Approval Date: May 6, 2020

Product: HEPLISAV-B

Proper Name: Hepatitis B Vaccine (Recombinant), Adjuvanted

Manufacturer: Dynavax Technologies Corporation

Indication: 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.

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.

BLA: 125428

Regulatory Milestone:

On April 26, 2012, Dynavax submitted a BLA for HEPLISAV-B to CBER, FDA. The original PDUFA due date was February 24, 2013. A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held November 15, 2012. Committee members noted that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering the novel adjuvant contained in HEPLISAV-B. CBER issued a 55-item Complete Response (CR) letter on February 22, 2013, which contained comments on clinical safety, bioresearch monitoring, CMC, facilities, and quality control and test procedures. In the original submission of April 2012, the Indication and Usage section of proposed

labeling specified use in adults 18-70 years of age. In the resubmission of March 2016, this was revised by Dynavax to 18 years of age and older.

PDUFA Goal Date: November 9, 2017

Package Insert: Package Insert - HEPLISAV-B

Summary Basis for Regulatory Approval: November 9, 2017 Summary Basis for Regulatory Action - HEPLISAV-B

European Public Assessment Report: None

Advisory Committee:

Due to the presence of a novel adjuvant in the vaccine a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held on November 15, 2012 to discuss efficacy and safety data. At the time of the November 2012 VRBPAC, the BLA submission included two phase 3, randomized, active-controlled, immunogenicity and safety studies (DV2-HBV-10 and -16; 3778 HEPLISAV-B recipients, 1086 recipients of the licensed hepatitis B vaccine ENGERIX-B, manufactured by GSK), and seven supportive trials, three of which included immunogenicity assessments. VRBPAC members voted 13:1 that the immunogenicity data submitted in the BLA were adequate to support the effectiveness of HEPLISAV-B for the prevention of hepatitis B virus infection in adults 18-70 years of age. The Committee voted 8:5, with one abstention, that the available data were not adequate to support the safety of HEPLISAV-B in the same age group. Committee members noted that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering the novel adjuvant contained in HEPLISAV-B. A second VRBPAC meeting was held on July 28,

2017 to discuss the safety of HEPLISAV-B, with attention given to the imbalance in AMI in DV2-HBV-23. The VRBPAC members voted 12: 1 with 3 abstentions that the available data support the safety of HEPLISAV-B when administered to adults 18 years and older. Further discussions from the committee focused on the requirements of the proposed pharmacovigilance plan (PVP) to further evaluate the safety of HEPLISAV-B post-licensure. The VRBPAC members identified a number of deficiencies and limitations in the PVP proposed by Dynavax including the need to assess potential acute myocardial events in recipients of HEPLISAV-B in a timely manner, address selection bias in recruitment of subjects and the development of an event driven analysis.

NCT Numbers:

- NCT03934736
- NCT04193189
- NCT04199715
- NCT04456504
- NCT03685708
- NCT00985426
- NCT04385524
- NCT03664648
- NCT04588077
- NCT02117934

EudraCT Numbers: None

Publications:

- Jackson, S., Lentino, J., Kopp, J., Murray, L., Ellison, W., Rhee, M., Shockey, G., Akella, L., Erby, K., Heyward, W. L., Janssen, R. S., & HBV-23 Study Group (2018). Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. *Vaccine*, *36*(5), 668–674. https://doi.org/10.1016/j.vaccine.2017.12.038
- Hyer, R., McGuire, D. K., Xing, B., Jackson, S., & Janssen, R. (2018). Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults. *Vaccine*, *36*(19), 2604–2611. https://doi.org/10.1016/j.vaccine.2018.03.067