PREHEVBRIO- hepatitis b vaccine (recombinant) injection, suspension
VBI Vaccines (Delaware) Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREHEVBRIO ™ safely and effectively. See full prescribing information for PREHEVBRIO.

PREHEVBRIO [Hepatitis B Vaccine (Recombinant)]

Injectable suspension, for intramuscular use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

PREHEVBRIO is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. PREHEVBRIO is approved for use in adults 18 years of age and older. (1)

DOSAGE AND ADMINISTRATION

For intramuscular injection.
Administer a series of three doses (1.0 mL each) of PREHEVBRIO on a 0-, 1- and 6-month schedule. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

PREHEVBRIO is an injectable suspension, for intramuscular use supplied as a single-dose vial. A single dose of PREHEVBRIO is 1.0 mL (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of PREHEVBRIO. (4)

ADVERSE REACTIONS

Individuals 18 through 44 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (52.0 – 58.3%) and tenderness (52.6 – 59.6%). The most common systemic reactions following each dose of PREHEVBRIO were headache (17.2 – 25.8%), fatigue (20.1- 28.3%) and myalgia (22.2 – 29.9%).
Individuals 45 through 64 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (42.2 – 48.8%) and tenderness (43.2 – 50.5%). The most common systemic reactions following each dose of PREHEVBRIO were headache (13.8 – 21.3%), fatigue (14.3 – 19.7%) and myalgia (16.7 – 24.1%).
Individuals ≥ 65 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (26.7 – 34.8%) and tenderness (30.2 – 32.8%). The most common systemic reactions following each dose of PREHEVBRIO were headache (7.3 – 12.2%), fatigue (11.5 – 14.5%) and myalgia (11.5 - 16.6%). (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact VBI Vaccines at 1-888-421-8808 (toll-free) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov .
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PREHEVBRIO is indicated for prevention of infection caused by all known subtypes of hepatitis B virus.

PREHEVBRIO is approved for use in adults 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection.

2.1 Dosage and Schedule

Administer a series of three doses (1.0 mL each) of PREHEVBRIO on a 0-, 1- and 6-month schedule.

2.2 Administration

Shake the vial of PREHEVBRIO well to obtain a slightly opaque, white suspension.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Administer PREHEVBRIO by intramuscular injection.

3 DOSAGE FORMS AND STRENGTHS

PREHEVBRIO is an injectable suspension, for intramuscular use supplied as a single-dose vial. A single dose of PREHEVBRIO is 1.0 mL [see *How Supplied/Storage and Handling* (16.1)].

4 CONTRAINDICATIONS

Do not administer PREHEVBRIO to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of PREHEVBRIO [see *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of PREHEVBRIO.

5.2 Immunocompromised Individuals

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to PREHEVBRIO.

5.3 Limitations of Vaccine Effectiveness

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.

6 ADVERSE REACTIONS

Individuals 18 through 44 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (52.0 – 58.3%) and tenderness (52.6 – 59.6%). The most common systemic reactions following each dose of PREHEVBRIO were headache (17.2 – 25.8%), fatigue (20.1- 28.3%) and myalgia (22.2 – 29.9%).

Individuals 45 through 64 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (42.2 – 48.8%) and tenderness (43.2 – 50.5%). The most common systemic reactions following each dose of PREHEVBRIO were headache (13.8 – 21.3%), fatigue (14.3 – 19.7%) and myalgia (16.7 – 24.1%).

Individuals ≥ 65 years of age: The most common local reactions following each dose of PREHEVBRIO were injection site pain (26.7 – 34.8%) and tenderness (30.2 – 32.8%). The most common systemic reactions following each dose of PREHEVBRIO were headache (7.3 – 12.2%), fatigue (11.5 – 14.5%) and myalgia (11.5 - 16.6%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of PREHEVBRIO was evaluated in 2 active-controlled clinical studies (Studies 1 and 2) involving 4,443 subjects who received at least 1 dose of PREHEVBRIO (n = 2,920) or Engerix-B [Hepatitis B Vaccine (Recombinant)] (n = 1,523) administered according to a 0-, 1- and 6-months schedule.

Study 1 in adults ≥18 years of age

Study 1 was a randomized, double-blind, active-controlled, multicenter study that enrolled subjects in the United States (US), Canada, Belgium and Finland in which 796 subjects received at least 1 dose of PREHEVBRIO and 811 subjects received at least 1 dose of Engerix-B. In the total study population at baseline the mean age was 57 years, 81% were age ≥45 years; 62% were women; 90% were White, 8% Black, 1% Asian, and 10% Hispanic/Latino; 37% were obese (body mass index [BMI] >30 kg/m ^{2}), 14% were current smokers and 8% had Type 2 diabetes mellitus. Demographic and baseline characteristics were similar in both vaccine groups.

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 Study 1

are shown by age subgroup in Table 1 to Table 3.

Table 1: Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination (18 through 44 years of age)

	PREHEVBRIO Dose 1 (N=145) %	PREHEVBRIO Dose 2 (N=141) %	PREHEVBRIO Dose 3 (N= 134) %	Engerix-B Dose 1 (N=154) %	Engerix-B Dose 2 (N=152) %	Engerix-B Dose 3 (N=148) %
Local Reaction						
Pain	58.6	50.4	46.3	33.8	28.9	31.8
Pain, Grade 3 or greater [a]	0	0	0	0	0	0
Tenderness	53.8	50.4	42.5	32.5	32.2	36.5
Tenderness, Grade 3 or greater [b]	0.7	0	0.7	0.6	0.7	0.7
Itching	2.1	3.5	6.0	7.1	3.9	7.4
Itching, Grade 3 or greater [c]	0	0	0	0	0.7	1.4
Redness (≥ 2.5 cm)	0.7	1.4	1.5	0.6	1.3	0
Redness, Grade 3 or greater [d]	0	0	0	0	0	0
Swelling (≥ 2.5 cm)	2.8	1.4	0.7	0	1.3	2.0
Swelling, Grade 3 or greater [e]	0	0	0	0	0.7	1.4
Systemic Reaction						
Headache	33.8	24.1	20.9	29.9	19.1	13.5
Headache, Grade 3 or greater [a]	1.4	0.7	0	1.3	0.7	0
Fatigue	29.7	22.0	22.4	31.8	20.4	20.3
Fatigue, Grade 3 or greater [c]	1.4	0.7	0	0.6	2.0	1.4
Myalgia	27.6	24.1	21.6	20.8	11.8	10.1
Myalgia, Grade 3 or greater [c]	0.7	0	0	0	1.3	0
Diarrhea	9.7	5.7	4.5	9.7	5.9	7.4
Diarrhea, Grade 3 or greater [f]	0.7	0	0	0	0.7	0
Nausea/Vomiting	8.3	4.3	4.5	7.8	6.6	6.1
Nausea/Vomiting, Grade 3 or greater [f]	0	0.7	0	0	0.7	0
Fever (≥100.4°F)	0.7	0.7	0	1.3	0	0.7
Fever, Grade 3 or greater (≥102.1°F)	0.7	0	0	0	0	0

[a] Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

[b] Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

[c] Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

[d] Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

[e] Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis.

[f] Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

Table 2: Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination (45 through 64 years of age)

	PREHEVBRIO Dose 1 (N=355) %	PREHEVBRIO Dose 2 (N=350) %	PREHEVBRIO Dose 3 (N=343) %	Engerix-B Dose 1 (N=361) %	Engerix-B Dose 2 (N=357) %	Engerix-B Dose 3 (N=349) %

Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis.

Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

	PREHEVBRIO Dose 1 (N=355) %	PREHEVBRIO Dose 2 (N=350) %	PREHEVBRIO Dose 3 (N=343) %	Engerix-B Dose 1 (N=361) %	Engerix-B Dose 2 (N=357) %	Engerix-B Dose 3 (N=349) %
Local Reaction						
Pain	46.8	44.9	39.4	22.2	15.4	17.2
Pain, Grade 3 or greater [a]	0	0	0.3	0	0	0
Tenderness	48.7	42.6	40.5	23.8	16.5	17.5
Tenderness, Grade 3 or greater [b]	0.8	0.6	0.3	0	0	0.3
Itching	4.5	3.1	3.8	3.9	2.0	3.4
Itching, Grade 3 or greater [c]	0	0.3	0	0	0	0
Redness (≥ 2.5 cm)	1.7	0.6	0.3	1.1	0.3	1.1
Redness, Grade 3 or greater [d]	0	0	0	0.8	0.3	0.6
Swelling (≥ 2.5 cm)	1.4	0.3	0.9	0	0.6	0.3
Swelling, Grade 3 or greater [e]	0	0	0.3	0	0	0
Systemic Reaction						
Headache	21.4	13.7	15.7	20.5	11.2	14.0
Headache, Grade 3 or greater [a]	0	0	0.3	0.3	0.3	0.3
Fatigue	16.6	16.9	12.5	22.2	11.5	12.3
Fatigue, Grade 3 or greater [c]	0.6	0	0.3	0.6	0.3	0.6
Myalgia	21.4	20.0	15.5	16.1	8.4	9.5
Myalgia, Grade 3 or greater [c]	0.6	0	0	0	0	0
Diarrhea	4.8	4.0	3.2	6.4	3.6	3.7
Diarrhea, Grade 3 or greater [f]	0	0	0	0	0	0
Nausea/Vomiting	4.2	2.9	2.3	6.4	3.6	2.6
Nausea/Vomiting, Grade 3 or greater [f]	0	0	0	0	0	0
Fever (≥100.4°F)	0.6	0	0	0.3	0.3	0.6
Fever, Grade 3 or greater (≥102.1°F)	0	0	0	0	0	0.3

[a] Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

[b] Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

[c] Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

[d] Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

[e] Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis.

[f] Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

Table 3: Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination (≥ 65 years of age)

	PREHEVBRIO Dose 1 (N=296) %	PREHEVBRIO Dose 2 (N=288) %	PREHEVBRIO Dose 3 (N=281) %	Engerix-B Dose 1 (N=296) %	Engerix-B Dose 2 (N=292) %	Engerix-B Dose 3 (N= 288) %
Local Reaction						
Pain	34.8	28.8	26.7	16.2	12.0	11.1
Pain, Grade 3 or greater [a]	0	0	0	0.3	0	0
Tenderness	32.8	30.2	31.0	14.2	12.0	10.1

Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis.

Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

	PREHEVBRIO Dose 1 (N=296) %	PREHEVBRIO Dose 2 (N=288) %	PREHEVBRIO Dose 3 (N=281) %	Engerix-B Dose 1 (N=296) %	Engerix-B Dose 2 (N=292) %	Engerix-B Dose 3 (N= 288) %
Tenderness, Grade 3 or greater [b]	0	0	0	0	0	0
Itching	6.1	3.8	5.0	4.1	1.4	2.4
Itching, Grade 3 or greater [c]	0	0	0	0	0	0
Redness (≥ 2.5 cm)	1.0	0.3	1.4	0.7	0.3	0
Redness, Grade 3 or greater [d]	0.3	0	0.4	0	0.3	0
Swelling (≥ 2.5 cm)	1.0	0.7	1.1	1.4	0.3	0.3
Swelling, Grade 3 or greater [e]	0.3	0	0	0	0.3	0
Systemic Reaction						
Headache	12.2	7.3	7.8	12.8	5.8	6.9
Headache, Grade 3 or greater [a]	0	0	0	0	0	0
Fatigue	14.5	11.5	12.5	17.9	9.9	10.1
Fatigue, Grade 3 or greater [c]	0	0	0	0.7	0	0.3
Myalgia	16.6	11.5	13.2	12.8	8.2	6.9
Myalgia, Grade 3 or greater [c]	0	0	0	0	0.3	0
Diarrhea	6.4	4.2	1.1	6.4	2.4	3.5
Diarrhea, Grade 3 or greater [f]	0.3	0	0	0.3	0	0
Nausea/Vomiting	3.7	0.7	1.1	1.7	1.7	0.7
Nausea/Vomiting, Grade 3 or greater [f]	0	0	0	0.3	0	0.3
Fever (≥100.4°F)	0	0	0.7	0	0	0.7
Fever, Grade 3 or greater (≥102.1°F)	0	0	0	0	0	0

[a] Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

[b] Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

[c] Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

[d] Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

[e] Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis.

[f] Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

The median duration of local and systemic solicited adverse reactions was 1-2 days in both treatment groups. Among all subjects who received PREHEVBRIO, the frequencies of the most commonly reported solicited reactions extending beyond the 7-day assessment period were as follows: fatigue (4.1%), injection site pain (2.0%), headache (1.9%) and myalgia (1.9%).

Study 2 in adults 18 through 45 years of age

Study 2 was a randomized, double-blind, active-controlled, multicenter study that enrolled subjects in the US, Canada, Belgium, Finland, Germany and the United Kingdom in which 2,124 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% were women; 92% were White, 6% Black, 2% Asian, and 10% Hispanic/Latino; 18% were obese (BMI >30 kg/m ^{2}) and 19% were current smokers. Demographic and baseline characteristics were similar in both vaccine groups.

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 Study 2 are shown in Table 4.

Table 4: Study 2: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination (18 through 45 years of age)

	PREHEVBRIO Dose 1 (N=2122) [a] %	PREHEVBRIO Dose 2 (N=2071) %	PREHEVBRIO Dose 3 (N=1967) %	Engerix-B Dose 1 (N=712) %	Engerix-B Dose 2 (N=701) %	Engerix-B Dose 3 (N=671) %
Local Reaction						
Pain	58.2	52.2	52.5	35.1	29.2	32.5
Pain, Grade 3 or greater [b]	0.3	0.3	0.4	0.1	0	0.3
Tenderness	59.9	52.9	55.5	37.6	30.4	33.8
Tenderness, Grade 3 or greater [c]	0.8	0.9	0.8	0.6	0.1	0.1
Itching	5.7	5.7	6.7	6.6	5.3	5.4
Itching, Grade 3 or greater [d]	0	0	0.1	0.3	0.1	0
Redness (≥ 2.5 cm)	1.1	1.1	1.3	0.6	0.4	1.0
Redness, Grade 3 or greater [e]	0.2	0	0.2	0.1	0.1	0.1
Swelling (≥ 2.5 cm)	1.2	0.9	1.1	0.6	0	0.4
Swelling, Grade 3 or greater [f]	0.1	0	0.1	0	0	0
Systemic Reaction						
Headache	25.1	16.7	17.4	24.2	15.0	18.3
Headache, Grade 3 or greater [b]	0.3	0.2	0.5	0.4	0.4	0.6
Fatigue	28.4	19.8	20.2	27.1	17.8	22.1
Fatigue, Grade 3 or greater [d]	0.5	0.8	0.6	0.4	0.6	0.6
Myalgia	30.3	21.9	23.6	17.7	13.0	18.5
Myalgia, Grade 3 or greater [d]	0.3	0.6	0.5	0.4	0.1	0.4
Diarrhea	7.4	5.0	4.4	9.6	4.9	5.4
Diarrhea, Grade 3 or greater [g]	0.2	0.1	0.1	0	0	0
Nausea/Vomiting	6.7	3.7	4.7	7.0	3.6	3.9
Nausea/Vomiting, Grade 3 or greater [g]	0	0	0.2	0	0.1	0
Fever (≥100.4°F)	0.3	0.3	0.6	0.4	0.3	0.9
Fever, Grade 3 or greater (≥102.1°F)	0	0.1	0.1	0.1	0	0

[a] Two subjects without solicited adverse event data following dose 1 of PREHEVBRIO were excluded from this analysis.

[b] Grade 3 or greater pain and headache: defined as use of narcotic pain reliever or prevents daily activity; or ER visit or hospitalization

[c] Grade 3 or greater tenderness: defined as significant discomfort at rest; or ER visit or hospitalization

[d] Grade 3 or greater itching, fatigue and myalgia: defined as prevents daily activity; or ER visit or hospitalization

[e] Grade 3 or greater redness: defined as > 10 cm or skin necrosis or exfoliative dermatitis

[f] Grade 3 or greater swelling: defined as > 10 cm or prevents daily activity; or skin necrosis

[g] Grade 3 or greater diarrhea and nausea/vomiting: defined as prevents daily activity or requires outpatient IV hydration; or ER visit or hospitalization.

The median duration of local and systemic solicited adverse reactions was 1-2 days in both treatment groups. Among all subjects who received PREHEVBRIO, the frequencies of the most commonly reported solicited reactions extending beyond the 7-day assessment period were as follows: fatigue (3.5%), injection site pain (2.0%), headache (1.9%) and myalgia (1.8%).

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. 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%), general pruritus/itchiness (0.2%), arthralgia (0.2%), urticaria/hives (0.2%) and lymphadenopathy/lymph node pain (0.1%).

Serious Adverse Events (SAEs)

In both studies, SAEs were collected from first vaccination through 6 months following the last vaccination. In both studies combined, SAEs were reported by 0.9% and 0.6% within 28 days of vaccination with PREHEVBRIO or Engerix-B, respectively. SAEs were reported by 2.5% of subjects in the PREHEVBRIO group and 1.6% in the Engerix-B group from the first vaccination through 6 months following the third vaccination. There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to PREHEVBRIO.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Immune Globulin

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.

7.2 Interference with Laboratory Tests

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PREHEVBRIO during pregnancy. Women who receive PREHEVBRIO during pregnancy are encouraged to contact 1-888-421-8808 (toll-free).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In clinically recognized pregnancies in the US general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20%.

There are no adequate and well-controlled studies of PREHEVBRIO in pregnant women. Available human data on PREHEVBRIO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of PREHEVBRIO on four occasions; twice prior to mating, twice during gestation. The study revealed no evidence of harm to the fetus due to the vaccine [see Animal Data below].

Data

Animal Data

A developmental toxicity study has been performed in female rats using a dose equivalent to the adult human dose. In the study, female rats received 0.5 mL (2 x 0.25 mL injections) of a vaccine formulation containing 10 mcg HBsAg (S, pre-S1, pre-S2) adsorbed on to aluminum hydroxide by intramuscular injection 30 days and 15 days prior to mating and on gestation days 4 and 15. No adverse effects of pre-weaning development were observed. There was no evidence of fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether PREHEVBRIO is excreted in human milk. Data are not available to assess the effects of PREHEVBRIO on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREHEVBRIO and any potential adverse effects on the breastfed child from PREHEVBRIO or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of PREHEVBRIO have not been established in individuals less than 18 years of age.

8.5 Geriatric Use

Study 1 included 296 adults 65 through 86 years of age who received PREHEVBRIO. Among subjects who received PREHEVBRIO, a seroprotective level of antibody to HBsAg was achieved in 83.6% of those ≥ 65 years of age compared to 94.8% in adults 45 through 64 years of age and 99.2% in adults 18 through 44 years of age [see *Evaluation of Immunogenicity* (14.1)].

Frequencies of local and systemic solicited adverse reactions were generally lower in elderly subjects ≥65 years of age than in younger subjects [see *Adverse Reactions* (6)].

8.6 Adults on Hemodialysis

Safety and effectiveness of PREHEVBRIO have not been established in adults on hemodialysis.

11 DESCRIPTION

PREHEVBRIO [Hepatitis B Vaccine (Recombinant)] is a sterile suspension for intramuscular injection.

PREHEVBRIO contains the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens, co-purified from genetically modified CHO (Chinese Hamster Ovary) cells cultured in growth medium containing vitamins, amino acids, minerals, and fetal bovine serum.

The hepatitis B surface antigens are co-purified from the supernatant of CHO cells by a series of physicochemical steps as virus-like particles containing CHO cell membrane lipids.

Each 1.0 mL dose is formulated to contain 10 mcg hepatitis B surface antigens (S, pre-S1 and pre-S2) adsorbed on aluminum hydroxide [$Al(OH)_3$] as an adjuvant (aluminum content of 0.5 mg/mL).

Each 1.0 mL dose of PREHEVBRIO also contains sodium chloride (NaCl) (8.45 mg/dose), potassium chloride (KCl) (0.02 mg/dose), disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4.12H_2O$) (0.38 mg/dose), potassium dihydrogen phosphate anhydrous (KH_2PO_4) (0.02 mg/dose) and water for injections (WFI). Each dose may contain residual amounts of CHO cell proteins (up to 2.5 ng/dose), CHO cell DNA (up to 10 pg/dose), Bovine Serum Albumin (up to 2.5 ng/dose) and Formaldehyde (up to 500 ng/dose) from the manufacturing process.

PREHEVBRIO does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PREHEVBRIO induces antibodies to HBsAg. Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PREHEVBRIO has not been evaluated for carcinogenic, mutagenic potential or male infertility in animals. In a developmental toxicity study in rats with a vaccine formulation containing 10 mcg HBsAg (S, pre-S1, pre-S2) adsorbed on to aluminum hydroxide there were no effects on female fertility [see *Animal Data* (8.1)].

14 CLINICAL STUDIES

14.1 Evaluation of Immunogenicity

The immunogenicity of PREHEVBRIO was evaluated in comparison with a US-licensed hepatitis B vaccine (Engerix-B) in 2 randomized, active controlled, double-blind, multi-center Phase 3 clinical trials in adults. PREHEVBRIO and Engerix-B were administered according to a 0-, 1- and 6-month schedule. For subject baseline characteristics, see section 6.1.

The trials compared the seroprotection rates (SPR), defined as the proportion of participants with anti-HBs titers ≥ 10 mIU/mL, induced by PREHEVBRIO and Engerix-B. Non-inferiority was met if the lower bound of the

95% confidence interval (CI) of the difference in SPR (PREHEVBRIO minus Engerix-B) was greater than -5%.

Study 1 in adults ≥18 years of age

The immunogenicity population included 718 subjects who received PREHEVBRIO and 723 subjects who received Engerix-B. The mean age was 57 years in both groups. The primary analysis compared the SPR, 4 weeks after receiving the third dose of PREHEVBRIO or Engerix-B in subjects ≥ 18 years of age. The SPR induced by PREHEVBRIO compared to Engerix-B was non-inferior in subjects ≥ 18 years of age (Table 5).

Table 5: Study 1: 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]

Abbreviations: N=number of subjects in the analysis set; SPR= Seroprotection Rate (percent of subjects with anti-HBs titers ≥10 mIU/mL)

[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] The SPR following PREHEVBRIO was statistically significantly higher than following Engerix-B (lower bound of the 95% CI of the difference in SPR was > 0%).

[e] Exploratory analysis

Study 2 in adults 18 through 45 years of age

The immunogenicity population included 1,753 subjects who received PREHEVBRIO and 592 subjects who received Engerix-B. The mean age was 34 years in the PREHEVBRIO group and 33 years in the Engerix-B group. The study compared the SPR, 4 weeks after receiving the third dose of PREHEVBRIO or Engerix-B in all subjects. The SPR induced by PREHEVBRIO compared to Engerix-B was non-inferior (Table 6).

Table 6: Study 2: 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)
Age 18-45	1753	99.3 (98.7. 99.6)	592	94.8 (92.7, 96.4)	4.5 (2.9, 6.6) *

SPR= Seroprotection Rate (percent of subjects with anti-HBs titers ≥10 mIU/mL)

*Non-inferiority was met because the lower bound of the 95% CI of the difference in SPR (PREHEVBRIO - Engerix-B) was > -5%.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single dose vial, 1.0 mL (NDC number 75052-001-01)

Supplied as a package of 10 single dose vials (NDC number: 75052-001-10)

The vial stoppers are not made with natural rubber latex.

16.2 Storage Conditions

Store in a refrigerator at 2°C to 8°C (36°F to 46°F). 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.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks associated with vaccination with PREHEVBRIO, as well as the importance of completing the immunization series.
- Emphasize that PREHEVBRIO contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Manufactured by: VBI Vaccines Inc.
160 Second St., 3rd Floor, Cambridge, MA, USA, 02142
U.S. License No. 2219

Principal Display Panel - 10 mcg/mL Carton Label

NDC 75052-001-10

Hepatitis B Vaccine
(Recombinant)

PreHevbrio

Rx only

For adults 18 years or older

10
mcg/mL

10 x 1 mL
single-dose vials

For
intramuscular
administration

VBI
VACCINES

Principal Display Panel - 10 mcg/mL Vial Label

NDC 75052-001-01

Hepatitis B Vaccine
(Recombinant)

PreHevbrio

For IM administration

Rx only

Storage:
2°C to 8°C

1

Dose
(1 mL)

PREHEVBRIO

hepatitis b vaccine (recombinant) injection, suspension

Product Information

Product Type	VACCINE	**Item Code (Source)**	NDC:75052-001
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM S) (UNII: 2U8266YW9L) (RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM S) - UNII:2U8266YW9L)	RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM S)	10 ug in 1 mL
RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM M) (UNII: SND8HL4KQG) (RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM M) - UNII:SND8HL4KQG)	RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM M)	1.1 ug in 1 mL
RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM L) (UNII: C6PFS5DX5Y) (RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM L) - UNII:C6PFS5DX5Y)	RECOMBINANT HEPATITIS B SURFACE ANTIGEN (ISOFORM L)	0.6 ug in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8450 ug in 1 mL
POTASSIUM CHLORIDE (UNII: 660YQ98I10)	20 ug in 1 mL
SODIUM PHOSPHATE, DIBASIC, DODECAHYDRATE (UNII: E1W4N241FO)	380 ug in 1 mL
MONOBASIC POTASSIUM PHOSPHATE (UNII: 4J9FJ0HL51)	20 ug in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
ALUMINUM HYDROXIDE (UNII: 5QB0T2IUN0)	1500 ug in 1 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:75052-001-10	10 in 1 CARTON		
1	NDC:75052-001-01	1 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125737	03/02/2022	

Labeler - VBI Vaccines (Delaware) Inc. (103812236)

Establishment

Name	Address	ID/FEI	Business Operations
BioReliance		505004556	analysis

Establishment

Name	Address	ID/FEI	Business Operations
SciVac Ltd		514477301	api manufacture, analysis, pack, label, manufacture

Establishment

Name	Address	ID/FEI	Business Operations
Envigo CRS (Israel) Limited		514627793	analysis

Establishment

Name	Address	ID/FEI	Business Operations
Hy-Labs		600013676	analysis

Establishment

Name	Address	ID/FEI	Business Operations
IMI TAMI Institute for Research and Development Ltd.		600045280	analysis