DYNAVAX

Safety Data Sheet

BRK-SDS-0009

Revision: 05

Effective Date: 22 Dec 2023

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name: **HEPLISAV-B™ [Hepatitis B Vaccine (Recombinant), Adjuvanted]**

Product Description: HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] contains Hepatitis B surface antigen (HBsAg, non-infectious, yeast-cell derived recombinant protein) and a single-stranded 22-base synthetic cytidine-phospho-guanosine phosphorothioate oligodeoxynucleotide (CpG 1018® Adjuvant, an agonist of the Toll-like Receptor 9 (TLR9) with immunostimulatory properties), in a sterile phosphate buffered saline solution. For the purpose of this SDS, HEPLISAV-B may be provided as formulated bulk material or in pre-filled syringes (PFS) for clinical and commercial applications.

Intended Use: 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. HEPLISAV-B is a regulated medicinal product, and is approved by the US FDA (Dynavax Technologies Corporation 2023b), by the European Commission (EC) (Dynavax Technologies Corporation 2023a), and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). This safety data sheet is written to provide health, safety and environmental information for people handling this formulated product in the workplace. It is not intended to provide information relevant to medicinal use of the product. In this instance patients should consult prescribing information package or insert product label or consult with pharmacist or physician.

Manufacturer:
Dynavax Technologies Corporation
2100 Powell Street, Suite 720
Emeryville, CA 94608
(510)-848-5100 *(office hours 8 :00 AM to 5 :00 PM PST)*

2. HAZARD IDENTIFICATION

Classification of the Substance: Exempt from requirements – product regulated as medicinal product (human vaccine; PFS).

Label Elements:

Signal Word: Warning

Hazard Statement(s): Health Hazards: Specific Target Organ Toxicity (Repeated or Prolonged Exposure), (Appendix A, Hazard Communication Standard, 29 CFR 1910.1200 A.9). Not classified. May cause damage to the kidneys, liver, spleen and hematopoietic system with prolonged or repeated exposure through parenteral route (Hazard Code H373).

Precautionary Statement(s): Normal precautions common to safe manufacturing practice should be followed in handling and storage. Handle in accordance with good industrial hygiene and safety practices.

Store refrigerated at temperatures from 2°C to 8°C (Storage Code P411).

Symbols:

Hazard Not Otherwise Classified: None.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance:

Ingredient/Chemical Name	CAS Number	Concentration (% weight)
Hepatitis B surface antigen (HbsAg)	None	0.004%
Cytidine-phospho-guanosine phosphorothioate oligodeoxynucleotide (CpG-ODN) CpG 1018 with 22 bases	937402-51-2	0.6%
Polysorbate 80	9005-65-6	0.01%
Phosphate buffered saline	None	Diluent (pH 6.5 to 7.5)

4. FIRST AID MEASURES

Eye Contact: Immediately irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 15 minutes. Obtain medical attention.

Skin Contact: After contact with skin, wash immediately with plenty of water. Take off all contaminated clothing and wash before reuse. Obtain medical attention if ill effects occur.

Inhalation: Remove from exposure and move to fresh air, keep warm and at rest. Obtain medical attention if ill effects occur. Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Ingestion: If swallowed, wash out mouth with water and give 200 to 300 mL of water to drink (only if person is conscious). Do NOT induce vomiting as a First-Aid measure. Obtain medical attention if ill effects occur.

Most Important Symptoms/Effects, Acute and Delayed: This material is a human vaccine and is a regulated medicinal product. In adults 18 years and older, the most frequent effects in individuals receiving HEPLISAV-B included injection-site reactions (pain, redness, swelling), malaise, headache, and fatigue. HEPLISAV-B may contain yeast protein from the manufacturing process of HBsAg which could affect yeast-sensitive individuals; anaphylaxis has been reported with other commercial recombinant hepatitis B vaccines produced in yeast. May activate the immune system and cause skin rashes and flu-like symptoms such as fever. Refer to HEPLISAV-B US prescribing information.

Toxicological Information with repeated exposure by parenteral route (See Section 11).

Indication of Immediate Medical Attention and Special Treatment Needed: Symptomatic treatment and supportive therapy as indicated. Emergency medical treatment advice varies within different countries. For further information refer to the current prescribing information for HEPLISAV-B or consult the Local National Poisons Information Services.

5. FIRE-FIGHTING MEASURES

Suitable Extinguishing Media: Not combustible (see Section 15).

Unsuitable Extinguishing Media: None known.

Special Hazards Arising From the Chemical: None known.

Special Protective Equipment and Precautions for Firefighters: A self-contained breathing apparatus and suitable protective clothing should be worn in fire conditions.

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions: Ensure suitable personal protection during removal of spillage (see Section 8). Prevent entry into drains, sewers or watercourses.

Methods and Materials for Containment and Clean-up: Collect spill with absorbent material for disposal and wash the spillage area with water. Transfer absorbent materials to a container for disposal.

7. HANDLING AND STORAGE

Precautions for Safe Handling: Avoid contact with skin and eyes. Handle in accordance with good industrial hygiene and safety practices.

Conditions for Safe Storage, Including Any Incompatibilities: Store and ship refrigerated at 2 to 8°C. DO NOT FREEZE.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Occupational Exposure Limit Values: No Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) or American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) assigned.

Occupational Health Categorization (OHC) for CpG 1018 ™ Adjuvant Statement: Category 3 of 4 (0.03 - 10 µg/m^3) in the SafeBridge occupational health categorization system (SafeBridge, 2002). This categorization is based primarily on the moderate therapeutic dose (an indicator of pharmacological potency), the spectrum and relatively moderate severity of adverse effects (e.g., immunostimulation and flu like symptoms), lack of chronic studies and limited clinical information. Consideration was given to the relatively low inhalation bioavailability of the oligonucleotide and evidence of local lung effects (Gauvreau *et al.*, 2006). However, based on available compound-specific data, a control target within a range between 1 and 10 µg/m3 should be implemented, with a containment performance target of 1 µg/m^3 being recommended for each task or operation. The OHC given is based upon an analysis of all currently available data; as such, this value may be subject to revision when new information becomes available.

Appropriate Engineering Controls: Atmospheric levels should be controlled using the principles of good occupational hygiene practice as specified in a workplace risk assessment. Prevent entry into drains, sewers, or watercourses.

Individual Protection Measures, Such as Personal Protective Equipment (PPE):

Hands: Impervious gloves to prevent skin contact and absorption.

Eye/Face: Wear chemical safety goggles or protective eyeglasses.

Skin: Laboratory coat or other appropriate protective clothing.

Respiratory Protection: As necessary, use National Institute for Occupational Safety and Health/Mine Safety and Health Administration (NIOSH/MSHA) approved respiratory protection consistent with the workplace risk assessment. Consult a qualified safety and health professional for additional guidance, as needed.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: Clear, colorless liquid

Odor: Not available.

Odor Threshold: Not available.

pH: 6.5 to 7.5

Melting Point/Freezing Point: Not available.

Initial Boiling Point and Boiling Range: Not available.

Flash Point: Not available.

Evaporation Rate: Not Available.

Flammability (Solid, Gas): Not Available.

Upper/Lower Flammability or Explosive Limits: Not Available.

Vapor Pressure: Not available.

Vapor Density: Not Available.

Relative Density: Not Available.

Solubility: Freely soluble in aqueous phosphate buffered saline at a neutral pH.

Partition Coefficient: Not Available.

Auto-ignition Temperature: Not Available.

Decomposition Temperature: Not Available.

Viscosity: Not available.

10. STABILITY AND REACTIVITY

Reactivity: No reactivity hazards known under normal (ambient) conditions.

Chemical Stability: Stable under normal (ambient) storage and handling conditions.

Possibility of Hazardous Reactions: No dangerous reaction known under normal (ambient) conditions.

Conditions to Avoid: Avoid exposure to oxidizers.

Incompatible Materials: Oxidizers.

Hazardous Decomposition Products: None known.

11. TOXICOLOGY INFORMATION

The toxicological properties of this material (CpG 1018 ± HBsAg in buffered solution) have been investigated in mice and rats and no significant toxicities were observed. HEPLISAV-B is a human vaccine.

Repeat-dose Toxicity (Species, Regimen, Route, Dose, Target Organs, Endpoint):

- Mice: 3 doses (every 2-weeks X 3); intramuscular; 0.5 mcg/dose HBsAg combined with 1, 5 or 50 mcg CpG 1018/dose (highest dose level ~ 2 mg/kg); there was no mortality in mice associated with CpG 1018 alone or in the vaccine combination [a]; hematopoietic system, spleen, liver, and injection-sites; the mouse NOAEL was not defined in the report, but there were no severe toxicities; findings related to immunostimulation; the NOAEL is presumed to be ~ 2 mg/kg.
- Rats: 4 doses (every 2-weeks X 4); intramuscular; 4 mcg HBsAg + 600 mcg 1018/dose or 20 mcg HBsAg + 3000 mcg 1018/dose (highest dose level ~ 10 mg/kg); there was no mortality in rats associated with CpG 1018 in the vaccine combination [a]; spleen, liver, lymph nodes, bone marrow, injection-sites; findings related to immunostimulation; the rat NOAEL was defined as 20 mcg HBsAg + 3000 mcg CpG 1018 (~ 10 mg/kg).

Reproductive and Developmental Toxicity (Species, Regimen, Route, Dose, Target Organs, Endpoint):

- Rats, 4 doses (prior to mating on Day 1 and 19, and on gestation Day 6 and 18); intramuscular; 2.5 mcg HBsAg + 1.5, 15, 300 or 3000 mcg CpG 1018/dose (highest dose level ~ 10 mg/kg); mortality in 5 out of 97 pregnant dams at the highest dose of CpG 1018 alone or in vaccine combination [a]; injection sites; liver, kidneys, adrenals, spleen, lymph nodes (dams only) findings related to immunostimulation; the rat NOAEL for reproductive and developmental toxicity and growth and development of the F1 generation was 3000 mcg CpG 1018 alone or in vaccine combination [a] (2.5 mcg HBsAg+ 3000 mcg CpG 1018).

NOAEL = no observed adverse effect level.
[a] CpG 1018 in the HEPLISAV-B® vaccine formulation.

Effects of Repeat-dose in Humans:

The HEPLISAV-B formulation is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus. HEPLISAV-B is a non-infectious subunit viral vaccine consisting of surface antigen of hepatitis B virus produced

in recombinant yeast cells in combination with CpG 1018 adjuvant. In studies involving adults 18 years of age or older, the most frequent effects in individuals receiving HEPLISAV-B included injection-site reactions (pain, redness, swelling), malaise, headache, and fatigue. Refer to HEPLISAV-B package insert.

Likely Routes of Exposure:

Ingestion: Not available. Health injuries are not known or expected under normal use. May be harmful if swallowed. However, ingestion is not likely to be a primary route of occupation exposure.

Inhalation: Not available. Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Skin Contact: Not available. Health injuries are not known or expected under normal use.

Eye Contact: Not available. Health injuries are not known or expected under normal use. Direct contact with eyes may cause temporary irritation.

Symptoms Related to the Physical, Chemical and Toxicological Characteristics: Parenteral exposure could generate an immune response to the protein antigen (HBsAg) resulting in systemic and local responses (e.g., antibody seroconversion, positive skin reaction). May contain yeast protein from the manufacturing process of HBsAg which could affect yeast-sensitive individuals; anaphylaxis has been reported with other commercial recombinant hepatitis B vaccines produced in yeast. May activate the immune system and cause skin rashes and flu-like symptoms such as fever. Refer to HEPLISAV-B US prescribing information.

https://www.heplisavb.com/assets/pdfs/HEPLISAV-B-Prescribing-Information.pdf

Delayed and Immediate Effects and Chronic Effects from Short- and Long-Term Exposure:

Acute Toxicity: Not available. Expected to be a low hazard for usual industrial or commercial handling by trained personnel.

Skin Corrosion/Irritation: Not available. Health injuries are not known or expected under normal use.

Serious Eye Damage/ Eye Irritation: Not available. Health injuries are not known or expected under normal use. Direct contact with eyes may cause temporary irritation.

Local Effects: Non-adverse injection site reactions (erythema, edema) observed in rats given 4 intramuscular doses 4 mcg HBsAg + 600 mcg CpG 1018/dose or 20 mcg HBsAg + 3000 mcg CpG 1018/dose. Parenteral exposure to HBsAg + CpG 1018 could generate an immune response locally (e.g., positive skin reaction; e.g., erythema and swelling in skin tissues).

Respiratory Sensitization: Not available.

Skin Sensitization: Not available.

Germ Cell Mutagenicity: Not available for HBsAg + CpG 1018 vaccine formulation. CpG 1018 adjuvant alone was negative for mutagenic and clastogenic effects in vitro and in vivo assays (i.e., bacterial reverse mutation, chromosome aberration, mouse erythrocyte micronucleus assay).

Carcinogenicity: Not available.

Reproductive Toxicity: In a multi-generation Developmental and Reproductive Toxicity (DART) study in rats there were no reproductive or developmental effects observed for CpG 1018 alone or in vaccine combination [a].

[a] CpG 1018 in the HEPLISAV-B® vaccine formulation.

Specific Target Organ Toxicity, Single Exposure: Not available.

Specific Target Organ Toxicity, Repeated Exposure: May cause damage to the kidneys, liver, spleen, and hematopoietic system with prolonged exposure through parenteral route.

Aspiration Hazard: Not available.

12. ECOLOGICAL INFORMATION

Ecotoxicity: Not available.

Persistence and Degradability: Not available.

Bio accumulative Potential: Not available.

Mobility in Soil: Not available.

Other adverse Effects: Not available.

13. DISPOSAL CONSIDERATIONS

Disposal should be in accordance with applicable U.S. Federal, State and local laws and regulations. The information presented below only applies to the material as supplied. The identification based on characteristic(s) or listing may not apply if the material has been used or otherwise contaminated. It is the responsibility of the waste generator to determine the toxicity and physical properties of the material generated to determine the proper waste identification and disposal methods in compliance with applicable regulations.

14. TRANSPORT INFORMATION

U.S. DOT (ground): Not regulated as a hazardous material for transport.

ICAO/IATA (air): Not regulated as a hazardous material for transport.

Harmonized Tariff Schedule (HTS): 3002.41.0000 - Vaccines for human medicine per Harmonized Tariff Schedule of the United States Revision (2023)

15. REGULATORY INFORMATION

U.S. Federal Regulations: Not listed on the U.S. Toxic Substances Control Act (TSCA) chemical substance inventory. This product is a drug and is exempt from TSCA regulation when manufactured, processed, or distributed in commerce for use as a drug.

SARA 301 Extremely Hazardous Substance: No

SARA 311/312 Hazardous Chemical: Chronic Health Hazard

U.S. State Regulations:

California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): This material is not known to contain any chemicals currently listed as carcinogens or reproductive toxins.

US State Right-to-Know Regulations: This medicinal product (human vaccine) is regulated by the Food and Drug administration and is therefore exempt from State Right-to-Know Regulations.

National Fire Protection Association (NFPA) Rating:

Health: 1

Fire: 0

Reactivity: 0

Special: None

EU specific information:

Other regulatory information on the substance or mixture that is not already provided in the safety data sheet: Not applicable. The mixture/substance concerns a proprietary component of medicinal products covered by EU directive 2001/83/EC.

Union safety, health and environmental provisions and any other national measures: not applicable

Chemical safety assessment: The chemical safety of this proprietary mixture/substance has not been assessed.

16. OTHER INFORMATION

Disclaimer: The information provided here is believed to be accurate and represents the best information currently available, and while it is provided in good faith, it is without warranty of any kind, expressed or implied. The information contained herein is designated only as guidance for safe handling, storage and use of the substance and is not a specification nor does it guarantee any specific properties. Only competent personnel, within a controlled environment should handle these materials. Since the information contained in this document may be applied under conditions beyond our control, we cannot accept responsibility for any loss, injury or damage by any person acting or refraining from action as a result of this information.

References

Occupational Health Categorization for CpG 1018 ™ Adjuvant (2023).

Dynavax Technologies Corporation. 2023a. HEPLISAV-B SmPC.

Dynavax Technologies Corporation, Prescribing Information. 2023b. HEPLISAV-B® United States Package Insert.

Gauvreau, GM et al. (2006) Immunostimulatory Sequences Regulate Interferon-inducible Genes but not Allergic Airway Responses. Am J Respir Crit Care Med 174: 15-20.

Harmonized Tariff Schedule of the United States Revision 5 (2023).

SafeBridge Consultants, Inc. (2002) Occupational health toxicity/potency categorization and handling practices. 5th Revision.

REVISION HISTORY

Rev	Summary of Changes
05	Section 1: Added trade mark symbol to CpG 1018 ™ Adjuvant; Manufacturer address updated to new location. Section 3: Added CAS number for CpG 1018. Section 8: Added SafeBridge OHC statement for CpG 1018™ Adjuvant. Section 11: Updated toxicological information to be specific to CpG 1018 ± HBsAg in buffered solution. Section 14: Added HTS code. Section 15: Added EU specific information. Section 16: Added the relevant citations.
04	Biennial review. Section 1: Clarification this is a regulated medicinal product; revised address to current company address; indicated that for the purpose of this SDS, HEPLISAV-B may be provided as formulated bulk material or in pre-filled syringes (PFS). Section 2: Classification updated based on data available and for consistency with GHS guidance; clarified on Exempt from requirements product regulated as medicinal product (human vaccine) when supplied in PFS. Throughout document update name for adjuvant as CpG 1018. Section 4: edits for clarity, and updated most important symptoms in humans and referenced the package insert for HEPLISAV-B. Section 6 and 7: Edits for clarity on clean-up methods and safe handling. Section 8: Added definition to acronyms. Section 11: Revised to provide further clarification on determination of NOAEL for repeat-dose toxicity studies and DART study; likely routes of exposure and delayed and immediate effects under normal use. Section 15: Added the Right-to-Know regulation exemption for FDA regulated medicinal products; Section 16: Added disclaimer statement.