Summary Basis for Regulatory Action

Date: September 11, 2015

From: CAPT. Katherine Berkhousen, RN, Chair of the Review Committee

BLA/STN#: 103239/5486

Applicant Name: GlaxoSmithKline Biologicals

Date of Submission: November 20, 2014

PDUFA Goal Date: September 20, 2015

Proprietary Name/Established Name: Hepatitis B Vaccine (Recombinant); Engerix-B ®

Indication: Engerix-B is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☐ I concur with the summary review.
☐ I concur with the summary review and include a separate review to add further analysis.
☐ I do not concur with the summary review and include a separate review.

Material Reviewed/Consulted Reviewer Name – Document(s) Date

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1. Introduction

Engerix-B® (Hepatitis B Vaccine (Recombinant) is a hepatitis B virus (HBV) vaccine developed by GlaxoSmithKline (GSK) and is indicated for immunization against infection caused by all known subtypes of hepatitis B virus. Engerix-B can be administered to all age groups. In children (birth through 19 years of age), the vaccine is administered as a series of 3 doses of 0.5 ml intra-muscular injections given on a 0-, 1-, and 6-month schedule. In adults (20 years of age and older), the vaccine is administered as a series of 3 doses of 1.0 ml also given on a 0-, 1-, and 6-month schedule.

Engerix-B is a recombinant protein vaccine. The adult, 1.0 mL dose consists of 20 µg of noninfectious hepatitis B surface antigen (HBsAg) adsorbed on 0.5 mg aluminum as aluminum hydroxide. It is supplied as a suspension for intramuscular injection in vials or prefilled syringes. Engerix-B has been approved in the United States since August 1989. Adult and Pediatric presentations of Engerix-B vaccine are currently approved in over 110 countries. GSK estimates that doses of the vaccine have been distributed to date.

In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended to vaccinate all adults with diabetes against hepatitis B virus. However, the effect of type 2 diabetes mellitus on the immune response to hepatitis B vaccine had not been well defined. As a result, GSK initiated study HBV-323 “A phase IV, open-label, multicenter study to assess the immunogenicity and safety of GSK Biologicals’ hepatitis B vaccine, Engerix-B administered at 0, 1, and 6 months in adults with or without type 2 diabetes mellitus.” This was the first large prospective controlled study to assess the safety and immunogenicity of Engerix-B in diabetics compared with those not diagnosed with type 2 diabetes mellitus.

The applicant, GlaxoSmithKline (GSK) Biologicals, has submitted this efficacy supplement to the BLA, with the intent of adding language describing the HBV-323 study and results to the Engerix-B, US Prescribing Information (PI).

2. Background

HBV infection causes both acute and chronic disease and is a serious public health problem. Manifestations of acute infection can range from an asymptomatic hepatitis to fulminant liver failure. Chronic infection can cause a chronic carrier state or progress to hepatic cirrhosis, liver failure, and death.

In 1991, in the US, the ACIP recommended universal HBV immunization of infants. From 1990 to 2005, the incidence of acute HBV infection in the US declined 78%. The greatest decrease occurred among infants and adolescents, coincident with the increase in hepatitis B vaccination coverage. Despite a robust public health effort, unvaccinated US adults at high risk for hepatitis B virus transmission continue to become infected.

The prevalence of diabetes mellitus is also of great public health concern and is increasing in the US and worldwide. The risk of acquiring HBV infection may be higher for persons with diabetes. Because of this, in October 2011, the ACIP recommended hepatitis B vaccination
for unvaccinated diabetic adults ages 19 – 59 years and vaccination at the discretion of a physician for unvaccinated diabetic adults, 60 years of age and older.

In September 2011, GSK submitted a Type C Meeting Request to discuss GSK’s plan to conduct an open-label clinical study to assess the immunogenicity and safety of Engerix-B in adults with type 2 diabetes mellitus and to submit the results of that study in a supplement to the Engerix BLA. Because older age and higher body mass index (BMI) are two factors that may be associated with lower immune responses to HBV vaccination, CBER recommended that GSK consider including a non-diabetic control group and stratify the entire study population into eight groups based upon age and weight. GSK agreed and redesigned the study to include a non-diabetic control group. Both study groups were stratified by age and BMI.

3. **Chemistry Manufacturing and Controls (CMC)**

No manufacturing changes or information were submitted for this supplement as the clinical study was performed with a licensed product.

There are no ongoing or impending investigations or compliance actions with respect to GSK’s facilities or products.

4. **Nonclinical Pharmacology/Toxicology**

No new Pharmacology/toxicology data were submitted as part of this supplement.

5. **Clinical Pharmacology**

No clinical pharmacology or pharmacokinetic study information was submitted in this supplement.

6. **Clinical/Statistical**

The safety and immunogenicity of Engerix-B were evaluated in Study HBV-323, a phase 4, open-label, multicenter study to assess the immunogenicity and safety of GSK Biological’s hepatitis B vaccine, Engerix-B in adults with diabetes diagnosed within the previous five years and in a parallel group of adults without diabetes. The study was conducted at multiple centers in Australia, Canada, New Zealand, and the US. Subjects 20 years of age and above were vaccinated with Engerix-B at 0, 1 and 6 months intramuscularly. Anti-hepatitis B surface (HBs) antibody was assessed at screening and at one month following the third vaccination. The primary objective was to assess the immunogenicity of Engerix-B in type 2 diabetic and non-diabetic control subjects, based on seroprotection rates defined as the presence of anti-HBs antibody concentrations ≥10 mIU/mL, one month after the third vaccine dose. The immune response to Engerix-B by geometric mean concentrations (GMCs), and the safety and reactogenicity of the vaccine were evaluated as secondary endpoints.

Because older age and higher body mass index BMI are two factors that may be associated with lower immune responses to HBV vaccination, all study subjects were stratified by age (four categories) and BMI (two categories). A total of 674 subjects were enrolled in the total
vaccinated cohort, 416 diabetic subjects and 258 controls, who received at least one immunization with Engerix-B. Despite best efforts to enroll and extending the recruitment period, investigators had difficulty enrolling subjects with type 2 diabetes in three of the eight strata (20-39, BMI< 30, 20-39, BMI> 30, and 40-49 BMI <30). Due to incomplete enrollment in these three strata, GSK proposed a matching and elimination procedure of subjects in the control group to preserve the 2:1 enrollment ratio. This algorithm was reviewed and considered acceptable by CBER. Sixteen percent of the total vaccinated cohort was not included in the per protocol immunogenicity assessment, partially as a result of this enrollment algorithm.

The per-protocol immunogenicity cohort of 567 subjects, included 378 diabetic subjects and 189 matched control subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects, the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m² (range: 17 to 64 kg/m²); 88% were white, 3% were American Indian or Alaskan Native, 3% were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino. Racial and ethnic minorities were not well represented in this study. Fifty-one percent of all subjects were male. While the overall study population was balanced with respect to the proportion of males and females, the proportion of females in the diabetic and control groups was approximately 44% and 59%, respectively. A trend suggesting greater immunogenicity in females was observed.

Of the 567 subjects analyzed in the per protocol immunogenicity cohort, similar proportions of diabetic and non-diabetic subjects achieved seroprotection. The associated 95% confidence intervals (CIs) are presented for descriptive purpose only, and are not intended for inference. The proportions achieving seroprotection were: 75% (95% confidence interval (CI) 71, 80%) of subjects with diabetes and 82% (95% CI 76, 87%) of control subjects. The seroprotection rates in those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in these same age-groups were 100%, 86%, 82% and 70%, respectively. Subjects with diabetes and a BMI of at least 30 kg/m² had a seroprotection rate of 72% (95% CI, 66,78) compared with 80%(95% CI, 72, 86) in diabetic subjects with lower BMIs. In control subjects, seroprotection rates were 82% (95% CI, 73,88) in those with a BMI of at least 30 kg/m² and 83% (95% CI, 72, 90) in those with lower BMIs.

The anti-HBs antibody GMC at one month post-third vaccination, in subjects with diabetes was 148 mIU/mL (95% CI, 110, 198) and in control subjects was 384 mIU/mL (95% CI, 255, 580), well above the anti-HBs antibody level ≥ 10 mIU/mL, the threshold that confers protection against infection with hepatitis B virus. The clinical significance of this difference in GMCs between study groups is likely minimal.

All subjects who received at least one study vaccine the total vaccinated cohort, were included in the safety analysis. Solicited local and systemic reactogenicity were similar between the diabetes and control groups. Injection site pain (reported by 41% of subjects) and fatigue (28%) were the most commonly reported solicited adverse events across the entire study population of Study HBV-323. The incidence of subjects reporting injection site pain and fatigue in this study appears higher than is reported in the currently circulating (12/2013)
package insert (22% and 14% respectively). It appears that the rate in the 12/2013 version of the PI may represent average frequency of injection site pain and fatigue reported per dose. In Study HBV-323, GSK performed an analysis of general solicited AE’s reported by dose. The average incidence of injection site pain and fatigue per dose is similar in both the diabetes and control groups. Therefore the HBV-323 per dose rates are similar to that reported in the 12/2013 version of the PI. Unsolicited adverse events and reactions were reported at the same rate in the Diabetes/Control study groups. There were 192/416 (46%) subjects in the Diabetes Group and 11/258 (43%) in the Control Group who experienced a unsolicited AE during the seven-month study period. Subjects with diabetes had a two-fold higher rate of serious adverse events (SAE) during the 7-month study period (Diabetes Group: 16/416 (3.8%); Control Group: 4/257 (1.6%). A total of 33 SAEs were reported by 20 subjects during the 7 months. No events were considered by the study investigator and the CBER clinical reviewer to be related to the study vaccine. The safety of Engerix-B characterized in this study is acceptable.

The benefit of the vaccine is based on the ability of the vaccine to induce serum antibody responses as measured by anti-HBsAg (b) (4) assay. The methodology, performance and quality of the anti-HBsAg assay used for the clinical study in this application was supported with detailed methodologies and validation reports. The assay was found to perform adequately for its intended use.

b) Pediatrics

This supplement does not change the licensed indication, dose, regimen, formulation, or route of administration. An assessment as per the requirements of PREA did not apply to this submission.

c) Other Special Populations

No data have been collected on the use of Engerix-B in diabetic children, diabetic pregnant women, diabetic lactating women, or diabetic immunocompromised patients.

d) Bioresearch Monitoring Review

Protocol HBV-323 was conducted in twenty one centers in four countries (Australia, Canada, New Zealand, and the United States). Ten sites located in the US enrolled 48% of the subjects in the total vaccinated cohort. The three clinical sites selected for Bioresearch Monitoring inspection represented 14% of the total subjects vaccinated (97 out of 416). The clinical sites were selected based on subject enrollment, previous inspectional history, and geographic location. No significant inspectional findings were identified. No sponsor findings were identified. The Bioresearch Monitoring inspection of three clinical investigators did not reveal substantive problems that impact the data submitted in the application.
7. **Advisory Committee Meeting**

The review team and CBER management determined that the discussion of the review of Engerix-B by the Vaccines and Related Biological Products Advisory Committee was not necessary because of CBER’s experience with the currently licensed Engerix-B. Our review of the supplement did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

8. **Other Relevant Regulatory Issues**

There were no other relevant regulatory issues raised during the review of this supplement.

9. **Labeling**

The main changes to the package insert were as follows: Section 6.1 Clinical Trial Experience was updated to incorporate safety data; Section 7.2, Interference with Laboratory Tests, was added to remind providers that hepatitis B surface antigen derived from a hepatitis B vaccine has been transiently detected in blood; Section 14.2, Efficacy and Immunogenicity in Specific Populations was revised to include efficacy data from Study HBV-323.

10. **Recommendations and Risk/ Benefit Assessment**

   a) **Recommended Regulatory Action**

   Following the review of all submitted supportive data the review committee recommends approving this BLA supplement.

   b) **Risk/ Benefit Assessment**

   HBV infection causes both acute and chronic disease and is a serious public health problem with acute infections ranging from an asymptomatic hepatitis to fulminant liver failure. The risk of acquiring HBV infection appears to be higher in diabetics.

   Study HBV-323 was the first large prospective controlled study to assess the safety and immunogenicity of Engerix-B in type 2 diabetics compared to non-diabetics. The most substantial risks of vaccination with Engerix-B in Study HBV-323 were associated with local and systemic reactogenicity which was similar between the diabetic and non-diabetic control groups.

   Engerix-B was approved in the United States in August 1989 and since then has been approved in over 110 countries. An estimated doses have been distributed to date. The well-documented safety profile coupled with the recent data from Study HBV-323 indicates that the risk of vaccination with Engerix-B is likely to be minor.
The review team has determined that no new concerns were identified in Study HBV-323. The risk-benefit assessment has not changed with review of these additional data and remains positive.

c) Recommendation for Postmarketing Risk Management Activities

The review committee does not recommend any postmarketing risk management activities.

d) Recommendation for Postmarketing Activities

The review committee does not recommend any postmarketing commitments or requirements.