL of suspension.

You should not receive PREHEVBRIO if:

- if you are allergic to the active medicinal ingredient or any of the other non-medicinal ingredients of vaccine. Signs of an allergic reaction may include breathing difficulty, swelling, light-headedness, fast heartbeat, sweating, and loss of consciousness.
- if you have ever previously had a sudden, life-threatening allergic reaction to any vaccine against hepatitis B.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PREHEVBRIO. Talk about any health conditions or problems you may have, including if you:

- are pregnant, think you may be pregnant or plan to become pregnant. Your healthcare professional will tell you if you should receive PREHEVBRIO.
- are breast-feeding. It is unknown whether PREHEVBRIO is excreted in human milk. Your healthcare professional will tell you if you should receive PREHEVBRIO.
- are ill with a high fever. Your healthcare professional will tell you if you should receive PREHEVBRIO.
- have low blood platelets or any blood-clotting disorders, then bleeding or bruising may occur after you are given the injection.

Other warnings you should know about:

- If you are on dialysis for a kidney problem or if you have a weakened immune system your doctor may need to do a blood test to check if the vaccination has worked well enough to protect you against hepatitis B.
- Fainting can occur following, or even before, any needle injection, therefore tell your healthcare professional if you fainted with a previous injection
- PREHEVBRIO may not prevent hepatitis B infection if you already have an unrecognised hepatitis B infection at the time of vaccine administration.
- As with any vaccine, PREHEVBRIO may not protect all people who are vaccinated.
- PREHEVBRIO does not protect you against other liver infections such as hepatitis A, C, and E.
- PREHEVBRIO should not be given to individuals under 18 years of age.
- In addition to PREHEVBRIO, you may be given an injection of hepatitis B 'immuno-globulins'. This will give you immediate short-term protection against hepatitis B infection. If this happens, your healthcare professional will make sure that the two injections are given in different parts of the body.
- PREHEVBRIO is unlikely to have any effect on the ability to drive and use machines. If you feel tired, or have a headache or feel dizzy after having the vaccine, do not drive or use any machines until you feel well again.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PREHEVBRIO:

There is no information on the use of PREHEVBRIO with other vaccines or medications.
Tell your healthcare professional if you are taking, have recently taken, or might take any other medications, including any other vaccine.

How to take PREHEVBRIO:

PREHEVBRIO will be given to you by a healthcare professional in a healthcare setting.

Usual dose:

- PREHEVBRIO will be injected into a muscle in your upper arm.

You will be given a total of three injections. Each injection will be given on separate visits:

- 1st injection: on a date agreed with your healthcare professional;
- 2nd injection: 1 month after the 1st injection;
- 3rd injection: 6 months after the 1st injection.

- The recommended dose for each injection is 10 micrograms (1.0 mL of injection suspension).
- It is very important that you return for all injections, or the vaccine may not work as well.
- If you have any further questions on the use of PREHEVBRIO, ask your healthcare professional.

If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice.

Overdose:

If you think you, or a person you are caring for, have been administered too much PREHEVBRIO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice.

What are possible side effects from using PREHEVBRIO?

These are not all the possible side effects you may have when taking PREHEVBRIO. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people):

- feeling very tired;
- pain or tenderness at the injection site;
- rash and itching at the injection site;
- muscle pain;
- headache.

Common (may affect up to 1 in 10 people):

- diarrhea;
- feeling sick (nausea/vomiting);
- redness, bruising or swelling at the injection site;
- fever.

Uncommon (may affect up to 1 in 100 people):

- swollen lymph nodes;
- hives or itchy skin;
- dizziness;
- stomach pain;
- flushing or hot flushes;
- rash.

If you have a troublesome symptom or side effects that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and VBI Vaccines Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

PREHEVBRIO should be stored, supplied, and administered by a healthcare professional.

Store in a refrigerator at 2°C to 8°C. Protect from light.

Do not freeze; discard if the vaccine has been frozen.

Do not use the vaccine after the expiration date shown on the vial label after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice any foreign particulate matter and/or discoloration.

Keep out of reach and sight of children.

If you want more information about PREHEVBRIO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-888-421-8808.

This leaflet was prepared by VBI Vaccines Inc.

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