



HEPLISAV-B™ is now approved for prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age or older.^{1,2}

DISEASE BACKGROUND

Hepatitis B virus is a highly infectious and resilient disease that can lead to serious complications and death.³ It remains an important cause of acute and chronic liver disease, and is a major global health problem associated with high healthcare costs.⁴ In the United States, chronic HBV infection is a widespread and growing public health challenge, with an estimated prevalence of 850,000 to 2.2 million people living with HBV.⁵ Since 2014, there has been an increase in the rate of new HBV infections.⁵ The heroin and opioid epidemics are among significant contributing causes to the increase in HBV infection rates, with some states affected by the epidemics having experienced a 114% increase in HBV infection rates from 2006 to 2013.⁶ Each year, an estimated 5,000 individuals in the United States die from chronic liver disease due to HBV infection.⁴

There is no cure for HBV infection, and effective vaccination is critical to reducing the spread of the disease.⁷ Despite historical vaccination and public awareness efforts, chronic HBV infection remains a significant cause of morbidity and mortality.⁴ Conventional (alum-adjuvanted) HBV vaccines require 3 doses given over 6 months to achieve protection in adult patients, which presents compliance challenges that may potentially leave patients at risk.⁸⁻¹⁰ A Vaccine Safety Datalink study of more than 88,000 adult hepatitis B vaccine recipients found that 81% received at least 2 doses and only 54% received all 3 doses within 1 year.^{11,*}

The Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) includes recommendations for HBV vaccinations, including proactive vaccination of adults at risk for HBV infection.⁷

*Calculation based on a weighted average of patients aged 18 years or older (n=88,711) initiating a hepatitis B vaccination series in a large population-based, retrospective cohort study of the Vaccine Safety Datalink population of approximately 8.8 million medical care organization enrollees.

HEPLISAV-B BACKGROUND

HEPLISAV-B is manufactured by Dynavax Technologies Corporation and was approved by the U.S. Food and Drug Administration (FDA) on November 9, 2017.² This approval was based on data from 3 head-to-head, phase 3 noninferiority trials of HEPLISAV-B versus Engerix®-B comprising nearly 10,000 adult participants who received HEPLISAV-B.¹ Two doses of HEPLISAV-B in 1 month provided higher rates of protective immunity to 90% or more of patients in the groups studied versus Engerix-B, including patients with factors that typically affect the immune response, such as older (>40 years of age) adults, men, persons with diabetes, obese persons, and persons who smoke.^{1,4} The safety and effectiveness of HEPLISAV-B have not been established in individuals less than 18 years of age.¹

HEPLISAV-B contains a TLR9-agonist adjuvant that was shown in clinical studies to allow for improved immune responses after only 2 doses, including in populations that may respond poorly to current vaccines.⁴

HEPLISAV-B offers a 2-dose regimen with a shorter administration schedule and a reduced burden of administration compared with conventional vaccines.⁴

INDICATION AND USAGE

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

DOSAGE AND ADMINISTRATION

Administer 2 doses (0.5 mL each) of HEPLISAV-B intramuscularly, 1 month apart.¹

CLINICAL PHARMACOLOGY

Infection with HBV can have serious consequences, including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma. Antibody concentrations ≥ 10 mIU/mL against hepatitis B surface antigen (HBsAg) are recognized as conferring protection against HBV infection.¹

HEPLISAV-B is considered to act by using an adjuvant that activates TLR9 in plasmacytoid dendritic cells (pDCs) that, when combined with HBsAg, leads to production of HBsAg-specific antibodies.²

IMPORTANT SAFETY INFORMATION¹

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast.

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

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

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

The most common patient-reported adverse reactions reported within 7 days of vaccination were injection site pain (23%-39%), fatigue (11%-17%), and headache (8%-17%).

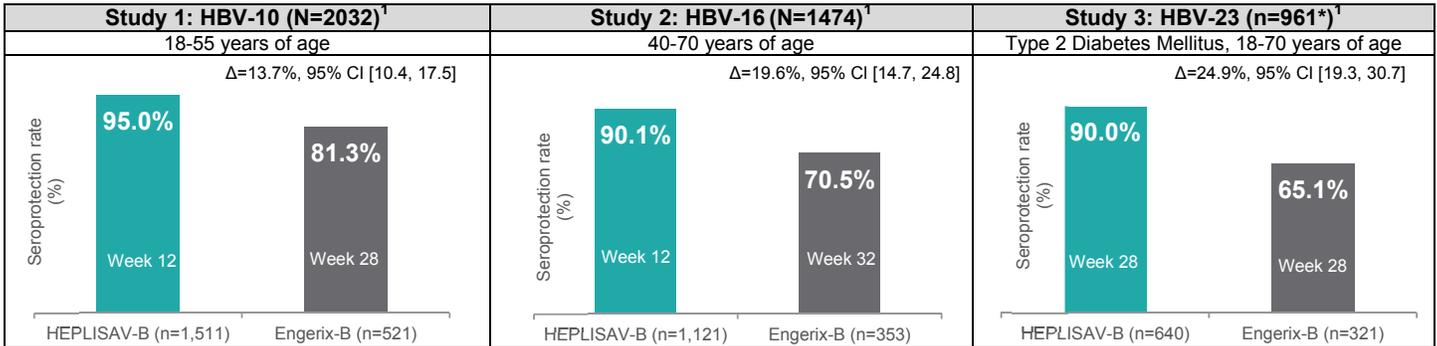
To report SUSPECTED ADVERSE REACTIONS, contact Dynavax at 1-844-889-8753 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

Please see full Important Safety Information and accompanying full Prescribing Information.

EFFICACY OUTCOMES

The immunogenicity of HEPLISAV-B was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in 3 randomized, active-controlled, observer-blinded, multicenter, phase 3 clinical trials of adults with no history of hepatitis B vaccination or infection. Seroprotection rates (SPRs) following injection with 2 doses of HEPLISAV-B were compared with rates following injection with 3 doses of Engerix-B. In all 3 trials, HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by placebo (saline) at 6 months, whereas Engerix-B was given at 0, 1, and 6 months.¹

Two doses of HEPLISAV-B provided higher rates of protection (≥90%) in more adults across 3 pivotal clinical trials compared with 3 doses of Engerix-B.¹



*In Study 3, the immunogenicity population comprised 4537 subjects who received HEPLISAV-B and 2289 subjects who received Engerix-B. The primary analysis above shows outcomes in subjects with type 2 diabetes mellitus.¹

SAFETY OUTCOMES

The safety profile of HEPLISAV-B was demonstrated in 3 pivotal clinical trials of nearly 10,000 subjects with up to 12 months of follow-up.¹ The overall safety profile of HEPLISAV-B was similar to that of Engerix-B⁴:

- HEPLISAV-B had a lower frequency of systemic postinjection reactions (including fever) and a similar frequency of local postinjection reactions compared with Engerix-B
- Adverse events (AEs) and medically-attended AEs were balanced in type and frequency between the HEPLISAV-B and Engerix-B treatment groups
- Frequency of immune-mediated disease in recipients of HEPLISAV-B was balanced with that of Engerix-B

The most common local reaction was injection site pain (23%-39%). The most common systemic reactions were fatigue (11%-17%) and headache (8%-17%).¹

BILLING CODES: FOR INFORMATIONAL PURPOSES ONLY

NDC ¹	10-digit NDC number:		11-digit NDC number:	
	Vial, 1 dose (0.5 mL)	43528-002-01	43528-0002-01	
Package of 5 single-dose vials	43528-002-05	43528-0002-05		
CPT* VACCINE CODE ¹²	90739; hepatitis B vaccine (HepB), adult dosage, 2-dose schedule, for intramuscular use			
CPT ADMINISTRATION CODE ¹²	90471; immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); 1 vaccine (single or combination vaccine/toxoid)			
HCPCS ¹³	G0010; administration of hepatitis B vaccine			
ICD-10-CM ¹⁴	Z23; encounter for immunization			
MVX CODE ¹⁵	DVX	Dynavax		
CVX CODE ¹⁵	189	Hepatitis B vaccine (recombinant), adjuvanted		

CPT®, Current Procedural Terminology; CVX, vaccine administered code; HCPCS, Healthcare Common Procedure Coding System; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; MVX, manufacturers of vaccines; NDC, national drug code.

*CPT is a registered trademark of the American Medical Association (AMA).

ACQUISITION COSTS

WHOLESALE ACQUISITION COST (WAC) ¹⁶	Vial, 1 dose: \$115.00 Package of 5 single-dose vials: \$575.00
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FOR MORE INFORMATION, VISIT HEPLISAVB.COM OR CALL 1-84-HEPLISAV (1-844-375-4728).

References: 1. Hepelisav-B [package insert]. Berkeley, CA: Dynavax Technologies Corporation; 2017. 2. U.S. Food and Drug Administration. Summary Basis for Regulatory Action. <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM590190.pdf>. Published November 9, 2017. Accessed January 12, 2018. 3. Walayat S, Ahmed Z, Martin D, Puli S, Cashman M, Dhilon S. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. *World J Hepatol*. 2015;7(24):2503-2509. 4. Dynavax Technologies Corporation. FDA Advisory Committee Briefing Document: HEPLISAV-B™ [Hepatitis B Vaccine (Recombinant), Adjuvanted]. Presented at: Meeting of the Vaccines and Related Biological Products Advisory Committee; Silver Spring, MD; July 28, 2017. 5. Centers for Disease Control and Prevention. Viral hepatitis surveillance: United States, 2015. <https://www.cdc.gov/hepatitis/statistics/2015surveillance/pdfs/2015HepSurveillanceRpt.pdf>. Accessed October 6, 2017. 6. Harris AM, Iqbal K, Schillie S, et al. Increases in acute hepatitis B virus infections – Kentucky, Tennessee, and West Virginia, 2006-2013. *MMWR Morb Mortal Wkly Rep*. 2016;65:47-50. DOI: <http://dx.doi.org/10.15585/mmwr.mm6503a2>. 7. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep*. 2006;55(RR-16):1-33. 8. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2011;60(50):1709-1711. 9. Engerix-B [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2015. 10. Recombivax HB [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014. 11. Nelson JC, Bittner RCL, Bounds L, et al. Compliance with multiple-dose vaccine schedules among older children, adolescents, and adults: results from a vaccine safety datalink study. *Am J Public Health*. 2009;99(suppl 2):S389-S397. 12. American Medical Association. American Medical Association Code Manager website. <https://apps.ama-assn.org/CptSearch/user/search/cptSearchSubmit.do?locality=7&keyword=90739>. Accessed December 14, 2017. 13. HCPCS release & code sets. Centers for Disease Control and Prevention website. <https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS-Items/2017-Alpha-Numeric-HCPCS-File.html>. Accessed December 14, 2017. 14. International classification of diseases, 10th revision, clinical modification (ICD-10-CM). Centers for Disease Control and Prevention website. <http://www.icd10data.com/ICD10CM/Codes/Z00-Z99/Z20-Z29/Z23-Z23>. Accessed December 14, 2017. 15. Immunization Information Systems (IIS). Centers for Disease Control and Prevention website. <https://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?pt=tradenam>. Accessed January 3, 2018. 16. RED BOOK Online®. Micromedex Healthcare Series [database online]. Greenwood Village, CO: Truven Health Analytics; 2018. Accessed January 10, 2018.



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HEPLISAV-B™ safely and effectively. See full prescribing information for HEPLISAV-B.

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] Solution for Intramuscular Injection
Initial US Approval: 2017

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

For intramuscular administration

Administer two doses (0.5 mL each) of HEPLISAV-B intramuscularly one month apart. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

HEPLISAV-B is a solution for injection supplied as a single-dose vial. A single dose of HEPLISAV-B is 0.5 mL. (3)

CONTRAINDICATIONS

Severe allergic reaction, such as anaphylaxis, after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast. (4)

ADVERSE REACTIONS

The most common local reaction was injection site pain (23% - 39%). The most common systemic reactions were fatigue (11% - 17%) and headache (8% - 17%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dynavax at 1-844-889-8753 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

A pregnancy registry is available for HEPLISAV-B. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For intramuscular administration.

2.1 Dose and Regimen

Administer two doses (0.5 mL each) of HEPLISAV-B one month apart.

2.2 Administration

HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution.

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 HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.

3 DOSAGE FORMS AND STRENGTHS

HEPLISAV-B is a sterile solution for injection available in 0.5 mL single-dose vials. [see [How Supplied/Storage and Handling \(16.1\)](#)].

4 CONTRAINDICATIONS

Do not administer HEPLISAV-B 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 HEPLISAV-B, including yeast [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 HEPLISAV-B.

5.2 Immunocompromised Individuals

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

5.3 Limitations of Vaccine Effectiveness

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

6 ADVERSE REACTIONS

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.

A total of 9597 individuals 18 through 70 years of age received at least 1 dose of HEPLISAV-B in 5 clinical trials conducted in the United States, Canada, and Germany. Data from three of these trials are provided below.

Study 1 in Subjects 18 through 55 Years of Age

Study 1 was a randomized, observer-blind, active-controlled, multicenter study in Canada and Germany in which 1810 subjects received at least 1 dose of HEPLISAV-B and 605 subjects received at least 1 dose of Engerix-B® [Hepatitis B Vaccine (Recombinant)]. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 40 years; 46% of the subjects were men; 93% were white, 2% black, 3% Asian and 3% Hispanic; 26% were obese, 10% had hypertension, 8% had dyslipidemia, and 2% had diabetes mellitus. These 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 are shown in Table 1.

Reaction	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
	1	2	1	2	3
Local	N=1810	N=1798	N=605	N=603	N=598
Injection Site Pain	38.5	34.8	33.6	24.7	20.2
Injection Site Redness†	4.1	2.9	0.5	1.0	0.7
Injection Site Swelling‡	2.3	1.5	0.7	0.5	0.5
Systemic					
Fatigue	17.4	13.8	16.7	11.9	10.0
Headache	16.9	12.8	19.2	12.3	9.5
Malaise	9.2	7.6	8.9	6.5	6.4
	N=1784	N=1764	N=596	N=590	N=561
Fever‡	1.1	1.5	1.8	1.7	1.8

Note: only subjects having data are included. Clinical trial number: NCT00435812

*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months

† Redness and swelling ≥ 2.5 cm.

‡ Oral temperature $\geq 100.4^\circ\text{F}$ (38.0°C).

Unsolicited Adverse Events:

Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 42.0% of HEPLISAV-B recipients and 41.3% of Engerix-B recipients.

Serious Adverse Events (SAEs)

Subjects were monitored for serious adverse events for 7 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 1.5% in the HEPLISAV-B group and 2.1% in the Engerix-B group. No acute myocardial infarctions were reported. No deaths were reported.

Potentially Immune-mediated Adverse Events

Potentially immune-mediated adverse events that occurred within 7 months of the first dose of vaccine were reported in 0.2% (n = 4) of HEPLISAV-B recipients and 0.7% (n = 4) of Engerix-B recipients. The following events were reported in the HEPLISAV-B group in one subject each: granulomatosis with polyangiitis, lichen planus, Guillain-Barré syndrome, and Grave's disease. The following events were reported in the Engerix-B group in one subject each: Bell's palsy, Raynaud's phenomenon, and Grave's disease. One additional Engerix-B recipient with a history of mixed connective tissue disease had p-ANCA-positive vasculitis.

Study 2 in Subjects 40 through 70 Years of Age

Study 2 was a randomized, observer-blind, active-controlled, multicenter study in Canada and the United States in which 1968 subjects received at least 1 dose of HEPLISAV-B and 481 subjects received at least 1 dose of Engerix-B. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Enrolled subjects had no history of hepatitis B vaccination or infection. Engerix-B was given at 0, 1, and 6 months. In the total population, the mean age was 54 years; 48% of subjects were men; 82% were white, 15% black, 1% Asian and 6% Hispanic; 44% were obese, 30% had hypertension, 30% had dyslipidemia, and 8% had diabetes mellitus. These 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 experienced local and systemic reactions are shown in Table 2.

Reaction	HEPLISAV-B		Engerix-B		
	%		%		
	Post-Dose*		Post-Dose*		
	1	2	1	2	3
Local	N=1952	N=1905	N=477	N=464	N=448
Injection Site Pain	23.7	22.8	18.4	15.9	13.8
Injection Site Redness†	0.9	0.7	0.6	0.2	0.2
Injection Site Swelling†	0.9	0.6	0.6	0.6	0.2
Systemic					
Fatigue	12.6	10.8	12.8	12.1	9.4
Headache	11.8	8.1	11.9	9.5	8.5
Malaise	7.7	7.0	8.6	7.1	5.1
Myalgia	8.5	6.4	9.6	8.0	4.5
	N=1923	N=1887	N=472	N=459	N=438
Fever‡	0.6	0.6	0.6	0.9	0.7

Note: only subjects having data are included. Clinical Trial Number: NCT01005407

*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months

† Redness and swelling ≥ 2.5 cm

‡ Oral temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C).

Unsolicited Adverse Events:

Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 35.4% of HEPLISAV-B recipients and 36.2% of Engerix-B recipients.

Serious Adverse Events

Subjects were monitored for serious adverse events for 12 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 3.9% in the HEPLISAV-B group and 4.8% in the Engerix-B group. Acute myocardial infarction occurred in 0.1% (n=2) of HEPLISAV-B recipients and 0.2% (n=1) of Engerix-B recipients.

Autoimmune Adverse Events

Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 12 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.2% (n=3) of HEPLISAV-B recipients: two subjects with hypothyroidism and one subject with vitiligo. None of these events was considered related to vaccination by the expert group. No new-onset autoimmune adverse events were reported in the Engerix-B group. Although not referred to the external group of experts, one HEPLISAV-B recipient was determined to have Tolosa-Hunt syndrome which is presumed to have an immune-mediated etiology. This event was not considered related to vaccination.

Deaths

One subject (0.05%) died of a pulmonary embolism in the HEPLISAV-B group and 1 subject (0.2%) died of heart failure in the Engerix-B group. Neither death was considered related to vaccination.

Study 3 in Subjects 18 through 70 Years of Age

Study 3 was a randomized, observer-blind, active-controlled, multicenter study in the United States in which 5587 subjects received at least 1 dose of HEPLISAV-B and 2781 subjects received at least 1 dose of Engerix-B. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 50 years; 51% were men; 71% were white, 26% black, 1% Asian, and 9% Hispanic; 48% were obese, 36% had hypertension, 32% had dyslipidemia, and 14% had type 2 diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Unsolicited Medically-Attended Adverse Events

Subjects were monitored for unsolicited medically-attended adverse events, those for which a subject sought medical care, for 13 months after the first dose of vaccine. Overall, medically-attended adverse events were reported in 46.0% of HEPLISAV-B recipients and 46.2% of Engerix-B recipients. Herpes zoster was reported in 0.7% of HEPLISAV-B recipients and 0.3% of Engerix-B recipients. Unsolicited medically-attended adverse events within 28 days following any injection, including placebo, were reported by 20.1% of both HEPLISAV-B and Engerix-B recipients.

Serious Adverse Events

Subjects were monitored for serious adverse events for 13 months after the first dose of vaccine. The percentage of subjects who reported serious adverse events was 6.2% in the HEPLISAV-B group and 5.3% in the Engerix-B group. Acute myocardial infarction (AMI) was reported in 0.25% (n=14) of HEPLISAV-B recipients and 0.04% (n=1) of Engerix-B recipients. An analysis of serious adverse events likely representing myocardial infarction (MI) was conducted using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for MI. This analysis identified a total of 19 HEPLISAV-B subjects (0.3%) and 3 Engerix-B subjects (0.1%) with events included in the SMQ for MI (these events include the 15 reports of AMI). Additional evidence, including information on temporal relationship and baseline risk factors, does not support a causal relationship between HEPLISAV-B administration and AMI. Among the 19 events identified as MI in HEPLISAV-B recipients, three occurred within 14 days, nine occurred within 53-180 days, and seven occurred more than 180 days following any dose of HEPLISAV-B. Among the three events identified as MI in Engerix-B recipients, one each occurred 13, 115, and 203 days following any dose. All 19 HEPLISAV-B recipients and 3 Engerix-B recipients reported one or more baseline risk factors for cardiovascular disease.

Autoimmune Adverse Events

Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 13 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts who were blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.1% (n=4) of HEPLISAV-B recipients [one each

of: alopecia areata, polymyalgia rheumatica, ulcerative colitis, and autoimmune thyroiditis (with concurrent diagnosis of papillary thyroid carcinoma)]. None of these events was considered to be related to vaccination by the external experts. No new-onset autoimmune adverse events were reported in the Engerix-B group.

Deaths

During the study death was reported in 25 subjects (0.4%) in the HEPLISAV-B group and 7 subjects (0.3%) in the Engerix-B group. No death was considered related to vaccination.

7 DRUG INTERACTIONS

7.1 Use with Immune Globulin

There are no data to assess the concomitant use of HEPLISAV-B with immune globulin. When concomitant administration of HEPLISAV-B 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 HEPLISAV-B.

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 HEPLISAV-B during pregnancy. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734.

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 clinical studies of HEPLISAV-B in pregnant women. Available human data on HEPLISAV-B administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg cytosine phosphoguanine (CpG) 1018 adjuvant was administered to female rats prior to mating and during gestation. These animal studies revealed no evidence of harm to the fetus due to this vaccine formulation [*see Data*].

Data

Animal data

Developmental toxicity studies were conducted in female rats. Animals were administered 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant twice prior to mating, and on gestation days 6 and 18 (a single human dose of HEPLISAV-B contains 20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant). No adverse effects on pre-natal and post-natal development up to the time of weaning were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation

Risk Summary

It is not known whether HEPLISAV-B is excreted in human milk. Data are not available to assess the effects of HEPLISAV-B 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 HEPLISAV-B and any potential adverse effects on the breastfed child from HEPLISAV-B 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 HEPLISAV-B have not been established in individuals less than 18 years of age.

8.5 Geriatric Use

Clinical trials included 909 adults 65 through 70 years of age who received HEPLISAV-B.

Among subjects who received HEPLISAV-B, a seroprotective level of antibody to HBsAg was achieved in 90% of those 65 through 70 years of age compared to 96% of those aged 18 through 64 years of age.

Safety and effectiveness of HEPLISAV-B in adults older than 70 years of age were extrapolated from findings in subjects younger than 70 years of age.

8.6 Adults on Hemodialysis

Safety and effectiveness of HEPLISAV-B have not been established in adults on hemodialysis.

11 DESCRIPTION

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is a sterile solution for intramuscular injection.

The HBsAg is expressed in a recombinant strain of *Hansenula polymorpha* yeast. The fermentation process involves growth of the recombinant *H. polymorpha* on chemically-defined fermentation media containing vitamins and mineral salts.

The HBsAg is expressed intra-cellularly in the yeast cells. It is released from the yeast cells by cell disruption and purified by a series of physicochemical steps. Each dose may contain residual amounts of yeast protein ($\leq 5.0\%$ of total protein), yeast DNA (< 20 picogram), and deoxycholate (< 0.9 ppm) from the HBsAg manufacturing process.

HEPLISAV-B is prepared by combining the purified HBsAg together with the CpG 1018 adjuvant, a 22-mer phosphorothioate linked oligodeoxynucleotide in a phosphate buffered saline (sodium chloride, 9.0 mg/mL; sodium phosphate, dibasic dodecahydrate, 1.75 mg/mL; sodium phosphate, monobasic dihydrate, 0.48 mg/mL; and polysorbate 80, 0.1 mg/mL).

Each 0.5-mL dose is formulated to contain 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant.

The vial stoppers are not made with natural rubber latex.

HEPLISAV-B is formulated without preservatives. [see [How Supplied/Storage and Handling \(16\)](#)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

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

HEPLISAV-B has not been evaluated for carcinogenicity, mutagenic potential or male infertility in animals. Vaccination of female rats with a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant had no effect on fertility [see *Use in Specific Populations* (8)].

14 CLINICAL STUDIES

14.1 Evaluation of Seroprotection

The immunogenicity of HEPLISAV-B was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in 3 randomized, active controlled, observer-blinded, multi-center Phase 3 clinical trials of adults. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 months followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months.

The trials compared the seroprotection rates (% with antibody concentration ≥ 10 mIU/mL) induced by HEPLISAV-B and Engerix-B. Noninferiority was met if the lower bound of the 95% confidence interval of the difference in seroprotection rates (HEPLISAV-B minus Engerix-B) was greater than -10%.

Study 1: Seroprotection in Adults 18 through 55 Years of Age

In Study 1, the immunogenicity population comprised 1511 participants who received HEPLISAV-B and 521 who received Engerix-B. The mean age was 40 years for both groups. The primary analysis compared the seroprotection rate at Week 12 for HEPLISAV-B with that at Week 28 for Engerix-B. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 3).

Timepoint	Table 3 Study 1: Seroprotection Rate of HEPLISAV-B and Engerix-B (ages 18 through 55 years)		
	HEPLISAV-B N = 1511	Engerix-B N = 521	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 12 (HEPLISAV-B) Week 28 (Engerix-B)	95% (93.9, 96.1)	81.3% (77.8, 84.6)	13.7% (10.4, 17.5)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).

* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%.
Clinical trial number: NCT00435812

Study 2: Seroprotection in Adults 40 through 70 Years of Age

In Study 2, the immunogenicity population comprised 1121 subjects who received HEPLISAV-B and 353 subjects who received Engerix-B. The mean age was 54 years for both groups. The primary analysis compared the seroprotection rate at Week 12 for HEPLISAV-B with that at Week 32 for Engerix-B. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 4).

Timepoint	Table 4 Study 2: Seroprotection Rate of HEPLISAV-B and Engerix-B (ages 40 through 70 years)		
	HEPLISAV-B N = 1121	Engerix-B N = 353	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 12 (HEPLISAV-B) Week 32 (Engerix-B)	90.1% (88.2, 91.8)	70.5% (65.5, 75.2)	19.6% (14.7, 24.8)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).

* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%.
The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

Clinical trial number: NCT01005407

Study 3: Seroprotection in Adults 18 through 70 Years of Age Including those with Type 2 Diabetes Mellitus

In Study 3, the immunogenicity population comprised 4537 subjects who received HEPLISAV-B and

2289 subjects who received Engerix-B. The mean age was 51 years and 14% of subjects had type 2 diabetes mellitus (defined as having a clinical diagnosis of type 2 diabetes and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin).

The primary analysis compared the seroprotection rate at Week 28 for HEPLISAV-B (n= 640) with that at Week 28 for Engerix-B (n= 321) in subjects with type 2 diabetes mellitus. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 5).

Timepoint	Table 5 Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (subjects with type 2 diabetes mellitus ages 18 through 70 years)		
	HEPLISAV-B N = 640	Engerix-B N = 321	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 28	90.0% (87.4, 92.2)	65.1% (59.6, 70.3)	24.9% (19.3, 30.7)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs \geq 10 mIU/mL).

* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

Clinical trial number: NCT02117934

A secondary analysis compared the seroprotection rate at Week 24 for HEPLISAV-B with that at Week 28 for Engerix-B in the total study population. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 6).

Timepoint	Table 6 Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (total study population ages 18 through 70 years)		
	HEPLISAV-B N = 4376	Engerix-B N = 2289	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 24 (HEPLISAV-B) Week 28 (Engerix-B)	95.4% (94.8, 96.0)	81.3% (79.6, 82.8)	14.2% (12.5, 15.9)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs \geq 10 mIU/mL).

Clinical trial number: NCT02117934

* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

Another secondary analysis compared the seroprotection rate at Week 24 for HEPLISAV-B with that at Week 28 for Engerix-B, by age group. For each age stratum non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 7).

Age (years)	Table 7 Study 3: Seroprotection Rates of HEPLISAV-B and Engerix-B ^a (ages 18 - 70 years)				
	HEPLISAV-B ^a		Engerix-B ^a		Difference in SPRs (HEPLISAV-B minus Engerix-B)
	N	SPR (95% CI)	N	SPR (95% CI)	Difference (95% CI)
18-29	174	100.0% (97.9, 100.0)	99	93.9% (87.3, 97.7)	6.1% (2.8, 12.6)*
30-39	632	98.9% (97.7, 99.6)	326	92.0% (88.5, 94.7)	6.9% (4.2, 10.4)*
40-49	974	97.2% (96.0, 98.2)	518	84.2% (80.7, 87.2)	13.1% (9.9, 16.6)*
50-59	1439	95.2% (94.0, 96.3)	758	79.7% (76.6, 82.5)	15.5% (12.6, 18.7)*
60-70	1157	91.6% (89.9, 93.1)	588	72.6% (68.8, 76.2)	19.0% (15.2, 23.0)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs \geq 10 mIU/mL).

^a Week 24 for HEPLISAV-B and Week 28 for Engerix-B

Clinical trial number: NCT02117934

* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- Vial, 1 dose (0.5 mL) - (NDC number: 43528-002-01)
- Package of 5 single dose vials - (NDC number: 43528-002-05)

The vial stoppers are not made with natural rubber latex.

16.2 Storage Conditions

Store in a refrigerator at 2°C to 8°C (35°F to 46°F).

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, as well as the importance of completing the immunization series.
- Emphasize that HEPLISAV-B 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).

The logo for Dynavax Technologies Corporation, featuring the word "DYNAX" in a stylized font. The letters "D", "Y", "A", and "X" are green, while "N" and "V" are blue. The letters are bold and sans-serif.

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