Important Safety Information

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%).

HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

U.S. Food and Drug Administration–approved indication
HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.¹

Contents

• Introduction
• Disease State Overview
• Indication, Dosage, and Administration
• Chemistry and Clinical Pharmacology
• Clinical Studies
• Safety Considerations
• P&T Committee Considerations
• Conclusion
• References

This publication is designed for payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economics making decisions regarding access, coverage, and reimbursement for HEPLISAV-B.

This publication of P&T was developed in collaboration with and with support from Dynavax Technologies Corporation.

Please see INDICATION and IMPORTANT SAFETY INFORMATION and accompanying FULL PRESCRIBING INFORMATION.
The Product Profiler

The Product Profiler publication provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler supplies information about pharmacology, clinical studies, FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package.

About the Authors
Ryan D. Alfonso, MPH, is a scientist and medical writer with more than 15 years of experience in the pharmaceutical and healthcare industries. He has written peer-reviewed scientific articles and a variety of educational materials, including patient, clinician, and payer-focused materials in a wide range of clinical therapeutic areas. Mr. Alfonso received a master of public health degree with an emphasis in infectious disease from the University of California, Berkeley School of Public Health.

Yangmin (Mimi) Chen, PharmD, RPh, is a medical writer and a part-time community pharmacist. She has written manuscripts across the spectrum of experimental to clinical research on diverse therapeutic areas, as well as having created various payer-specific pieces. Previously trained as a preclinical scientist, Dr. Chen has produced multiple publications and presentations for international audiences. Her prior roles include those of a medical information specialist and a supporting consultant in the areas of managed care, health policy, and regulatory strategy. Dr. Chen received her doctor of pharmacy degree from the Ernest Mario School of Pharmacy at Rutgers University.

Disclosures
Dynavax Technologies Corporation provided funding for this publication. Ryan Alfonso and Yangmin Chen report they have no financial arrangement or affiliation with Dynavax Technologies Corporation that might constitute a conflict of interest with respect to this publication.
HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

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Please see INDICATION and IMPORTANT SAFETY INFORMATION and accompanying FULL PRESCRIBING INFORMATION.
Introduction

This Product Profiler introduces HEPLISAV-B, a vaccine indicated for prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age and older. HEPLISAV-B was approved by the US Food and Drug Administration (FDA) on November 9, 2017. The CDC’s Advisory Committee on Immunization Practices (ACIP) included HEPLISAV-B in its list of recommended adult hepatitis B vaccines on February 21, 2018.

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 (HCC). Antibody concentrations ≥10 mIU/mL against hepatitis B surface antigen (HBsAg) are recognized as conferring protection against HBV infection.

The following presents an overview of the disease state and the efficacy and safety considerations for the use of HEPLISAV-B in adults 18 years of age and older.

Disease State Overview

HBV infection is caused by the hepatitis B virus, an enveloped deoxyribonucleic acid (DNA) virus, which infects the liver, triggering hepatocellular necrosis and inflammation. An estimated 20,900 new cases of acute HBV infection occurred in adults in the United States in 2016. Worldwide, an estimated 2 billion individuals have been infected with HBV, and 257 million persons currently have chronic, lifelong infections. Each year, HBV infection accounts for approximately 5000 deaths in the United States and contributes to an estimated 887,000 deaths worldwide (Table 1).

Transmission and Risk Factors for Adults

Hepatitis B is a highly infectious disease that is transmitted through activities that involve percutaneous or mucosal contact with infectious blood or body fluid. In bodily fluids, such as blood, semen, vaginal fluids, saliva, and mucus, HBV is 50 to 100 times more infectious than the human immunodeficiency virus (HIV) and can also survive outside of the body on environmental surfaces and fomites for at least 7 days. Common risk factors for HBV transmission include injection drug use, sexual activity with infected individuals, treatment with hemodialysis, and other activities and conditions (Table 2).

Acute Versus Chronic HBV Outcomes

The outcomes of HBV infection depend on whether an individual acquires acute or chronic disease. Acute HBV infection is usually symptomatic but can range from subclinical disease to fulminant hepatic failure. Symptoms such as fever, fatigue, nausea, and vomiting are typically self-limited and

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>HBV Infection Statistics, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals infected with HBV in the United States</td>
<td>800,000–2.2 million^4,6</td>
</tr>
<tr>
<td>Individuals infected with HBV worldwide</td>
<td>~2 billion^4</td>
</tr>
<tr>
<td>Annual US deaths from HBV infection</td>
<td>~5000^4</td>
</tr>
<tr>
<td>Annual worldwide deaths from HBV infection</td>
<td>887,000^7</td>
</tr>
<tr>
<td>Annual new acute HBV infections in the United States</td>
<td>~20,900^6</td>
</tr>
<tr>
<td>Individuals who currently have chronic HBV infections worldwide</td>
<td>257 million^7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>HBV Transmission Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sexual intercourse with infected individuals^6,7,10</td>
<td></td>
</tr>
<tr>
<td>• Contact with blood or open sores of an infected person^5,9</td>
<td></td>
</tr>
<tr>
<td>• Injection drug use that involves sharing needles, syringes, or drug preparation equipment^4,6,10</td>
<td></td>
</tr>
<tr>
<td>• Healthcare and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids^9</td>
<td></td>
</tr>
<tr>
<td>• Needle sticks or sharp instrument exposure^6,7,8</td>
<td></td>
</tr>
<tr>
<td>• Diabetes^6</td>
<td></td>
</tr>
<tr>
<td>• Treatment with hemodialysis^4</td>
<td></td>
</tr>
<tr>
<td>• Traveling to countries with intermediate or high HBV infection prevalence^10</td>
<td></td>
</tr>
</tbody>
</table>
resolve spontaneously without treatment.\textsuperscript{5,11,13} Most adult patients with acute HBV infection recover fully, with clearance of the virus and development of lifelong immunity.\textsuperscript{4} However, in rare cases, individuals with the acute form of the virus may develop fulminant hepatitis, subsequently leading to chronic infection. Patients with chronic HBV infection may develop cirrhosis and HCC, and have the potential to transmit the disease for years to come.\textsuperscript{13} (See Figure 1.)

**Acute HBV Treatment**

Currently, no specific treatment for acute HBV infection exists.\textsuperscript{7} Incidence of acute HBV infection in US adults is depicted in Figure 2. The most recent Centers for Disease Control and Prevention (CDC) surveillance data show an increase of 20.7% in reports of acute hepatitis B from 2014 to 2015.\textsuperscript{6}

The CDC acknowledges that many cases go unreported and estimates that 20,900 people developed acute HBV infection in 2016.\textsuperscript{6} The rate of acute infections is highest among adults aged 30 to 39. In 2016, this age group had 2.4 cases per 100,000 people.\textsuperscript{6}

At least some of the recent increase in HBV transmission is likely due to the increase in the misuse of prescription opioids and associated intravenous heroin use among persons who inject drugs. In Kentucky, Tennessee, and West Virginia, in the Appalachian region, acute hepatitis B increased 114% from 2006 to 2013.\textsuperscript{17}

**Chronic HBV Treatment**

Chronic HBV treatment typically involves prolonged therapy with oral antiviral agents.\textsuperscript{5} The FDA has approved 2 interferons (IFNs) and 6 nucleotide analogue reverse transcriptase inhibitors (NtRTIs) to treat chronic HBV infection (Table 3).\textsuperscript{18}

Primary treatment goals for using these therapies to
manage chronic HBV infection include reducing viral load to limit progressive liver disease and maintaining or improving quality of life.⁵ Note that although antiviral therapy has been shown to slow progression of cirrhosis, reduce the incidence of HCC, and extend survival, it does not cure HBV infections in most cases, and only suppresses viral replication.⁵

**Prevention**

The CDC recommends that specific groups of individuals, such as men who have sex with men, injection drug users, and others, prophylactically receive an HBV vaccine in an attempt to eradicate the spread of this disease (Table 4).¹²

Although hepatitis B is a highly infectious disease, it can be prevented.⁵ For the past 20 years, conventional HBV vaccines, which are composed of recombinant HBsAg derived from yeast cells with an aluminum hydroxide adjuvant, have been the most effective form of preventing infection with the virus.⁴¹¹ These typically have a 3-dose immunization schedule administered at 0, 1, and 6 months (Table 5).²⁰⁻²²

Two conventional aluminum hydroxide adjuvanted single-antigen HBV vaccines and 1 HBV and hepatitis A virus (HAV) combination vaccine have been approved for adult use by the FDA (Table 5).¹²

**Vaccine Coverage in Adults at Risk for HBV Infection**

Successfully vaccinating adults at high risk for HBV infection is an ongoing challenge partly because of the lack of systematic access to such persons and lack of formal
programs for adult immunization. In a 2011 study, only 34.7% of adults in groups at high risk for hepatitis B had ever received a hepatitis B vaccine.23

In 2010, an estimated 77.2% of adults with diabetes 59 years of age and younger had not received 3 doses of HBV vaccine.24 A 2015 study estimated that 75.6% of such persons had not been vaccinated.25 This study also identified HBV coverage rates in healthcare workers and travelers (Figure 3).25

TABLE 4
CDC Advisory Committee on Immunization Practices (ACIP) Recommendations: People Who Should Receive the HBV Vaccine12

Persons at risk for infection by sexual exposure
- Sex partners of hepatitis B surface antigen (HBsAg)-positive persons
- Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than 1 sex partner during the previous 6 months)
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Men who have sex with men

Persons at risk for infection by percutaneous or mucosal exposure to blood
- Current or recent injection drug users
- Household contacts of HBsAg-positive persons
- Residents and staff of facilities for developmentally disabled persons
- Healthcare and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- People with diabetes aged 19 to 59 years; persons with diabetes aged 60 years and older at the discretion of the treating clinician

Others
- International travelers to regions with high or intermediate levels (HBsAg prevalence ≥2%) of endemic HBV infection
- Persons with chronic liver disease
- Persons with HIV infection
- All other persons seeking protection from HBV infection
- People who are incarcerated

Unmet Needs in HBV Vaccine
From a public health perspective, the opportunity to prevent HBV infection before it occurs, by vaccination, is a more desirable approach than managing HBV infection with drugs and other interventions post exposure. Conventional HBV vaccines are very effective, but have some limitations.26

Reduced Seroprotection: Many adults do not respond adequately to the 3-dose hepatitis B vaccines. The proportion of adults protected by 3 doses of the current vaccines drops off notably after age 40 and is less than 75% by age 60.4 One important challenge is that some populations with high HBV incidence rates also have reduced seroprotection rates. For example, men have a higher incidence of HBV infection than women and have reduced immune responses to currently licensed 3-dose hepatitis B vaccines.27,28 Individuals with diabetes mellitus also have an increased risk of contracting HBV infection and have reduced rates of seroprotection.26,29

Delayed Seroprotection: With standard 3-dose HBV vaccines, 45% to 70% of persons 40 years and younger do not achieve seroprotection until after the third dose at 6 months.1,30 Because of this, individuals remain at risk for HBV infection until after receiving the third dose.30 The time period needed to achieve seroprotection can be a particular issue for individuals at risk of imminent exposure to HBV, such as healthcare workers, injection drug users, or travelers.31
TABLE 5
Conventional HBV Vaccines Approved for Use in the United States

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Year Approved</th>
<th>Indication</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGERIX-B® [hepatitis B vaccine (recombinant)] suspension for intramuscular injection</td>
<td>1989&lt;sup&gt;20&lt;/sup&gt;</td>
<td>• Prevention of infection caused by all known subtypes of HBV&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Birth to 19 years of age:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Approved for all ages&lt;sup&gt;20&lt;/sup&gt;</td>
<td>• Series of three 0.5-mL doses on a 0-, 1-, 6-month schedule&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 years of age and older:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Series of three 1-mL doses on a 0-, 1-, 6-month schedule&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adults on hemodialysis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Series of four 2-mL doses given as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>TWINRIX® [hepatitis A &amp; hepatitis B (recombinant) vaccine] suspension for intramuscular injection</td>
<td>2001&lt;sup&gt;21&lt;/sup&gt;</td>
<td>• Active immunization against disease caused by hepatitis A virus and infection by all known subtypes of HBV&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Standard:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Approved for persons 18 years of age or older&lt;sup&gt;21&lt;/sup&gt;</td>
<td>• Series of three 1-mL doses on a 0-, 1-, 6-month schedule&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Accelerated:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Series of four 1-mL doses given at days 0, 7, and 21-30, followed by a booster dose at month 12&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] suspension for intramuscular injection</td>
<td>1983&lt;sup&gt;22&lt;/sup&gt;</td>
<td>• Immunization against infection caused by all known subtypes of HBV&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Birth to 19 years of age:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Approved for all ages&lt;sup&gt;22&lt;/sup&gt;</td>
<td>• Series of three 0.5-mL doses on a 0-, 1-, 6-month schedule&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11 through 15 years of age:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Series of either three 0.5-mL doses on a 0-, 1-, 6-month schedule or series of two 1-mL doses on a 0- and 4- to 6-month schedule&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 years of age and older:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Series of three 1-mL doses on a 0-, 1-, 6-month schedule&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

TABLE 6
Completion Rates of Conventional 3-Dose HBV Vaccination Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Location (US)</th>
<th>Population</th>
<th>Did Not Complete HBV Vaccination Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin (2007)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Hartford, Connecticut</td>
<td>Opioid treatment</td>
<td>31%</td>
</tr>
<tr>
<td>Harris (2007)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Multiple cities</td>
<td>Sexually transmitted disease clinic</td>
<td>~70%</td>
</tr>
<tr>
<td>Hwang (2010)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Houston, Texas</td>
<td>Drug users</td>
<td>34%</td>
</tr>
<tr>
<td>Nelson (2009)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Multiple cities</td>
<td>Vaccine Safety Datalink population</td>
<td>35%-45%</td>
</tr>
</tbody>
</table>
Difficulty With Adherence to Conventional 3-Dose Vaccination Regimen in Adults: Not all individuals receive the complete 3-dose regimen, potentially leaving them susceptible to HBV infection. In a large retrospective Vaccine Safety Datalink study of more than 88,000 adult hepatitis B vaccine recipients, only 54% received all 3 doses within 1 year and only 64% of those vaccinated received all 3 doses of vaccine during an 8-year study period. Adherence is challenging in high-risk populations. For example, in a 6-year study of an STD clinic population of men who have sex with men, only 43% of the men received all 3 doses of a vaccine even when administered on an accelerated 0-, 1-, 4-month schedule.

Several studies demonstrate that other adult populations have difficulty adhering to a 3-dose, 6-month HBV vaccination schedule (Table 6).

Interestingly, even healthcare professionals, a group at high risk for HBV infection that is likely to be more informed about the morbidity and mortality associated with the virus and, presumably more motivated than the general population to complete prophylactic immunization, have difficulty adhering to a conventional vaccine schedule. In 2015, only 64.7% of US healthcare personnel completed a full 3 doses of HBV vaccine. In one survey of medical students, the key reasons for lack of adherence included forgetfulness or being too busy to complete treatment.

These adherence statistics are concerning because it is imperative that healthcare workers receive and complete an HBV vaccination schedule to be fully protected from the virus. Each year, healthcare workers experience between 600,000 and 800,000 exposures to blood through percutaneous injury, such as needle sticks or cuts with sharp objects, or contact of mucous membrane or nonintact skin with blood, tissue, or other body fluids that are potentially infectious. This can place these individuals at high risk for developing infectious diseases, such as HIV, hepatitis C virus (HCV), HBV, and many others. For example, in studies of healthcare workers who sustained injuries from needles contaminated with blood infected with HBV, the risk of developing clinical hepatitis if the blood was positive for both HBsAg and hepatitis B e antigen (HBeAg) was 22% to 31%, whereas the risk of developing serologic evidence of HBV infection was 37% to 62%.

Because of these limitations, alternative immunization options are needed to help provide improved protection for those who may not respond to conventional vaccines. This underscores the unmet need for vaccine options that include fewer injections administered over an accelerated treatment schedule to potentially improve immunization adherence and protection against HBV infection.
HEPLISAV-B: A 2-Dose Option in Adult HBV Vaccination

HEPLISAV-B is a single-antigen HBV vaccine that was approved by the FDA in November 2017 for prevention of infection caused by all known subtypes of HBV. This approval was based on data from three phase 3 noninferiority trials of nearly 10,000 adult participants who received HEPLISAV-B. The pivotal studies compared HEPLISAV-B administered in 2 doses over 1 month with Engerix-B administered in 3 doses over a 6-month schedule. Results from the largest phase 3 trial, which included 6665 participants, showed that HEPLISAV-B demonstrated a statistically significantly higher rate of protection of 95.4% compared with 81.3% for Engerix-B.1

HEPLISAV-B was also shown to provide HBV protection in subjects with type 2 diabetes mellitus.41 In all clinical trials, HEPLISAV-B was found to be well tolerated with an adverse event profile similar to that of Engerix-B.26,40 The safety profile of HEPLISAV-B has been demonstrated in 3 pivotal clinical trials of over 10,000 subjects with up to 12 months of follow-up.1 An extensive post hoc pooled analysis found that HEPLISAV-B did not increase the risk of autoimmune or cardiovascular events.42

Indication, Dosage, and Administration

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

Dose and Regimen: Administer 2 doses (0.5 mL each) of HEPLISAV-B one month apart.1

Administration: HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution.1

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.1

Administer HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.1

Dosage Form and Strength

HEPLISAV-B is a sterile solution for injection available in 0.5 mL single-dose prefilled syringes.5

How Supplied and Storage Conditions

HEPLISAV-B is supplied as a 0.5 mL dose prefilled syringe (NDC 43528-003-01), or in a package of 5 single-dose prefilled syringes (NDC 43528-003-05). The tip caps and stoppers of the prefilled syringes are not made with natural rubber latex.1

HEPLISAV-B should be stored 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 prefilled syringe label.1

Chemistry and Clinical Pharmacology

Chemical and Physical Properties

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is a sterile solution for intramuscular injection.1

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.1

The HBsAg is expressed intracellularly 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 (≤5.0% of total protein), yeast DNA (<20 pg), and deoxycholate (<0.9 ppm) from the HBsAg manufacturing process.1

HEPLISAV-B is prepared by combining the purified HBsAg together with cytosine phosphoguanine (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).1

Clinical Pharmacology and Mechanism of Action

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 HCC.1

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against HBV infection.1
Clinical Studies

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. 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 as a 3-dose regimen at 0, 1, and 6 months.1

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%.1

Study 1: HBV-10
Serpotection of HEPLISAV-B in Adults 18 Through 55 Years

Study 1 was a randomized, active-controlled, observer-blinded, multicenter phase 3 clinical trial in healthy adults 18 through 55 years of age.1,40 Participants were randomized in a 3:1 ratio to receive 2 doses of HEPLISAV-B or 3 doses of Engerix-B and were followed for 7 months after the first injection (Figure 4).40

In Study 1, the immunogenicity population consisted of 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. Noninferiority of the seroprotection rate induced by HEPLISAV-B compared with Engerix-B was demonstrated (Table 7, Figure 5).1

### TABLE 7
Study 1: Seroprotection Rates of HEPLISAV-B and Engerix-B (18 Through 55 Years)1

<table>
<thead>
<tr>
<th>Time Point</th>
<th>HEPLISAV-B N=1511</th>
<th>Engerix-B N=521</th>
<th>Difference in SPRs (HEPLISAV-B Minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 (HEPLISAV-B)</td>
<td>95% (93.9, 96.1)</td>
<td>81.3% (77.8, 84.6)</td>
<td>13.7% (10.4, 17.5)*</td>
</tr>
<tr>
<td>Week 28 (Engerix-B)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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: HBV-16
Seroprotection of HEPLISAV-B in Adults 40 Through 70 Years
Study 2 was a phase 3, multicenter, randomized, observer-blinded, active-controlled clinical trial. Adults 40 through 70 years of age, a population known to be less responsive to currently licensed vaccines, were randomly assigned in a 4:1 ratio to receive HEPLISAV-B or Engerix-B (Figure 6). In Study 2, the immunogenicity population consisted of 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. Noninferiority of the seroprotection rate induced by HEPLISAV-B compared with Engerix-B was demonstrated (Table 8, Figure 7).
TABLE 8
Study 2: Seroprotection Rates of HEPLISAV-B and Engerix-B (40 Through 70 Years)\textsuperscript{1}

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Study 2</th>
<th></th>
<th>Difference in SPRs (HEPLISAV-B Minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEPLISAV-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=1121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPR (95% CI)</td>
<td>90.1% (88.2, 91.8)</td>
<td></td>
<td>19.6% (14.7, 24.8)*</td>
</tr>
<tr>
<td>Engerix-B</td>
<td>N=353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPR (95% CI)</td>
<td>70.5% (65.5, 75.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 the SPR following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).
Clinical trial number: NCT01005407

FIGURE 7
Study 2: Patients Aged 40 Through 70\textsuperscript{143}
HEPLISAV-B provided statistically significantly higher rates of protection than Engerix-B at each time point

19.6% (95% CI, 14.7-24.8) difference in protective immunity between patient groups at primary endpoint

Patients Achieving Protective Immunity, %

HEPLISAV-B 2-dose series
Engerix-B 3-dose series
Dose 1
Dose 2
Dose 3
Primary endpoint
Study 3: HBV-23
Seroprotection of HEPLISAV-B in Adults 18 Through 70 Years

Study 3 was a phase 3, multicenter, randomized, observer-blinded, active-controlled clinical trial. In Study 3, the immunogenicity population consisted of 4537 subjects who received HEPLISAV-B and 2289 subjects who received Engerix-B (Figure 8).

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.

Noninferiority of HEPLISAV-B compared with Engerix-B was demonstrated as HEPLISAV-B induced a statistically significantly higher seroprotection rate at Week 28 for HEPLISAV-B with that at Week 28 for Engerix-B in the total study population. Noninferiority of HEPLISAV-B compared with Engerix-B was demonstrated as HEPLISAV-B induced a statistically significant higher seroprotection rate (Figure 9).

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, noninferiority of HEPLISAV-B compared with Engerix-B was demonstrated as HEPLISAV-B induced a statistically significant higher seroprotection rate (Table 10).

TABLE 9
Study 3: Seroprotection Rates of HEPLISAV-B and Engerix-B in Subjects With Type 2 Diabetes Mellitus (18 Through 70 Years)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEPLISAV-B</td>
</tr>
<tr>
<td>Week 28</td>
<td>90.0% (95% CI: 87.4, 92.2)</td>
</tr>
</tbody>
</table>

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 the SPR following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

Clinical trial number: NCT02117934
TABLE 10
Seroprotection Rates of HEPLISAV-B and Engerix-B by Age Group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Study 3</th>
<th>Difference in SPRs (HEPLISAV-B Minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEPLISAV-B</td>
<td>Engerix-B</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>SPR (95% CI)</td>
</tr>
<tr>
<td>18-29</td>
<td>174</td>
<td>100.0% (97.9, 100.0)</td>
</tr>
<tr>
<td>30-39</td>
<td>632</td>
<td>98.9% (97.7, 99.6)</td>
</tr>
<tr>
<td>40-49</td>
<td>974</td>
<td>97.2 (96.0, 98.2)</td>
</tr>
<tr>
<td>50-59</td>
<td>1439</td>
<td>95.2 (94.0, 96.3)</td>
</tr>
<tr>
<td>60-70</td>
<td>1157</td>
<td>91.6 (89.9, 93.1)</td>
</tr>
</tbody>
</table>

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

* Week 24 for HEPLISAV-B and Week 28 for Engerix-B.
† 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 the SPR following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

Clinical trial number: NCT02117934

Seroprotection in Adults With Diabetes

An analysis of the primary endpoint of Study 3 included subjects with type 2 diabetes mellitus (Figure 10).44

Results of this primary endpoint analysis revealed that 2 doses of HEPLISAV-B protected a larger proportion of subjects with type 2 diabetes mellitus against HBV compared with 3 doses of Engerix-B; the difference was statistically significant.44

FIGURE 9
Study 3: Peak Seroprotection Rates of HEPLISAV-B and Engerix-B (Total Study Population Ages 18 Through 70 Years)

Seroprotection in Adults With Diabetes

An analysis of the primary endpoint of Study 3 included subjects with type 2 diabetes mellitus (Figure 10).44

Results of this primary endpoint analysis revealed that 2 doses of HEPLISAV-B protected a larger proportion of subjects with type 2 diabetes mellitus against HBV compared with 3 doses of Engerix-B; the difference was statistically significant.44

FIGURE 10
HBV-23 Primary Immunogenicity Endpoint: SPR at Week 28 for Subjects With T2DM

CI=confidence interval; SPR=seroprotection rate; T2DM=type 2 diabetes mellitus.
Safety Considerations

Adverse Reactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.\(^1\)

A total of 9597 individuals 18 through 70 years of age received at least one dose of HEPLISAV-B in 5 clinical trials conducted in the United States, Canada, and Germany. Data from 3 of these trials are provided below.\(^1\)

HEPLISAV-B Safety Results From Pivotal Clinical Trials
Solicited Local and Systemic Adverse Reactions
In 2 randomized, observer-blind, active-controlled, multicenter trials in the United States, Canada, and Germany, 3778 subjects 18 years and older received HEPLISAV-B at 0 and 1 month, and 1086 subjects received Engerix-B at 0, 1, and 6 months.\(^1\) Enrolled subjects had no history of hepatitis B vaccination or infection. In these studies, subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination.\(^1\) The percentage of subjects who experienced local and systemic reactions is shown in Tables 11 and 12.\(^1\)

Unsolicited Adverse Events
Unsolicited adverse events within 28 days following any injection, including placebo, were reported by HEPLISAV-B recipients and Engerix-B recipients for Studies 1 and 2. The percentage of subjects with an unsolicited adverse event was similar between treatment groups in Study 1 (42.0% of HEPLISAV-B recipients and 41.3% of Engerix-B recipients), and similar between treatment groups in Study 2 (35.4% of HEPLISAV-B recipients and 36.2% of Engerix-B recipients).\(^1\)

In Study 3, subjects were monitored for unsolicited medically attended adverse events (MAEs) for 13 months after the first dose of vaccine. MAEs 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 MAEs within 28 days following any injection were reported in 20.1% of both HEPLISAV-B and Engerix-B recipients (Table 13).\(^1\)

Serious Adverse Events and Deaths
In Study 1, patients were monitored for serious adverse events (SAEs) for 7 months after the first dose of vaccine. The percentage of subjects who experienced SAEs was 1.5% in the HEPLISAV-B group and 2.1% in the Engerix-B group. In Study 2, where patients were monitored for 12 months,

---

### TABLE 11

<table>
<thead>
<tr>
<th>Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPLISAV-B</strong></td>
</tr>
<tr>
<td><strong>Post-Dose</strong></td>
</tr>
<tr>
<td><strong>REACTION</strong></td>
</tr>
<tr>
<td><strong>Local</strong></td>
</tr>
<tr>
<td>Injection Site Pain</td>
</tr>
<tr>
<td>Injection Site Redness*</td>
</tr>
<tr>
<td>Injection Site Swelling*</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Fever*</td>
</tr>
</tbody>
</table>

* Redness and swelling ≥2.5 cm.
† Oral temperature ≥100.4°F (38.0°C).
Clinical trial number: NCT00435812
the percentage of subjects who experienced SAEs was 3.9% in the HEPLISAV-B group and 4.8% in the Engerix-B group. In Study 3, where patients were monitored for 13 months, the percentage of subjects who experienced SAEs was 6.2% in the HEPLISAV-B group and 5.3% in the Engerix-B group.1 During the HEPLISAV-B trials, 0.28% of HEPLISAV-B recipients and 0.21% of Engerix-B recipients died. None of the deaths were considered to be related to vaccination with HEPLISAV-B.1

Autoimmune Adverse Events
The potential link between vaccination and immune mediated disorders in patients given HEPLISAV-B was assessed retrospectively in Study 1 and prospectively in Studies 2 and 3 (N=9365).1,43 A blinded external panel of experts evaluated new-onset immune mediated events in Studies 2 and 3 and determined that there was no relationship to vaccine administration and the observed immune mediated disorders listed in the PI.1

### TABLE 12

<table>
<thead>
<tr>
<th>REACTION</th>
<th>HEPLISAV-B Post-Dose</th>
<th>Engerix-B Post-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>23.7%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Injection Site Redness†</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Injection Site Swelling†</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12.6%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>11.8%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Malaise</td>
<td>7.7%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
<td></td>
</tr>
</tbody>
</table>

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 ≥100.4°F (38.0°C).

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

### TABLE 13

<table>
<thead>
<tr>
<th>Study</th>
<th>HEPLISAV-B</th>
<th>Unsolicited Adverse Events</th>
<th>Serious Adverse Events</th>
<th>Immune-Mediated Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>HEPLISAV-B</td>
<td>Within 28 days of any injection</td>
<td>42.0%</td>
<td>Within 7 months of the first vaccine dose</td>
</tr>
<tr>
<td></td>
<td>Engerix-B</td>
<td>N=1810</td>
<td>41.3%</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>HEPLISAV-B</td>
<td>Within 28 days of any injection</td>
<td>35.4%</td>
<td>Within 12 months of the first vaccine dose</td>
</tr>
<tr>
<td></td>
<td>Engerix-B</td>
<td>N=1968</td>
<td>36.2%</td>
<td></td>
</tr>
<tr>
<td>Study 3*</td>
<td>HEPLISAV-B</td>
<td>Within 28 days of any injection</td>
<td>20.1%</td>
<td>Within 13 months of the first vaccine dose</td>
</tr>
<tr>
<td></td>
<td>Engerix-B</td>
<td>N=5587</td>
<td>20.1%</td>
<td></td>
</tr>
</tbody>
</table>

*For Study 3, only unsolicited medically attended adverse events, those for which a subject sought medical care, were captured.
Cardiovascular Adverse Events
An extensive analysis was conducted to evaluate whether there was a causal relationship between the incidences of acute myocardial infarction and HEPLISAV-B. As noted in the PI, it was determined that there was not a causal relationship. Additionally, a post hoc pooled analysis found that HEPLISAV-B did not increase the risk of cardiovascular events.1

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.1

Warnings and Precautions
Managing Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.1

Immunocompromised Individuals
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.1

Limitations of Vaccine Effectiveness
Hepatitis B has a long incubation period. HEPLISAV-B may not prevent HBV infection in individuals who have an unrecognized HBV infection at the time of vaccine administration.1

Drug Interactions
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.1

Interference With Laboratory Tests: 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.1

Use in Specific Populations
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 1-844-443-7734.1
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%.1

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.1

In a developmental toxicity study, 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg 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 because of this vaccine formulation.1

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 antigen 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 prenatal and postnatal development up to the time of weaning were observed. No vaccine-related fetal malformations or variations were observed.1

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.1

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.1

Pediatric Use
Safety and effectiveness of HEPLISAV-B have not been established in individuals 18 years and younger.1

Geriatric Use
Clinical trials included 909 adults aged 65 through 70 who received HEPLISAV-B.1

Among subjects who received HEPLISAV-B, a seropre- tentive level of antibody to HBsAg was achieved in 90% of those aged 65 through 70 compared with 96% of those aged 18 through 64.1

Safety and effectiveness of HEPLISAV-B in adults 70 years and older were extrapolated from findings in subjects younger than 70 years of age.1

Adults on Hemodialysis
Safety and effectiveness of HEPLISAV-B have not been established in adults on hemodialysis.1
HBV Disease Burden

Hepatitis B is a significant public health problem that accounts for approximately 5000 fatalities in the United States and 887,000 deaths worldwide each year. The reported number of acute hepatitis B cases in the United States has generally been declining since 2000. However, the incidence of acute hepatitis B increased 20.7% from 2014 to 2015 (2791 to 3370 cases, respectively). At least some of the recent increase in HBV transmission is likely due to the increase in the misuse of prescription opioids and associated intravenous heroin use among persons who inject drugs. In Kentucky, Tennessee, and West Virginia, in the Appalachian region, acute hepatitis B increased 114% from 2006-2013.

Although the majority of patients who acquire the acute form of the infection recover and develop immunity to the virus, chronic HBV infection remains a significant cause of morbidity and mortality that is associated with high healthcare costs. Indeed, individuals who progress to chronic HBV infection are at an increased risk for developing serious and life-threatening complications, such as cirrhosis, HCC, polyarteritis nodosa, acute fulminant hepatitis, and immune-mediated membranous glomerulonephritis, which require expensive treatments for survival. Additionally, because antiviral therapy does not clear the virus completely, most patients need to remain on treatment for life, which increases the likelihood of adverse reactions, drug resistance, treatment nonadherence, and higher cost.

For more than 2 decades, immunization with an HBV vaccine has been the most effective form of inhibiting infection with the virus. Although largely effective, conventional HBV vaccines’ seroprotection rates decline with age, leaving many older adults at risk for HBV infection. Additionally, lower immunogenicity has been observed in men, obese individuals, smokers, and people with diabetes, placing them at risk for morbidity and mortality associated with HBV. Furthermore, research demonstrates that it remains difficult to encourage those who are at the highest risk of infection with HBV, such as injection drug users, to complete the 3-dose regimen.

HEPLISAV-B Clinical Considerations

HEPLISAV-B is a single-antigen HBV vaccine that was approved by the FDA in November 2017 for use in adults 18 years of age and older. Head-to-head studies comparing 2 doses of HEPLISAV-B with 3 doses of Engerix-B demonstrated that HEPLISAV-B achieved earlier seroprotection, with fewer intramuscular injections. See “Clinical Studies” section for further details.

Additionally, in a subanalysis of one phase 3 trial, HEPLISAV-B was also shown to have higher rates of seroprotection than Engerix-B in subjects with type 2 diabetes mellitus.

Across all 3 clinical trials, the unsolicited adverse events were the same or similar in HEPLISAV-B and Engerix-B recipients. The unsolicited adverse events within 28 days following any injection were reported as: Study 1: 42.0% of HEPLISAV-B and 41.3% of Engerix-B recipients. Study 2: 35.4% of HEPLISAV-B and 36.2% of Engerix-B recipients. Study 3: 20.1% for both HEPLISAV-B and Engerix-B recipients. A post-hoc pooled analysis of the 3 pivotal trials found no evidence that HEPLISAV-B increased the risk of autoimmune or cardiovascular events.

The CDC’s Advisory Committee on Immunization Practices (ACIP) provided guidance on hepatitis B vaccine interchangeability in April 2018. It recommends that when the manufacturer of the previously administered vaccine dose is unknown or unavailable, HEPLISAV-B can be used to complete a 3-dose series provided the standard 3-dose schedule minimum dosing intervals are adhered to.

HEPLISAV-B is supplied as a 0.5 mL dose prefilled syringe (NDC 43528-003-01) sold in a package of 5 single-dose prefilled syringes (NDC 43528-003-05). Each 0.5 mL dose is formulated to contain 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant. Vaccination with HEPLISAV-B requires that patients be given fewer doses and complete a shorter course of treatment (1 month) versus Engerix-B (6 months).

HEPLISAV-B Cost Considerations

The cost of HEPLISAV-B and 2 other hepatitis B vaccines, Engerix-B and Recombivax HB, appear in Table 14. This table also includes those vaccines for which the CDC has purchasing contracts supporting adult immunization programs. These prices reflect the WAC plus appropriate excise tax, current as of January 10, 2019.
### TABLE 14
Adult Vaccine Cost Per Dose and Regimen and Launch Year as of January 10, 2019

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Launch Year</th>
<th>Cost per Dose</th>
<th>Doses</th>
<th>Cost per Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Td Vaccine</td>
<td>Grifols</td>
<td>1970</td>
<td>$26.62</td>
<td>1</td>
<td>$26.62</td>
</tr>
<tr>
<td>Boostrix®</td>
<td>GlaxoSmithKline</td>
<td>2005</td>
<td>$43.44</td>
<td>1</td>
<td>$43.44</td>
</tr>
<tr>
<td>Adacel®</td>
<td>Sanofi</td>
<td>2005</td>
<td>$47.75</td>
<td>1</td>
<td>$47.75</td>
</tr>
<tr>
<td>Engerix-B®</td>
<td>GlaxoSmithKline</td>
<td>1989</td>
<td>$59.70</td>
<td>3</td>
<td>$179.10</td>
</tr>
<tr>
<td>Recombivax HB®</td>
<td>Merck</td>
<td>1983</td>
<td>$63.04</td>
<td>3</td>
<td>$189.12</td>
</tr>
<tr>
<td>Vaqta®</td>
<td>Merck</td>
<td>1996</td>
<td>$68.98</td>
<td>2</td>
<td>$137.96</td>
</tr>
<tr>
<td>Havrix®</td>
<td>GlaxoSmithKline</td>
<td>1995</td>
<td>$70.31</td>
<td>2</td>
<td>$140.62</td>
</tr>
<tr>
<td>M-M-R® II</td>
<td>Merck</td>
<td>2008</td>
<td>$77.29</td>
<td>1 to 2</td>
<td>$77.29 or $154.58</td>
</tr>
<tr>
<td>Pneumovax®-23</td>
<td>Merck</td>
<td>1983</td>
<td>$100.19</td>
<td>1</td>
<td>$100.19</td>
</tr>
<tr>
<td>Twinrix®</td>
<td>GlaxoSmithKline</td>
<td>2001</td>
<td>$105.50</td>
<td>3</td>
<td>$316.50</td>
</tr>
<tr>
<td>HEPLISAV-B®</td>
<td>Dynavax</td>
<td>2017</td>
<td>$115.75</td>
<td>2</td>
<td>$231.50</td>
</tr>
<tr>
<td>Menactra®</td>
<td>Sanofi</td>
<td>2005</td>
<td>$123.06</td>
<td>1</td>
<td>$123.06</td>
</tr>
<tr>
<td>Varivax®</td>
<td>Merck</td>
<td>1995</td>
<td>$130.05</td>
<td>1 to 2</td>
<td>$130.05 or $260.10</td>
</tr>
<tr>
<td>Menveo®</td>
<td>GlaxoSmithKline</td>
<td>2011</td>
<td>$131.50</td>
<td>1</td>
<td>$131.50</td>
</tr>
<tr>
<td>Trumenba®</td>
<td>Pfizer</td>
<td>2014</td>
<td>$134.37</td>
<td>2 to 3</td>
<td>$268.74 or $403.11</td>
</tr>
<tr>
<td>Shingrix®</td>
<td>GlaxoSmithKline</td>
<td>2017</td>
<td>$144.95</td>
<td>2</td>
<td>$289.90</td>
</tr>
<tr>
<td>Bexsero®</td>
<td>GlaxoSmithKline</td>
<td>2015</td>
<td>$171.50</td>
<td>2</td>
<td>$343.00</td>
</tr>
<tr>
<td>Prevnar 13™</td>
<td>Pfizer</td>
<td>2010</td>
<td>$180.80</td>
<td>1, 3, 4</td>
<td>$180.80, $542.39, or $723.19</td>
</tr>
<tr>
<td>Zostavax®</td>
<td>Merck</td>
<td>2006</td>
<td>$213.42</td>
<td>1</td>
<td>$213.42</td>
</tr>
<tr>
<td>Gardasil®9</td>
<td>Merck</td>
<td>2006</td>
<td>$217.86</td>
<td>2 to 3</td>
<td>$435.73 or $653.59</td>
</tr>
</tbody>
</table>

*a Includes current wholesale acquisition cost (WAC) plus Federal Excise Tax.
*b Vaccine cost includes $2.25 per dose Federal Excise Tax.
*c Vaccine cost includes $1.50 per dose Federal Excise Tax.
*d Vaccine cost includes $0.75 per dose Federal Excise Tax.
*e Merck will not be distributing Recombivax in 2019. GSK and Dynavax have sufficient supplies of adult hepatitis B vaccines to address the gap in Merck’s supply.51
*f Recombivax HB and Zostavax are not currently included in the CDC Adult Vaccines Price List.
*g No excise tax indicated on CDC Adult Vaccines Price List.
Conclusion

Hepatitis B is a highly infectious disease that is transmitted through percutaneous or mucosal contact with infectious blood or body fluid. The disease is a significant public health problem that accounts for approximately 5000 fatalities in the United States and contributes to an estimated 887,000 deaths worldwide each year. The reported number of acute hepatitis B cases in the United States has generally been declining since 2000. However, the incidence of acute hepatitis B increased 20.7% from 2014 to 2015 (2791 to 3370 cases, respectively). Infection with the virus can be prevented through the HBV vaccine, but conventional single-antigen vaccines may have limitations to their effectiveness, and lower immunogenicity has been observed in men, obese individuals, smokers, and people with diabetes, placing them at risk for morbidity and mortality associated with HBV infection. In addition, 3-dose, 6-month immunization schedules of conventional HBV vaccines are associated with suboptimal compliance rates.

HEPLISAV-B is a single-antigen HBV vaccine that was approved by the FDA in November 2017 for use in adults 18 years of age and older. The CDC’s Advisory Committee on Immunization Practices (ACIP) included HEPLISAV-B in its list of recommended adult hepatitis B vaccines in February 2018. The dosing schedule includes fewer intramuscular injections than 3-dose HBV vaccines. HEPLISAV-B demonstrated higher and earlier rates of seroprotection than Engerix-B.

HEPLISAV-B was also found to be well tolerated and effective in individuals who have poor treatment response risk factors, such as male sex, obesity, type 2 diabetes mellitus, and smoking.
References


hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40-70 years of age. *Vaccine*. 2013;31:5300-5305.


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 and prefilled syringe. 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: 03/2018

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4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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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 and prefilled syringes. [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.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>N=1810</th>
<th>N=1798</th>
<th>N=605</th>
<th>N=603</th>
<th>N=598</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Pain</td>
<td>38.5</td>
<td>34.8</td>
<td>33.6</td>
<td>24.7</td>
<td>20.2</td>
</tr>
<tr>
<td>Injection Site Redness‡</td>
<td>4.1</td>
<td>2.9</td>
<td>0.5</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Injection Site Swelling‡</td>
<td>2.3</td>
<td>1.5</td>
<td>0.7</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17.4</td>
<td>13.8</td>
<td>16.7</td>
<td>11.9</td>
<td>10.0</td>
</tr>
<tr>
<td>Headache</td>
<td>16.9</td>
<td>12.8</td>
<td>19.2</td>
<td>12.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Malaise</td>
<td>9.2</td>
<td>7.6</td>
<td>8.9</td>
<td>6.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Fever#</td>
<td>1.1</td>
<td>1.5</td>
<td>1.8</td>
<td>1.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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 ≥ 100.4°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.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>N=1952</td>
<td>N=1905</td>
</tr>
<tr>
<td></td>
<td>23.7%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Injection Site Redness</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12.6%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>11.8%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Malaise</td>
<td>7.7%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Fever</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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 ≥ 100.4°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 (≤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.

HEPLISAV-B is available in vials and prefilled syringes. The tip caps and stoppers of the prefilled syringes and 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).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
<th>Difference in SPRs (HEPLISAV-B minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 (HEPLISAV-B)</td>
<td>N = 1511</td>
<td>N = 521</td>
<td></td>
</tr>
<tr>
<td>SPR (95% CI)</td>
<td>95% (93.9, 96.1)</td>
<td>81.3% (77.8, 84.6)</td>
<td>13.7% (10.4, 17.5)*</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
<th>Difference in SPRs (HEPLISAV-B minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 (HEPLISAV-B)</td>
<td>N = 1121</td>
<td>N = 353</td>
<td></td>
</tr>
<tr>
<td>SPR (95% CI)</td>
<td>90.1% (88.2, 91.8)</td>
<td>70.5% (65.5, 75.2)</td>
<td>19.6% (14.7, 24.8)*</td>
</tr>
</tbody>
</table>

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).
### Table 5
Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (subjects with type 2 diabetes mellitus ages 18 through 70 years)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
<th>Difference in SPRs (HEPLISAV-B minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 28</td>
<td>N = 640</td>
<td>N = 321</td>
<td></td>
</tr>
<tr>
<td>SPR (95% CI)</td>
<td>90.0% (87.4, 92.2)</td>
<td>65.1% (59.6, 70.3)</td>
<td>24.9% (19.3, 30.7)*</td>
</tr>
</tbody>
</table>

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%).

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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).

### Table 6
Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (total study population ages 18 through 70 years)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
<th>Difference in SPRs (HEPLISAV-B minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24 (HEPLISAV-B)</td>
<td>N = 4376</td>
<td>N = 2289</td>
<td></td>
</tr>
<tr>
<td>Week 28 (Engerix-B)</td>
<td>SPR (95% CI)</td>
<td>95.4% (94.8, 96.0)</td>
<td>81.3% (79.6, 82.8)</td>
</tr>
</tbody>
</table>

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: NCT02117934

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).

### Table 7
Study 3: Seroprotection Rates of HEPLISAV-B and Engerix-B* (ages 18 - 70 years)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HEPLISAV-B</th>
<th>Engerix-B</th>
<th>Difference in SPRs (HEPLISAV-B minus Engerix-B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SPR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>18-29</td>
<td>174</td>
<td>100.0% (97.9, 100.0)</td>
<td>99</td>
</tr>
<tr>
<td>30-39</td>
<td>632</td>
<td>98.9% (97.7, 99.6)</td>
<td>326</td>
</tr>
<tr>
<td>40-49</td>
<td>974</td>
<td>97.2% (96.0, 98.2)</td>
<td>518</td>
</tr>
<tr>
<td>50-59</td>
<td>1439</td>
<td>95.2% (94.0, 96.3)</td>
<td>758</td>
</tr>
<tr>
<td>60-70</td>
<td>1157</td>
<td>91.6% (89.9, 93.1)</td>
<td>588</td>
</tr>
</tbody>
</table>

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
*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)
- Prefilled syringe, 1 dose (0.5 mL) - (NDC number: 43528-003-01)
- Package of 5 single dose prefilled syringes - (NDC number: 43528-003-05)

The tip caps and stoppers of the prefilled syringes and 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 or prefilled syringe 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).

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