# Vaccines and Related Biological Products Advisory Committee Meeting
# July 28, 2017

# Hepatitis B Vaccine (Recombinant), Adjuvanted (HBV Surface Antigen (HBsAg) Protein with CpG 1018 adjuvant) (HEPLISAV-B)

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# Currently Licensed Hepatitis B Vaccines

Approved for immunization against infection caused by all known subtypes of hepatitis B virus (HBV)

- **Engerix-B**
  - Manufactured by GlaxoSmithKline
  - Licensed in 1989
  - Recombinant HBV surface antigen produced from yeast cells
  - Adsorbed onto aluminum hydroxide

- **Recombivax HB**
  - Manufactured by Merck
  - Licensed in 1986
  - Recombinant HBV surface antigen produced from yeast cells
  - Adsorbed onto aluminum hydroxyphosphate sulfate

# Dosage and Administration

| Group | Dose | Schedule |
|---|---|---|
| • **Engerix-B (intramuscular administration)** | | |
| Persons from birth through 19 years of age | 0.5 mL<br>10 mcg rHBsAg | 0, 1, and 6 months |
| Persons 20 years of age and older | 1.0 mL<br>20 mcg rHBsAg | 0, 1, and 6 months |
| Adults on hemodialysis | 2.0 mL<br>40 mcg rHBsAg | 0, 1, 2, and 6 months |
| • **Recombivax HB (intramuscular administration)** | | |
| Persons from birth through 19 years of age | 0.5 mL<br>5 mcg rHBsAg | 0, 1, and 6 months |
| Persons 20 years of age and older | 1.0 mL<br>10 mcg rHBsAg | 0, 1, and 6 months |
| Adults on hemodialysis | 1.0 mL<br>40 mcg rHBsAg | 0, 1, and 6 months |

# Currently Licensed Combination Hepatitis B Vaccines

- **Manufactured by GlaxoSmithKline**

  Twinrix (hepatitis B and hepatitis A) (Persons 18 and older)

  Pediarix (diphtheria, tetanus, pertussis, hepatitis B, and polio) (Children 6 weeks through 6 years)

Hepatitis B component is the same as that contained in the monovalent Engerix-B

# Alternate Adult Dosing Schedules (Intramuscular Administration)

These may be used for specific populations e.g. persons who have or might have been recently exposed to the virus or for travelers to high-risk areas

| Vaccine | Dose | Schedule |
|---|---|---|
| • **Engerix-B** | 1.0 mL<br>20 mcg rHBsAg | 0, 1, 2 and 12 months |
| • **Twinrix** | 1.0 mL<br>20 mcg rHBsAg | 0, 7, 21-30 days and 12 months |

# Heplisav-B: Composition, Proposed Indication & Usage and Dosing Regimen

- Recombinant HBsAg produced from yeast cells
- Combined with CpG 1018 adjuvant (a cytosine phosphoguanosine oligodeoxynucleotide, CpG-ODN)
- This adjuvant is not contained in any currently licensed US vaccines
- Immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older
- 2 doses (0.5 mL each (20 mcg rHBsAg, 3000 mcg CpG 1018 adjuvant)) given on a 0 and 1 month schedule

# What are CpG-ODNs?

- Synthetic DNA molecules, oligodeoxynucleotides (ODNs) with phosphorothioate backbone, containing unmethylated cytosine phosphoguanosine (CpG) motifs
- CpG motifs occur at higher frequency in bacterial and viral DNA than vertebrate DNA
- CpG ODNs have different immune enhancement effects in different species
- CpG-ODN adjuvants have been found to trigger B cell activation and preferentially induce a Th1-like over a Th2-like CD4+ T helper immune response

# Th1 versus Th2 responses

- Th1 responses: characterized by the production of proinflammatory cytokines, such as IFN-γ and TNF-α, which leads to cell mediated immunity and an IgG2a isotype antibody response
- Th2 responses: characterized by interleukin-4 production which leads to a humoral immune response dominated by IgG1 and IgE antibodies

# CpG Mode of Action

- CpG ODNs are toll-like receptor (TLR) agonists
- TLRs are proteins on innate (“first-responder”) immune cells (monocytes and dendritic cells) that recognize molecules from invading microbes.
- TLRs recognize molecules shared by many different microbes, but these are distinguishable from host molecules.
- CpG ODNs function via TLR-9
- TLR-9 is expressed mainly on plasmacytoid dendritic cells and memory B cells

# CpG 1018 Adjuvant Proposed Mechanism of Action

CpG 1018 adjuvant:

- Stimulates TLR-9 in pDCs that have taken up rHBsAg
- Converts pDCs into activated DCs that present HBsAg epitopes to the immune system (CD4+ cells)
- Promotes differentiation of CD4+ cells that leads to antibody secretion by HBsAg-specific B cells

# Use of Anti-HBs to Predict Protection

- Early hepatitis B vaccine trials used prevention of HBV infection as the clinical endpoint
- Data from early HBV vaccine studies (using Heptavax, a plasma-derived HBsAg vaccine) showed antibody levels to HBsAg (anti-HBs) of > 10 mIU/mL correlated with protection (*Szmuness et al. 1981 Hepatology Vol 1 No.5 p 377*)
- Post-vaccination an anti-HBs level ≥ 10 mIU/mL is accepted as conferring protection
- This type of correlate of protection can be used as an indicator of clinical effectiveness in a traditional route for licensure.

# Levels of Anti-HBs and Protection

- Higher anti-HBs levels post vaccination have been associated with greater persistence of antibody in vaccinees
- However, decreased titers to <10 mIU/mL or complete disappearance of anti-HBs does not necessarily mean a loss of protection
- Immunological memory is maintained in vaccinees despite declines in anti-HBs levels
- Although anti-HBs may become undetectable in a substantial proportion of vaccine responders breakthrough infections are rare and mainly asymptomatic (*Mast et al. MMWR 2006*)

# Duration of Protection

- Data from prolonged follow-up studies using plasma-derived hepatitis B vaccine (*Bruce et al. JID 2016*) :
  - ≥ 94% of primary responders had evidence of continued protection after 30 years
  - no chronic infections were documented in vaccine recipients

- Recombinant HBsAg vaccines have also been shown to confer long-term protection and persistent immunological memory for at least 18 years (*Romanò et al. Hum Vaccin Immunother 2017*)

# Heplisav-B Clinical Studies

- Seroprotection rate (SPR) was used as the endpoint to support effectiveness
- SPR: the proportion of individuals achieving an anti-HBs concentration of ≥ 10 mIU/mL after vaccination
- All Phase 3 trials compared antibody responses following injection with either 2 doses of Heplisav-B or 3 doses of Engerix-B

# Heplisav-B Regulatory History

- The initial BLA was submitted in April 2012
- This included data from two Phase 3 trials (DV2-HBV-10 and DV2-HBV-16)
- A VRBPAC Meeting was held in November 2012 to discuss the immunogenicity and safety of the vaccine in adults 18 through 70 years of age
- The committee members voted 13:1 that the immunogenicity data were adequate to support effectiveness
- The committee members voted 5:8, with one abstention, that the available data were adequate to support safety
  - In view of the novel adjuvant, members recommended a larger pre-licensure safety database

# Heplisav-B Regulatory History

- Following the 2012 VRBPAC meeting, the Applicant conducted an additional Phase 3 safety and immunogenicity study (DV2-HBV-23)
- CBER considers that effectiveness was established in the two previous Phase 3 studies therefore this VRBPAC discussion will focus on the safety of Heplisav-B

# Questions to the Committee

1. Do the available data support the safety of Heplisav-B when administered to adults 18 years and older?

**Please vote Yes or No**

If yes,

2. Please comment on the proposed pharmacovigilance plan.

# Questions to the Committee

If no,

3. Do the presented data support usage in a more specific subpopulation?

**Please vote Yes or No**

4. What additional studies (pre- and post-licensure) are needed to further evaluate the safety of Heplisav-B in the general adult population and/or in specific subpopulations?