



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: Heplisav-B vaccine**  
**-January 2021-**



**Background:**

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) reviewed the 2-dose hepatitis B vaccine, Heplisav-B, at the Winter 2021 meeting. In 2010, the NPTC voted to include all current and future Advisory Committee of Immunization Practices (ACIP) recommended vaccines to the National Core Formulary (NCF). The ACIP recommends vaccination with a complete series of any FDA approved Hepatitis B vaccine as a primary means of preventing infections in all unvaccinated adults at risk for Hepatitis B infection or for any adults requesting protection.<sup>1</sup> Heplisav-B (HepB-CpG) was recommended by the ACIP in February 2018 as a novel adjuvanted option for vaccination against hepatitis B. **As such, no modifications were made to the NCF.**

**Discussion:**

Hepatitis B infection remains a leading cause of acute and chronic liver disease and complications from it. American Indians and Alaska Natives (AI/AN) are disproportionately affected by this disease and the incidence of acute hepatitis B infection in AI/AN is on the rise. Data collected from 2009-2011 show chronic liver disease is the 8<sup>th</sup> leading cause of death in AI/AN and data from the CDC in 2018 indicates that this population is at a significantly higher risk of chronic liver disease compared to other ethnicity groups.<sup>3,4</sup> Hepatitis B vaccination is critical to preventing future Hepatitis B cases as well as worse outcomes for those with existing underlying liver disease that may contract it.

Traditionally, Hepatitis B vaccines have been administered as a 3-dose series, as is the case for the products Recombivax-B and Engerix-B. The 3-dose series can be problematic as many individuals do not complete the series. Incomplete series' may result in inadequate protection from the Hepatitis B virus. Data shows that about 40% of health-care personnel and about 75% of adults 19 years and older did not complete all three doses.<sup>5,6</sup> This could be due, in part, to the 3-dose series being spaced out by a minimum of 6 months. Additionally, patients completing the 3-dose series had difficulty achieving immunity, defined as having an antibody concentration  $\geq 10\text{mIU/mL}$ .<sup>6</sup> After the first dose, 96% of patients failed to achieve immunity. After the second dose, this percentage improves, but data still shows that there are 73% of patient failing to achieve immunity. Even after successful completion of the series, 18.7% patients failed to achieve immunity. This percentage is also increased depending on patient health conditions. For example, about 35% of diabetics fail to achieve immunity after completion of the 3-dose series.

Heplisav-B (HepB-CpG) was FDA approved in November 2017 as the first new vaccine to prevent hepatitis B infection in 25 years. The ACIP has provided guidance on the interchangeability of this novel adjuvant, 2-dose series with the traditional 3-dose series.<sup>2</sup> The safety and immunologic response of Heplisav-B (HepB-CpG) was evaluated in a review of three active controlled clinical trials comparing the novel vaccine to HBsAg-Eng (Engerix-B).<sup>7</sup> Patients were followed for 28, 52, and 56 weeks after the first injection. Across the three trials, the AI/AN population was included as "other" and only comprised 1.7% of the overall study population. This review indicates that the safety profile of Heplisav-B (HepB-CpG) is similar to that of HBsAg-Eng (Engerix-B). There was a slight reduction observed in post-injection reactions and overall adverse reactions for patients receiving Heplisav-B (HepB-CpG), but the significance was not indicated.

Immunogenicity of Heplisav-B (HepB-CpG) was evaluated in a randomized, observer-blinded, active controlled clinical trial that compared the novel vaccine to HBsAg-Eng (Engerix-B).<sup>8</sup> Patients were followed for 56 weeks after the first injection, having blood draws for anti-HBs serum concentrations at week 24 and 28. Across all subjects, those who received the HBsAg-1018 (Heplisav-B) 2-dose series achieved a seroprotection rate (SPR) of 95.4%. Patients who received the HBsAg-Eng (Engerix-B) 3-dose series achieved a SPR of 81.3%. This calculates out to a difference in SPR of 14.2% favoring HBsAg-1018 (Heplisav-B). A subgroup analysis of interest in this trial is patients with diabetes mellitus. Patients with diabetes mellitus that received HBsAg-1018 achieved a SPR of 90% compared to the 65% that was achieved in patients that received HBsAg-Eng (Engerix-B).

Another trial, evaluating the difference in immunogenicity between HBsAg-1018 (Heplisav-B) and HBsAg-Eng (Engerix-B) in adults 40-70 years old, followed patients for 52 weeks after their first injection.<sup>9</sup> In this trial, it was observed that the SPR in the HBsAg-1018 (Heplisav-B) group was significantly higher than that in the HBsAg-Eng (Engerix-B) group at each visit from week 4 through week 52. Not only did the HBsAg-1018 (Heplisav-B) show a quicker rise in SPR, it was also significantly higher. The final lab draws in this trial showed the SPR was 91.9% in the HBsAg-1018 (Heplisav-B) group compared to 59% in the HBsAg-Eng (Engerix-B) group.

Risk Factor/Population Studied <sup>9</sup>	Heplisav-B® 2-Dose Series Seroprotection Rate (%)	Engerix-B® 3-Dose Series Seroprotection Rate (%)
Total Population (n=6665)	95%	81%
Diabetes (n=961)	90%	65%
Age 40-70 (n=5434)	95%	79%
Male sex (n=3353)	95%	79%
Obesity (n=3241)	95%	75%
Smokers (n=2082)	96%	79%

Currently, the longevity of immunity after completion the traditional Hepatitis B is believed to be at least 30 years, defined as having an antibody concentration  $\geq 10\text{mIU/mL}$ .<sup>12</sup> Since Heplisav-B is a relatively new vaccine, longevity data is lacking in clinical trials.

Cost may be a consideration when considering Heplisav-B (HepB-CpG) use. A completed Heplisav-B (HepB-CpG) 2-dose series costs considerably more when compared to a complete HBsAg-Eng (Engerix-B) 3-dose series.<sup>13</sup> However, this does not take into consideration direct costs (healthcare worker time, vaccination supplies, clinical space) and indirect costs (third visit for the patient, transportation, time away from work) associated with a third visit required for the traditional 3-dose Hepatitis B vaccine series. Additional cost considerations include the cost of delayed protection in high-risk individuals, and the cost of providing a vaccine with lower seroprotection rates. Rosenthal et al. assessed the cost-utility of Heplisav-B (HepB-CpG) versus a traditional 3-dose Hepatitis B vaccine series. This non-industry sponsored study found Heplisav-B (HepB-CpG) resulted in lower costs and increased benefits in all scenarios in which the vaccine was at least 80%. Heplisav-B (HepB-CpG) was regarded as a cost-saving strategy for adults with diabetes, chronic kidney disease, obesity, HIV, older adults, and people who inject drugs.<sup>14</sup>

#### Findings:

The incidence of Hepatitis B continues to rise in adults despite vaccinations being widely available. The traditional 3-dose series has shown to be difficult for patients to complete. Heplisav-B (HepB-CpG) seroprotection rates have been shown to be achieved earlier and are higher when compared with traditional 3-dose series products, such as HBsAg-Eng (Engerix-B). The safety profiles between the two products were shown to be similar. Heplisav-B (HepB-CpG) has a simplified dosing schedule which helps with completion of the vaccination series. ACIP provides guidance on interchangeability, which can be used when switching from traditional Hepatitis B vaccines to Heplisav-B (HepB-CpG) or vice versa. There are higher acquisition costs associated with Heplisav-B (HepB-CpG) but use of this vaccine has been proven to be cost effective with a lower overall cost when considering direct and indirect costs compared with a traditional 3-dose series.

*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

#### References:

- Kim DK, Hunter P. [Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule, United States, 2019](#). [published correction appears in *Ann Intern Med*. 2019 Apr 2;170(7):512]. *Ann Intern Med*. 2019;170(3):182-192.
- Schillie S, Harris A, Link-Gelles R, et al. [Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant](#). *MMWR Morb Mortal Wkly Rep*. 2018; 67(15):455-458.
- Indian Health Service. Fact Sheet (October 2019). [Mortality Disparity Rates American Indians and Alaska Natives \(AI/AN\) in the IHS Service Area 2009-2011 and U.S. All Races 2010](#). Accessed February 10, 2021.
- Centers for Disease Control and Prevention. [Summary Health Statistics: National Health Interview Survey 2018](#). Table A-4a.
- Immunization and Infectious Diseases. [Office of Disease Prevention and Health Promotion website](#). Accessed September 26, 2019.
- Williams WW, Lu PJ, O'Halloran A, et al. [Surveillance of Vaccination Coverage among Adult Populations - United States, 2015](#). *MMWR Surveill Summ*. 2017;66(11):1-28.
- Hyer R, McGuire DK, Xing B, et al. [Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults](#). *Vaccine*. 2018;36(19):2604-2611.
- Jackson S, Lentino J, Kopp J, et al. [Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults](#). *Vaccine*. 2018; 36(5):668-674.
- Heyward WL, Kyle M, Blumenau J, et al. [Immunogenicity and safety of an investigational hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant compared to a licensed hepatitis B vaccine in healthy adults 40-70 years of age](#). *Vaccine*. 2013; 31(46):5300-5.
- HEPLISAV-B [package insert]. Berkeley, CA: Dynavax Technologies Corporation; 2018.
- Janssen RS, Mangoo-Karim R, Pergola PE, et al. [Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant \(HBsAg-1018\) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease](#). *Vaccine*. 2013; 31(46):5306-13.
- Van Damme P. [Long-term Protection After Hepatitis B Vaccine](#). *J Infect Dis*. 2016; 214(1):1-3.
- McKesson Connect online. Accessed 14 January 2021.
- Rosenthal EM, Hall EW, Rosenberg ES, et al. [Assessing the cost-utility of preferentially administering Heplisav-B vaccine to certain populations](#). *Vaccine*. 2020; 38(51):8206-15.