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GAVIN NEWSOM
Governor

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TO: Vaccines for Adults (VFA) Providers

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SUBJECT: HEPLISAV-B (Hepatitis B Vaccine, Recombinant, Adjuvanted;
HepB-CpG) IS NOW AVAILABLE for VFA Providers

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SUMMARY

On November 9, 2017, the United States (U.S.) Food and Drug Administration (FDA) licensed Hepatitis B Vaccine Recombinant, Adjuvanted (Heplisav-B®, Dynavax Technologies Corporation) for the prevention of infections and complications caused by



hepatitis B virus (HBV) in persons aged 18 years and older. HepB-CpG (HepB-CpG) is a single-antigen hepatitis B vaccine with a novel immunostimulatory sequence

adjuvant and is administered as a 2-dose series (0, 1 month). On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP) recommended HepB-CpG for use in persons aged 18 years and older. The ACIP has not made a preferential recommendation for HepB-CpG over other hepatitis B vaccine product. The benefits of protection with 2 doses over 1 month make HepB-CpG an important option for the prevention of HBV. The California Department of Public Health, Immunization Branch is following ACIP's recommendations for the use of HepB-CpG. This letter summarizes information about the use of this newly-licensed hepatitis B vaccine.

BACKGROUND AND COMPOSITION

Hepatitis B virus (HBV) infection is common in the United States. In 2015, a total of 3,370 cases of acute HBV infection were reported to CDC, but the actual number of acute cases is believed to be 6.5 times the number of reported cases. The rate of reported acute HBV infections has declined 88.5% since recommendations for hepatitis B vaccination were first issued. On the basis of national health survey data, it is estimated that approximately 850,000 persons are living with chronic HBV infection in the United States, but it is likely that the total prevalence of chronic hepatitis B might be as high as 2.2 million persons.

HBV is transmitted through percutaneous (i.e., puncture through the skin) or mucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or body fluids. HBV is highly infectious, can be transmitted in the absence of visible blood, and remains viable on environmental surfaces for at least seven days. Persons with chronic infection (e.g., those with persistent hepatitis B surface antigen [HBsAg] in the serum for at least 6 months following acute infection) serve as the main reservoir for HBV transmission. Complications of chronic HBV infection include liver inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. No specific treatment exists for acute HBV infection; chronic infection may be managed with antiviral therapy, including antiviral therapy for some chronically infected pregnant women to reduce perinatal transmission.

HepB-CpG is a sterile suspension for intramuscular injection in the deltoid region of the upper arm. HepB-CpG contains yeast-derived recombinant HepB surface antigen (HBsAg) and is prepared by combining purified HBsAg with small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN) motifs (1018 adjuvant). The 1018 adjuvant binds to Toll-like receptor 9 to stimulate a directed immune response to HBsAg. HepB-CpG is available in prefilled syringes and is formulated without preservatives. Each dose contains 20 µg of HBsAg and 3,000 µg of 1018 adjuvant. HepB-CpG is a clear to slightly opalescent, colorless to slightly yellow solution.

The HBsAg is obtained by culturing 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. HepB-CpG 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 tip caps and stoppers of the prefilled syringes and vial stoppers are not made with natural rubber latex.

Studies assessing the effectiveness of HepB-CpG used antibody to hepatitis B surface antigen (anti-HBs) ≥ 10 mIU/mL as a serologic correlate of protection. Protection among 7,056 subjects receiving 2 doses of HepB-CpG was compared with protection among 3,214 subjects receiving 3 doses of Engerix-B. Seroprotective anti-HBs levels were achieved in 90.0%-100.0% of subjects receiving HepB-CpG, compared with 70.5%-90.2% of subjects receiving Engerix-B. The body of evidence for the benefits of protection against HBV infection was deemed to be GRADE evidence type 2 (i.e., evidence from randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies). The evidence type was downgraded for indirectness because immunogenicity was used as a surrogate for protection.

RECOMMENDATIONS FOR USE OF HEPB-CPG IN THE VFA PROGRAM

ELIGIBILITY

Eligible Persons for Receipt of VFA-Supplied HepB-CpG

Adults 19 years of age and older may receive VFA-funded HepB-CpG if they are:

- Uninsured – no public or private health insurance coverage, OR
- Underinsured – health insurance does not cover HepB-CpG

Eligibility information can be downloaded [here](#).

ACIP Hepatitis B Vaccine Recommendations

General use. Hepatitis B vaccine, including HepB-CpG, is recommended for the prevention of HBV infection. The ACIP has not made a preferential recommendation for HepB-CpG over other hepatitis B vaccine products, but the benefits of protection with 2 doses over 1 month make HepB-CpG an important option for the prevention of HBV in adults 18 years of age and older. Medical providers should identify adults for whom hepatitis B vaccination is indicated due to their increased risk for acute infection.

Adults for whom hepatitis B vaccination is recommended include:

- Persons at risk for infection through sexual exposure
- Sex partners of hepatitis B surface antigen (HBsAg)-positive persons
- Sexually active persons not in a long-term, mutually monogamous relationship
- Persons seeking evaluation or treatment for a sexually transmitted infection
- Men who have sex with men
- Persons with a history of current or recent injection drug use

- Persons at risk for infection by percutaneous or mucosal exposure to blood
 - Household contacts of HBsAg-positive persons
 - Residents and staff of facilities for developmentally disabled persons
 - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
 - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
 - Persons with diabetes mellitus aged <60 years; persons with diabetes mellitus aged ≥60 years at the discretion of the treating clinician
- International travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%)
- Persons with hepatitis C virus infection, persons with chronic liver disease (including, but not limited to, those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
- Persons with human immunodeficiency virus infection
- Incarcerated persons
- Other persons seeking protection from hepatitis B virus infection (even without acknowledgment of a specific risk factor)

Dosing schedule. HepB-CpG is administered as a 2-dose series. The second dose should be administered one month after the first dose of HepB-CpG. The 2-dose HepB vaccine series only applies when both doses in the series consist of HepB-CpG. Series consisting of a combination of 1 dose of HepB-CpG and a vaccine from a different manufacturer should consist of 3 total vaccine doses and should adhere to the 3-dose schedule minimum intervals of 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3. Doses administered at less than the minimum interval should be repeated. However, a series containing 2 doses of HepB-CpG administered at least 4 weeks apart is valid, even if the patient received a single earlier dose from another manufacturer.

SPECIAL POPULATIONS

Pregnancy and Lactation

There are no clinical studies of HepB-CpG in pregnant women. Available human data on HepB-CpG administered to pregnant women are insufficient to inform assessment of vaccine-associated risks in pregnancy. Until safety data are available for HepB-CpG, providers should continue to vaccinate pregnant women needing HepB vaccination with a vaccine from a different manufacturer. It is not known whether HepB-CpG is excreted in human milk. Data are not available to assess the effects of HepB-CpG 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 HepB-CpG and any potential adverse effects on the breastfed child from HepB-CpG or from the underlying maternal condition.

IMPORTANCE OF A STRONG MESSAGE FOR HEPB-CPG

For adults for whom hepatitis B vaccination is indicated, providers should give a strong recommendation for hepatitis B vaccine along with other adult vaccines. Hepatitis B (HepB) vaccination is the primary means of preventing infections and complications caused by hepatitis B virus (HBV).

ADMINISTRATION

HepB-CpG 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 HepB-CpG by intramuscular injection in the deltoid region using a sterile needle and syringe.

Providers should report any vaccine administration error and associated contributing factors to the National Vaccine Errors Reporting Program (VERP) at <http://verp.ismp.org/>. As a part of the report, providers can make recommendations for error prevention. This surveillance program aims to prevent future errors by identifying trends, creating targeted education efforts, and making changes to product labeling and design.

Administration with Other Vaccines

HepB-CpG can be administered concomitantly with other adult vaccines. Do not mix this vaccine or any of its components with any other vaccine or diluent in the same syringe or vial. All vaccines should be given at separate anatomic sites with separate syringes.

Use with Immune Globulin

There are no data to assess the concomitant use of HepB-CpG with immune globulin. When concomitant administration HepB-CpG and immune globulin is required, they should be given with different syringes at different injection sites.

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 vaccine.

PACKAGING

The vaccine is supplied in the following ways:

- 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)

Note: Only the package of 5 single-dose prefilled syringes (NDC number: 43528-003-05) will be available for 317-funded vaccine ordering.

The tip caps and stoppers of the prefilled syringes and vial stoppers are not made with natural rubber latex.

STORAGE

Store in a refrigerator at 2°C to 8°C (35°F to 46°F). Do not freeze; do not use if the vaccine has been frozen. Do not use the vaccine after the expiration date shown on the vial or prefilled syringe label.

POTENTIAL VACCINE REACTIONS

Safety profiles among 9,871 subjects receiving 2 or 3 doses of HepB-CpG were compared with those among 4,385 subjects receiving 3 or 4 doses of Engerix-B. Among subjects receiving HepB-CpG, 45.6%, 5.4%, and 0.27% experienced a mild adverse event, serious adverse event, or cardiovascular event, respectively. Among subjects receiving Engerix-B, 45.7%, 6.3%, and 0.14% experienced a mild adverse event, serious adverse event, or cardiovascular event, respectively. The body of evidence assessing adverse events was deemed to be GRADE evidence type 1 (evidence from randomized controlled trials, or overwhelming evidence from observational studies). Overall, the most common mild adverse events with HepB-CpG were injection site pain, fatigue, headache, and malaise.

One of the clinical studies for which outcomes were reported noted an increased rate of acute myocardial infarction (AMI) in subjects receiving HepB-CpG vs. Engerix-B (0.3% vs 0.1%). Additional evidence, including information on temporal relationship and baseline risk factors, did not support a causal relationship between HepB-CpG administration and AMI.

Providers should report suspected reactions to HepB-CpG or any other vaccine to the Vaccine Adverse Events Reporting System (VAERS) at 800-822-7967 (toll-free) or at <http://vaers.hhs.gov>.

CONTRAINDICATIONS

Do not administer HepB-CpG 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 HepB-CpG, including yeast.

PRECAUTIONS

Managing Allergic Reactions

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

Immunocompromised Individuals

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

Limitations of Vaccine Effectiveness

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

ORDERING

How to Order

HEPLISAV-B[®] is now available for ordering through the 317-vaccine order form. Ordering may occur during the quarterly cycle now in place for VFA providers

Before placing an order, assess your current hepatitis B supply for your VFA-eligible patients and plan to draw down that supply. The VFA Vaccine program expects participants to administer your current supply of hepatitis B vaccine even as you order HEPLISAV-B[®]. Any unexpired doses on hand cannot not be returned to the program and will be considered wasted.

BILLING

Billing information is for HepB-CpG that is NOT supplied by VFA. As you know, billing for VFA vaccines is not permitted.

DOCUMENTATION AND RESOURCES- HYPERLINKS

ACIP recommendations:

Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. MMWR, April 20, 2018; 67(15); 455-458.

<https://www.cdc.gov/mmwr/volumes/67/wr/mm6715a5.htm>

Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR, January 12, 2018; 67(1); 1-31.

<https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm>

Product Insert for Heplisav-B[®]

<https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm584762.pdf>

Vaccine Information Statement (VIS) for Hepatitis B vaccine

http://www.immunize.org/vis/hepatitis_b.pdf

Heplisav-B[®] (HepB-CpG) Information for Healthcare Professionals – CDC

<https://www.cdc.gov/vaccines/schedules/vacc-updates/heplisav-b.html>

Hepatitis B Fact Sheet- available soon. Please check <http://eziz.org/vfa-317/vfa-resources/>.