NEW DRUG APPROVAL

Brand Name	Prehevbrio™
Generic Name	Hepatitis B Vaccine (Recombinant)
Drug Manufacturer	VBI Vaccines (Delaware) Inc.

New Drug Approval

FDA Approval Date: November 30,2021

Review designation: N/A

Type of review: Biological License Application (BLA)- 125737

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV). HBV infection causes inflammation of the liver. When the liver is inflamed or damaged, its function can be affected.

- Hepatitis B is transmitted when blood, semen, or another body fluid from a person infected with HBV enters the body of someone who is not infected. This can happen through sexual contact; sharing needles, syringes, or other drug-injection equipment; or from mother to baby at birth.
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Hepatitis B in the United States

- Up to 2.4 million people are chronically infected.
- Rates of acute hepatitis B infection have risen 50%-450% in states impacted by the opioid crisis.
- For many countries, chronic hepatitis B rates are higher in males than females and have declined over the past three decades, but no consistent pattern is seen between rates for U.S. immigrants and residents.
- More than 50% of people living with chronic hepatitis B are of Asian, Pacific Islander or African descent. Hepatitis B and the resulting liver cancer are among the largest health disparities for these groups.
- The weighted average chronic hepatitis B prevalence for all foreign-born people in the U.S. in 2018 was about 3%. Around 59% of those U.S. residents with chronic hepatitis B in the U.S. in 2018 emigrated from Asia, 19% from the Americas and 15% from Africa.
- Only 25% of infected individuals are diagnosed.
- Thousands of people die each year from hepatitis B.

Earlier in November 2021, the U.S. Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) unanimously voted to recommend universal HBV vaccination for adults age 18 to 59, and for adults age 60+ with risk factors for infection, expanding the addressable adult population that should be vaccinated.

Efficacy

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 EngerixB 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: 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: 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%.

Safety

ADVERSE EVENTS

- 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%).

WARNINGS & PRECAUTIONS

- **Managing Allergic Reactions:** Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Prehevbrio™ .
- **Immunocompromised Individuals:** Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to Prehevbrio™ .
- **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.

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™.

Clinical Pharmacology

MECHANISMS OF ACTION

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

Dose & Administration

ADULTS

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

PEDIATRICS

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

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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