

Company

VBI Vaccines Inc.

Drug or Device Name

PreHevbrio™

Category

Biotechnology

Compound/Technical Name

Hepatitis B Vaccine (Recombinant)

Trade Name

PreHevbrio™

Date of Approval

11/30/2021

Therapeutic Categories

Hepatitis B prophylaxis

Indications

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 Please see Full Prescribing Information (attached as PDF).

Background

Hepatitis B is a highly infectious disease of the liver caused by the hepatitis B virus (HBV) which can present as a short-term acute infection or lifelong chronic illness. In chronically infected individuals, of which there are nearly 300 million, globally, HBV is the leading cause of liver disease, and can result in liver decompensation, cirrhosis, and hepatocellular carcinoma. Moreover, only about 10% of chronically infected individuals are aware of their infection status, increasing their likelihood of transmission. Despite the implementation of HBV vaccine guidelines in the 1980s, hepatitis B remains a persistent and significant public health problem. In fact, in the U.S., initial decreases in new HBV infections plateaued 10 years ago – rates are now highest among adults, with increasing rates in adults aged 40 years and older.(1) Each year in the U.S., there are approximately \$1 billion in direct costs spent on hepatitis B-related hospitalizations. HBV is an entirely vaccine-preventable disease, and yet only 30% of all adults in the U.S. are vaccinated against hepatitis B. Additionally, vaccination rates among adults with risk factors that may make vaccination with conventional single-antigen HBV vaccines less effective, including chronic liver disease, diabetes, and obesity, remain low in recent years.(2) To better fight HBV, public health bodies have recognized that new approaches and new tools are needed and, recently, there has been re-energized momentum to support this public health battle. In 2020, the U.S. Department of Health and Human Services published The Viral Hepatitis National Strategic Plan and

Healthy People 2030, both of which outline actions to increase awareness and decrease the number of acute cases and HBV-related deaths. Similarly, the World Health Organization (WHO) has adapted the goal of eliminating HBV globally by 2030, and in 2021 it released its first-ever global guidance for country validation of viral hepatitis B elimination. In November 2021, the CDC's Advisory Committee on Immunization Practices (ACIP) unanimously voted to upgrade the U.S. adult HBV vaccine recommendation from risk-based to universal for all adults age 19-59, maintaining a risk-based recommendation for adults age 60 years and older. Advocacy organizations across the country are also working to increase education and raise awareness of these new recommendations. References: 1)Weng M. Universal Adult Hepatitis B Vaccination: Work Group Considerations. Slides from Hepatitis Work Group presentation at November 3, 2021 meeting of the Advisory Committee on Immunization Practices. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/02-HepWG-weng-508.pdf> 2)Weng M, Doshani, M, Khan M, et al. Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices – United States, 2022. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report.2022;17;13:477-483.

Development

The HBV genome encodes for three distinct surface antigens, all of which are present on the surface of a wildtype virus – pre-S1, pre-S2, and S antigens. Originally developed at the Weizmann Institute of Science in Rehovot, Israel, PreHevbrio expresses all three of the hepatitis B virion's surface antigens, is void of infectious material, and is derived from a mammalian cell line. Under the brand name Bio-Hep-B (and later changed to Sci-B-Vac®), this vaccine first received marketing authorization in Israel in 2000. It was subsequently approved in other countries in Asia, Africa, and South America, and was marketed in Israel and Hong Kong. From 1989 to present, more than 22 clinical studies have been conducted assessing the safety, tolerability, and immunogenicity of this 3-antigen HBV vaccine. Additionally, there have been several investigator-initiated studies assessing immunogenicity and safety in specific adult subpopulations, including HIV patients, ESRD patients, and non-responders to conventional single-antigen HBV vaccines. The first studies to be conducted in North American and European countries were initiated in 2017 and were designed to support regulatory approvals in the U.S., Europe, and Canada. The two pivotal studies that supported marketing authorizations in the U.S. (granted in November 2021), the EU/EEA (granted in April 2022), and the UK (granted in May 2022), were named PROTECT and CONSTANT, both of which compared VBI's 3-antigen HBV vaccine against the most widely used single-antigen vaccine, GSK's Engerix-B. The Phase 3 program completed in early 2020. Data from these studies further demonstrated that PreHevbrio may be able to overcome some of the limitations of conventional single-antigen HBV vaccines in the adult setting, particularly in adults aged 45 and older where 10µg of PreHevbrio elicited statistically significantly higher seroprotection rates (SPR – defined as percentage of participants achieving anti-HBs titers greater than or equal to 10 mIU/mL) compared to 20µg of Engerix-B (89.4% vs. 73.1%). In these two studies, PreHevbrio was able to elicit higher SPR and antibody titers in all adults, including in key subgroups of interest based on age, gender, obesity, and diabetic status.(1) Regardless of age, BMI, or diabetes status, participants who received PreHevbrio had 5-8-fold higher antibody GMC compared to Engerix-B at Day 196.(1) The SPR of PreHevbrio was also higher than that of Engerix-B at each post-vaccination timepoint in participants 18 years and older and in each age subgroup, at Days 28, 56, 168, 196 and 336.(1) In both studies, PreHevbrio was well-tolerated with no unexpected reactogenicity. Following approvals in November 2021, April 2022, and May 2022, VBI's vaccine became the only approved 3-antigen HBV vaccine for adults in the U.S., EU/EEA, and UK, respectively. Brand names in each region include: PreHevbrio (U.S.), PreHevbri (EU/EEA, UK), and Sci-B-Vac (Israel). This vaccine is

manufactured at VBI's wholly owned GMP manufacturing facility in Rehovot, Israel. (1) Vesikari T., Langley J., Segal N., et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomized, double-blind, phase 3 trial. *The Lancet Infectious Diseases*. 2021; [https://doi.org/10.1016/S1473-3099\(20\)30780-5](https://doi.org/10.1016/S1473-3099(20)30780-5)

Innovation

PreHevbrio is an alum-adjuvanted HBV vaccine produced in mammalian cells that contains all three surface antigens of HBV – the pre-S1, pre-S2, and S – and which resembles the naturally-occurring HBV particles in terms of protein composition and glycosylation pattern, harboring all antigenic epitopes and domains of the HBV envelope. All other available adult HBV vaccines are yeast-derived single-antigen vaccines, expressing only the S antigen. Due to its 3-antigen conformation, PreHevbrio expresses highly immunogenic T and B cell epitopes present in the pre-S1 and pre-S2 antigens. (1) The pre-S1 and pre-S2 proteins serve as important roles in the viral invasion of hepatocytes, and in viral infection, viral assembly, viral replication, and stimulation of immune responses in the body. (2) PreHevbrio's extensive dataset includes (i) two pivotal Phase 3 studies (PROTECT and CONSTANT) that formed the basis of regulatory approvals in the U.S. and Europe, (ii) more than 22 additional clinical studies conducted outside of North America in adults, newborns, and adolescents that formed the basis of regulatory approval in Israel, (iii) several investigator-initiated studies in immunocompromised populations, including HIV and ESRD patients, and in non-responders to conventional single-antigen HBV vaccines, and (iv) commercial distribution data that suggests this 3-antigen vaccine has been administered to over 750,000 individuals in Israel. In clinical studies, PreHevbrio has elicited robust immunogenicity in all adults with a well-established safety profile. New guidelines, recommendations, and tools are needed to reignite the fight against hepatitis B as public health bodies and healthcare providers work to achieve the global goal of eradication of HBV by 2030. In the U.S., the ACIP has changed their approach, with a new universal recommendation for HBV vaccination for adults aged 19-59 and new guidelines for HBV screening. Now, healthcare providers also have a new, differentiated, and accessible intervention to support the vaccination of their adult patients – PreHevbrio. Priced similarly to Engerix-B, PreHevbrio is poised to be a meaningful new tool in the fight against Hepatitis B. References: (1) Vesikari T., Langley J., Segal N., et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomized, double-blind, phase 3 trial. *The Lancet Infectious Diseases*. 2021; [https://doi.org/10.1016/S1473-3099\(20\)30780-5](https://doi.org/10.1016/S1473-3099(20)30780-5) (2) Wang T, Dai Y, Zhang M, Cui D, Xu X, Sun C and Cheng J: Sequence analysis of the Pre-S gene in chronic asymptomatic HBV carriers with low-level HBsAg. *Int J Mol Med* 42: 2689-2699, 2018

Pubmed

Alon D, Stein GY, Hadas-Golan V, Tau L, Brosh T, Turner D. Immunogenicity of Sci-B-Vac (a Third-Generation Hepatitis B Vaccine) in HIV-Positive Adults. *Isr Med Assoc J*. 2017 Mar;19(3):143-146. PMID: 28457089. <https://pubmed.ncbi.nlm.nih.gov/28457089/> Atsmon J, Machluf N, Yayon-Gur V, Sabbah C, Spaans JN, Yassin-Rajkumar B, Anderson DE, Popovic V, Diaz-Mitoma F. Rapid and high seroprotection rates achieved with a tri-antigenic Hepatitis B vaccine in healthy young adults: Results from a Phase IV study. *Vaccine*. 2021 Feb 22;39(8):1328-1332. doi: 10.1016/j.vaccine.2020.12.050. Epub 2021 Jan 13. PMID: 33451780. <https://pubmed.ncbi.nlm.nih.gov/33451780/> Diaz-Mitoma F, Popovic V, Spaans JN. Assessment of immunogenicity and safety across two manufacturing lots of a 3-antigen hepatitis B vaccine, Sci-B-Vac®, compared with Engerix-B® in healthy Asian adults: A phase 3 randomized clinical trial. *Vaccine*. 2021 Jun 29;39(29):3892-3899. doi: 10.1016/j.vaccine.2021.05.067. Epub 2021 Jun 8. PMID: 34116873. <https://pubmed.ncbi.nlm.nih.gov/34116873/> Esaulenko EV, Yakovlev AA, Volkov GA, Sukhoruk AA, Surkov KG, Kruglyakov PV, Diaz-Mitoma F. Efficacy and Safety of a 3-Antigen (Pre-S1/Pre-S2/S)

Hepatitis B Vaccine: Results of a Phase 3 Randomized Clinical Trial in the Russian Federation. *Clin Infect Dis*. 2021 Nov 2;73(9):e3333-e3339. doi: 10.1093/cid/ciaa1649. PMID: 33119068; PMCID: PMC8563202. <https://pubmed.ncbi.nlm.nih.gov/33119068/> Gerlich WH. Prophylactic vaccination against hepatitis B: achievements, challenges and perspectives. *Med Microbiol Immunol*. 2015 Feb;204(1):39-55. doi: 10.1007/s00430-014-0373-y. Epub 2014 Dec 19. PMID: 25523195. <https://pubmed.ncbi.nlm.nih.gov/25523195/> Hellström UB, Madalinski K, Sylvan SP. PreS1 epitope recognition in newborns after vaccination with the third-generation Sci-B-Vac vaccine and their relation to the antibody response to hepatitis B surface antigen. *Virology*. 2009 Jan 20;6:7. doi: 10.1186/1743-422X-6-7. PMID: 19154574; PMCID: PMC2635352. <https://pubmed.ncbi.nlm.nih.gov/19154574/> Krawczyk A, Ludwig C, Jochum C, Fiedler M, Heinemann FM, Shouval D, Roggendorf M, Roggendorf H, Lindemann M. Induction of a robust T- and B-cell immune response in non- and low-responders to conventional vaccination against hepatitis B by using a third generation PreS/S vaccine. *Vaccine*. 2014 Sep 3;32(39):5077-82. doi: 10.1016/j.vaccine.2014.06.076. Epub 2014 Jun 24. PMID: 24975813. <https://pubmed.ncbi.nlm.nih.gov/24975813/> Madalinski K, Sylvan SP, Hellström U, Mikolajewicz J, Zembruska-Sadkowska E, Piontek E. Antibody responses to preS components after immunization of children with low doses of BioHepB. *Vaccine*. 2001 Oct 12;20(1-2):92-7. doi: 10.1016/s0264-410x(01)00312-7. PMID: 11567751. <https://pubmed.ncbi.nlm.nih.gov/11567751/> Madalinski K, Sylvan SP, Hellström U, Mikolajewicz J, Dzierzanowska-Fangrat K. Presence of anti-preS1, anti-preS2, and anti-HBs antibodies in newborns immunized with Bio-Hep-B vaccine. *Med Sci Monit*. 2004 Jan;10(1):PI10-7. PMID: 14704645. <https://pubmed.ncbi.nlm.nih.gov/14704645/> Milich DR, Thornton GB, Neurath AR, Kent SB, Michel ML, Tiollais P, Chisari FV. Enhanced immunogenicity of the pre-S region of hepatitis B surface antigen. *Science*. 1985 Jun 7;228(4704):1195-9. doi: 10.1126/science.2408336. PMID: 2408336. <https://pubmed.ncbi.nlm.nih.gov/2408336/> Milich DR, McLachlan A, Chisari FV, Kent SB, Thornton GB. Immune response to the pre-S(1) region of the hepatitis B surface antigen (HBsAg): a pre-S(1)-specific T cell response can bypass nonresponsiveness to the pre-S(2) and S regions of HBsAg. *J Immunol*. 1986 Jul 1;137(1):315-22. PMID: 2423607. <https://pubmed.ncbi.nlm.nih.gov/2423607/> Raz R, Dagan R, Gallil A, Brill G, Kassis I, Koren R. Safety and immunogenicity of a novel mammalian cell-derived recombinant hepatitis B vaccine containing Pre-S1 and Pre-S2 antigens in children. *Vaccine*. 1996 Feb;14(3):207-11. doi: 10.1016/0264-410x(95)00185-4. PMID: 8920701. <https://pubmed.ncbi.nlm.nih.gov/8920701/> Rendi-Wagner P, Shouval D, Genton B, Lurie Y, Rümke H, Boland G, Cerny A, Heim M, Bach D, Schroeder M, Kollaritsch H. Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine. *Vaccine*. 2006 Apr 5;24(15):2781-9. doi: 10.1016/j.vaccine.2006.01.007. Epub 2006 Jan 19. PMID: 16455169. <https://pubmed.ncbi.nlm.nih.gov/16455169/> Safadi R, Khoury T, Saed N, Hakim M, Jamalia J, Nijim Y, Farah N, Nuser T, Natur N, Mahamid M, Amer J, Roppert PL, Gerlich WH, Glebe D. Efficacy of Birth Dose Vaccination in Preventing Mother-to-Child Transmission of Hepatitis B: A Randomized Controlled Trial Comparing Engerix-B and Sci-B-Vac. *Vaccines (Basel)*. 2021 Apr 1;9(4):331. doi: 10.3390/vaccines9040331. PMID: 33915943; PMCID: PMC8066861. <https://pubmed.ncbi.nlm.nih.gov/33915943/> Shouval D, Ilan Y, Adler R, Deepen R, Panet A, Even-Chen Z, Gorecki M, Gerlich WH. Improved immunogenicity in mice of a mammalian cell-derived recombinant hepatitis B vaccine containing pre-S1 and pre-S2 antigens as compared with conventional yeast-derived vaccines. *Vaccine*. 1994 Nov;12(15):1453-9. doi: 10.1016/0264-410x(94)90155-4. PMID: 7533967. <https://pubmed.ncbi.nlm.nih.gov/7533967/> Shouval D. Hepatitis B vaccines. *J Hepatol*. 2003;39 Suppl 1:S70-6. doi: 10.1016/s0168-8278(03)00152-1. PMID: 14708681. <https://pubmed.ncbi.nlm.nih.gov/14708681/> Shouval D, Roggendorf H, Roggendorf M. Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine. *Med Microbiol Immunol*. 2015 Feb;204(1):57-68. doi: 10.1007/s00430-014-0374-x. Epub 2015 Jan 4. PMID: 25557605; PMCID: PMC4305084. <https://pubmed.ncbi.nlm.nih.gov/25557605/> Sylvan SP, Madalinski K, Hellström UB. Anti-preS responses

influence the anti-HBs response in newborns after vaccination with the third generation Sci-B-Vac vaccine. *Vaccine*. 2009 Dec 11;28(2):446-51. doi: 10.1016/j.vaccine.2009.10.023. Epub 2009 Oct 27. PMID: 19874926. <https://pubmed.ncbi.nlm.nih.gov/19874926/> Vesikari T, Langley JM, Segall N, Ward BJ, Cooper C, Poliquin G, Smith B, Gantt S, McElhaney JE, Dionne M, van Damme P, Leroux-Roels I, Leroux-Roels G, Machluf N, Spaans JN, Yassin-Rajkumar B, Anderson DE, Popovic V, Diaz-Mitoma F; PROTECT Study Group. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. *Lancet Infect Dis*. 2021 Sep;21(9):1271-1281. doi: 10.1016/S1473-3099(20)30780-5. Epub 2021 May 11. PMID: 33989539. <https://pubmed.ncbi.nlm.nih.gov/33989539/> van Bömmel F, Berg T. Three are better than one-increasing HBV seroprotection by a tri-antigenic vaccine. *Lancet Infect Dis*. 2021 Sep;21(9):1197-1198. doi: 10.1016/S1473-3099(20)30845-8. Epub 2021 May 11. PMID: 33989540. <https://pubmed.ncbi.nlm.nih.gov/33989540/> Vesikari T, Finn A, van Damme P, Leroux-Roels I, Leroux-Roels G, Segall N, Toma A, Vallieres G, Aronson R, Reich D, Arora S, Ruane PJ, Cone CL, Manns M, Cosgrove C, Faust SN, Ramasamy MN, Machluf N, Spaans JN, Yassin-Rajkumar B, Anderson D, Popovic V, Diaz-Mitoma F; CONSTANT Study Group. Immunogenicity and Safety of a 3-Antigen Hepatitis B Vaccine vs a Single-Antigen Hepatitis B Vaccine: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open*. 2021 Oct 1;4(10):e2128652. doi: 10.1001/jamanetworkopen.2021.28652. PMID: 34636914; PMCID: PMC8511978. <https://pubmed.ncbi.nlm.nih.gov/34636914/> Weinstein T, Chagnac A, Boaz M, Ori Y, Herman M, Zevin D, Schmilovitz-Weiss H, Gafer U. Improved immunogenicity of a novel third-generation recombinant hepatitis B vaccine in patients with end-stage renal disease. *Nephron Clin Pract*. 2004;97(2):c67-72. doi: 10.1159/000078403. PMID: 15218332. <https://pubmed.ncbi.nlm.nih.gov/15218332/>

Attachments

- 1654037255PreHevbrio-Full-Prescribing-Information.pdf
- 1654037607VBI_ACIP_Presentation_21_DEC_2021.pdf

Submit