

Summary Basis for Regulatory Action

Date: April 27, 2018

From: Joseph J. Temenak, Ph.D., Chair of the Review Committee

BLA/STN: 125347/309

Applicant Name: GlaxoSmithKline Biologicals

Date of Submission: June 30, 2017

PDUFA Goal Date: April 30, 2018

Proprietary Name/ Established Name: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)/Hiberix®

Additional Indication Proposed Under this Supplement: Hiberix® is indicated for the prevention of invasive disease caused by *Haemophilus influenzae* type b in children 6 weeks through 4 years of age. This sBLA intends to include clinical data from the booster phase of Study Hib-097, a comparative safety and immunogenicity study of primary and booster immunization with Hiberix relative to U.S. licensed control vaccines. These data verify and describe the clinical benefit of Hiberix administered as a booster dose for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b and thus, fulfill the accelerated approval required study #1 made under 21 CFR 601.41 (under the approval of BLA STN 125347/0 on August 19, 2009).

Recommended Action: Approval

Signatory Authority's Action: Approval

Office's Signatory Authority: Wellington Sun, M.D., Director, DVRPA

X 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.

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
Clinical Review	Tina Mongeau, M.D. – April 27, 2018
Statistical Review (Clinical)	Ruoxuan Xiang, Ph.D. – February 2, 2018
Statistical Review (Serology Assays)	Rong Fu, Ph.D. – February 22, 2018
Epidemiology Review	Faith Barash, M.D., M.P.H. – April 06, 2018
CMC/Product Review (Hep B Serology Assays)	Marian Major, Ph.D. – January 17, 2018
CMC/Product Review (Poliovirus Serology Assays)	Majid Laassri, Ph.D. – March 09, 2018
CMC/Product Review (Pertussis Serology Assays)	Rebecca Brady, Ph.D. – January 22, 2018
CMC/Product Review (Diphtheria and Tetanus Serology Assays)	Chris Mocca, M.S. – January 4, 2018
CMC/Product Review (Hib/Strep PS Serology Assays)	Mustafa Akkoyunlu, M.D., Ph.D. – January 09, 2018
Bioresearch Monitoring Review	Bhanu Kannan, BS – September 19, 2017
Advertising/Promotion Labeling	Sonny Saini, Pharm.D., M.B.A. – March 16, 2018

1. INTRODUCTION

Hiberix® [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] was approved under the Accelerated Approval regulations (21 CFR 601 Subpart E) in 2009 for active immunization as a booster dose in children 15 months through 4 years of age (prior to fifth birthday) for the prevention of invasive disease caused by *Haemophilus influenzae* type b. On January 14, 2016, an efficacy supplement to the Biologics License Application (sBLA) for Hiberix was approved to include safety and effectiveness data to describe the clinical benefit of Hiberix administered as the primary series in children 6 weeks to 14 months of age for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b to satisfy the PREA requirement. On June 30, 2017, GlaxoSmithKline Biologicals (GSK) submitted the current supplement to verify and support licensure of Hiberix for use in children 15 months through 4 years of age (prior to fifth birthday) and to transition the booster dose from accelerated to traditional approval.

With this sBLA, GSK is seeking to fulfill an accelerated approval post marketing requirement listed in the August 19, 2009 letter approving their Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Hiberix. GSK is also seeking to update the Hiberix Package Insert (PI) with immunogenicity and safety data from the booster epoch of confirmatory Study Hib-097.

2. BACKGROUND

GSK's Hiberix is a lyophilized vaccine containing 10 µg purified capsular polyribosylribitol phosphate (PRP) of Hib, covalently bound to Tetanus Toxoid (TT), per 0.5 mL dose. Since the initial launch in Germany in 1996, Hiberix has been licensed in

99 countries as a stand-alone vaccine and in over 100 countries when combined contemporaneously with other vaccines.

Hiberix was licensed in the US on August 19, 2009 (under STN 125347/0), for use as a booster dose in children 15 months to 4 years of age (prior to fifth birthday) for the prevention of invasive disease caused by *Haemophilus influenzae type b* (Hib) under the Accelerated Approval Regulations (21 CFR 601 Subpart E) to address the shortage of Hib vaccine in the US at that time.

To satisfy the requirement under accelerated approval of Hiberix for booster immunization, GSK conducted an adequate and well-controlled study (study Hib-097) to verify and describe the clinical benefit. CBER requested the submission of two separate efficacy supplements as follows: 1) An efficacy supplement to include the data for the primary series in children 6 weeks to 14 months of age to satisfy the PREA requirement and 2) An efficacy supplement to include the data for the booster vaccine dose in children 15 months to 4 years of age to confirm the clinical benefit of Hiberix in accordance with the requirements of accelerated approval of biological products regulations (21. CFR 601 40-46).

GSK submitted the first efficacy supplement (STN 125347/231, Primary series/PREA) on March 16, 2015, which was approved January 14, 2016. In the current efficacy supplement, GSK submitted revised labeling (PI) and the supporting clinical and safety data from the booster phase of the single trial Hib-097 describing the 'confirmatory' study to fulfill the Accelerated Approval post-marketing requirement.

3. CHEMISTRY, MANUFACTURING and CONTROL (CMC) AND CLINICAL SEROLOGICAL ASSAY INFORMATION

Hiberix product formulation (per 0.5 mL dose) is as follows: Active ingredient: 10 ug purified capsular polyribosylribitol phosphate (PRP) of Hib conjugated to ~25 ug TT (tetanus toxoid). The excipient lactose (12.6 mg per dose) is used as a stabilizer. GSK confirmed that no changes were implemented for the manufacturing of the clinical lots used in study Hib-097 compared to the manufacturing process described in the BLA.

Documentation of assay performance was provided for measurement of the immune responses to Hib (PRP) and to antigens contained in other vaccines administered concomitantly. For the (b) (4) used to measure antibodies to PRP, diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN) and pneumococcal polysaccharides, documentation included validation reports, SOPs, assay stability data and clinical data line listings. No assay performance issues or aberrant assay data were noted at the time of initial testing upon completion of Study Hib-097 (primary series portion) in November 2012. GSK has since begun a revalidation program, and is working in close cooperation with CBER to update and/or modernize their current assays. Overall, the assays are considered adequate for their intended use in study Hib-097 for the following reasons: 1) the lack of any data that would indicate that the assays were not performing adequately, 2) the absence of any indication that the assays are unstable, 3) the absence of any data in the study that are unusual or anomalous, and 4) the internally controlled design of the study. The poliovirus neutralization assay was validated in 1998, and is

performed per the WHO guidelines. GSK provided additional information to demonstrate assay performance stability between 2002 and 2013, and CBER concluded that the poliovirus neutralization assay is acceptable for determining poliovirus sero-responses in Study Hib-097.

The assay for quantitation of antibodies to hepatitis B surface antigen (HBs, in-house (b) (4)) was validated in 2006. In 2012, this in-house assay was found to have a specificity issue characterized by overestimation of antibody concentrations in the low range (b) (4). The investigations and associated data were submitted under IND 2846, Amendment 183 (Engerix-B) on December 20, 2013. The investigation indicated that the results of previous clinical trials (to include the Hib-097 study) were not impacted by the specificity issue with the anti-HBs (b) (4). The method validation report (b) (4) - MVR- 03 was submitted to the current supplement. The reviewer determined that the assay was acceptable for assessing anti-HBs responses in serum samples.

The supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (a). The FDA concluded that this request is justified as this action will not increase the use of the active moiety and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Given the extent of human experience with Hiberix, nonclinical data were not required and no new nonclinical data was submitted to support this sBLA.

5. CLINICAL PHARMACOLOGY/PHARMACOVIGILANCE

GSK did not submit a new pharmacovigilance plan in the current supplement (125347/309). The pharmacovigilance plan from 2015 was reviewed under the previous efficacy supplement (STN 125347/231) to include the results from study Hib-097, and was found to be adequate. No new safety concerns were identified in the submitted data, and the pharmacovigilance plan did not need updating. Post marketing adverse experiences will be reported to CBER in accordance with 21 CFR 600.80, and distribution reports provided to CBER in accordance with 21 CFR 600.81. No safety PMR or REMS is required.

6. CLINICAL/ STATISTICAL

The booster dose epoch of Study Hib-097 was initiated on 12-July-2011 and completed on 17-July-2013 and was conducted at 67 sites in the United States under US IND 14151. It was a phase 3, randomized, multicenter study and double-blinded for the immunogenicity and consistency evaluation of 3 lots of Hiberix, single-blinded and controlled for the evaluation of the safety and immunogenicity of Hiberix compared to ActHIB, a monovalent Hib vaccine [Sanofi Pasteur, Inc.] and open-label for the comparison of the immunogenicity of Hiberix with Pentacel, a combination DTPa-IPV-HIB vaccine [Sanofi Pasteur, Inc.]. The study vaccines were administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended pediatric vaccines co-administered at separate sites.

For the booster vaccination phase, the primary objective assessing non-inferiority of *Hiberix* to *ActHIB* was the percentage of subjects with post-booster anti-PRP antibody concentrations ≥ 1.0 $\mu\text{g}/\text{mL}$ within a 10% margin.

Secondary objectives (prior to the booster vaccination) included Anti-PRP GMCs and concentrations ≥ 0.15 $\mu\text{g}/\text{mL}$, ≥ 1.0 $\mu\text{g}/\text{mL}$; Anti-HBs GMCs and concentrations ≥ 10.0 mIU/mL (seroprotection) and concentrations ≥ 6.2 mIU/mL (seropositivity); Anti-poliovirus types 1, 2, and 3 GMTs and titers ≥ 8 (seroprotection); Anti-D GMCs and concentrations ≥ 0.1 IU/mL (seroprotection) and ≥ 1.0 IU/mL; Anti-T GMCs and concentrations ≥ 0.1 IU/mL (seroprotection) and ≥ 1.0 IU/mL; Anti-PT GMCs and concentrations ≥ 5 EL.U/mL (seropositivity); Anti-FHA GMCs and concentrations ≥ 5 EL.U/mL (seropositivity); and Anti-PRN GMCs and concentrations ≥ 5 EL.U/mL (seropositivity). Also, the additional secondary objectives tested one month after the booster dose, were as follows: Anti-PRP GMCs and concentrations ≥ 0.15 $\mu\text{g}/\text{mL}$, ≥ 1.0 $\mu\text{g}/\text{mL}$; Anti-D GMCs and concentrations ≥ 0.1 IU/mL (seroprotection) and ≥ 1.0 IU/mL; Anti-T GMCs and concentrations ≥ 0.1 IU/mL (seroprotection) and ≥ 1.0 IU/mL; Anti-PT GMCs and concentrations ≥ 5 EL.U/mL (seropositivity); Anti-FHA GMCs and concentrations ≥ 5 EL.U/mL (seropositivity); and Anti-PRN GMCs and concentrations ≥ 5 EL.U/mL (seropositivity).

Study Hib-097 was a phase 3, randomized, active-controlled, 3-arm, multicenter study conducted in the U.S. From a clinical perspective, the primary objective for the booster epoch could be assessed even though the co-primary objectives for the primary epoch did not strictly meet statistical criteria for lot consistency and non-inferiority (measured by the percentage of subjects with PRP antibody concentration ≥ 1.0 $\mu\text{g}/\text{mL}$) of *Hiberix* to *ActHIB* after the 3rd Hib dose. Supportive immunogenicity data indicated that, after primary vaccination with any of the *Hiberix* vaccine lots, the percentage of subjects with PRP antibody levels ≥ 1.0 $\mu\text{g}/\text{mL}$ prior to the booster dose was similar to the percentage seen in subject who received *ActHIB* as their primary series. The data suggest that persistence of PRP antibodies following *Hiberix* vaccination was likely to stay above the level considered protective until the booster immunization. Thus, prior to the booster dose, *Hiberix* was likely to provide similar protection against invasive Hib disease compared to a licensed Hib vaccine. Therefore, from a clinical perspective, demonstration of immunological non-inferiority following the booster dose is acceptable to support the booster indication for *Hiberix*.

The primary objective of the booster vaccination phase of the study (the subject of this sBLA) was to demonstrate the non-inferiority of a booster dose of *Hiberix* (co-administered with *Infanrix* in subjects 15-18 months of age who received 3 primary doses of *Hiberix*) to a booster dose of *ActHIB* (co-administered with *Infanrix* in subjects 15-18 months of age who received 3 primary doses of *ActHIB*), in terms of immune response to PRP. The pre-specified primary endpoint was defined as an anti-PRP antibody concentration of 1.0 $\mu\text{g}/\text{mL}$ or greater one month after the *Hiberix* booster vaccination (dose 4 at 15-18 months of age). The study successfully demonstrated that a booster dose of *Hiberix* co-administered with *Infanrix* in subjects 15-18 months of age (who received 3 primary vaccine doses of *Hiberix*) is non-inferior to a booster dose of *ActHIB* co-administered with *Infanrix* in subjects 15-18 months of age who received 3

primary vaccine doses of ActHIB. The lower limit of the 97.5% CI on the difference in the proportion of subjects with anti-PRP antibody concentration ≥ 1.0 $\mu\text{g}/\text{mL}$ by (b) (4) at 1 month after the booster vaccination was greater than the pre-specified -10% non-inferiority criterion (-1.2%). Subjects who received a booster dose of Hiberix concomitantly with Infanrix at 15-18 months of age had no evidence for reduced antibody responses to pertussis antigens (PT, FHA and PRN), diphtheria toxoid, and tetanus toxoid relative to responses in control subjects administered ActHIB concomitantly with Infanrix at 15-18 months of age. The safety data following the booster dose of Hiberix are generally consistent with the safety profile of Hiberix currently described in the package insert.

Anti-PRP persistence and response:

The percentages of subjects with anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g}/\text{mL}$ and ≥ 1.0 $\mu\text{g}/\text{mL}$ and GMCs by group before and one month after booster vaccination are as follows: 1) Prior to the booster vaccination, Anti-PRP antibody concentration ≥ 0.15 $\mu\text{g}/\text{mL}$ was seen in 75.1% of subjects in the Hiberix group, 76.1% of subjects in the ActHIB group, and 66.3% of subjects in the Pentacel group, 2) One month after booster vaccination, at least 99.6% subjects had anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g}/\text{mL}$ in the Hiberix, ActHIB, and Pentacel groups, and 3) The percentages of subjects with anti-PRP antibody concentrations ≥ 1.0 $\mu\text{g}/\text{mL}$ were 99.1%, 97.9%, and 98.9% in the Hiberix, ActHIB, and Pentacel groups, respectively.

Anti-D and anti-T persistence and response including booster response:

The percentages of subjects with anti-D, anti-T antibody concentrations ≥ 0.1 IU/mL, ≥ 1.0 IU/mL, and GMCs by group before and one month after booster vaccination are as follows: 1) Prior to the booster vaccination, at least 96.5% of subjects had persisting seroprotective antibodies against diphtheria and at least 86.7% of subjects had persisting seroprotective antibodies against tetanus in all three groups, 2) One month after the booster vaccination, all subjects had anti-diphtheria and anti-tetanus seroprotective concentrations (≥ 0.1 IU/mL), 3) At least 99.2% of subjects in all three groups had anti-diphtheria antibody concentrations ≥ 1 IU/mL, and 4) At least 98.2% of subjects in the Hiberix and ActHIB groups and at least 96.8% of subjects in the Pentacel group had anti-tetanus antibody concentrations ≥ 1 IU/mL.

The Bioresearch Monitoring (BIMO) reviewer noted that in 2015, CBER completed a review of the study data submitted in STN 125347/231 and conducted three clinical investigator inspections covering four clinical sites. Those BIMO inspections did not reveal substantive problems impacting the data submitted in STN125347/231 as reflected in the BIMO review summary memo dated November 24, 2015. It was therefore determined that BIMO inspections were not warranted for this BLA supplement.

Pediatric Research Equity Act (PREA)

PREA requirements do not apply to this supplemental application, as this sBLA does not support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or route of administration. That said, with Study Hib-

097 the applicant had completed all requirements for pediatric assessment under PREA within the previous efficacy supplement (STN 125347/231).

7. SAFETY

The safety objective was to evaluate the safety and reactogenicity of a booster dose of *Hiberix* co-administered with *Infanrix*, a booster dose of *ActHIB* co-administered with *Infanrix* and a booster dose of *Pentacel*, at 15-18 months.

Booster dose safety analyses were conducted on the Booster Total Vaccinated Cohort (TVC) based on the treatment administered. The Booster-TVC included all subjects from the primary TVC that received the booster vaccine dose. The Primary TVC included all subjects with at least one vaccine administration documented. The numbers per group evaluated are as follows: 1) Hiberix Group (Hiberix + *Infanrix*) 2337 subjects, ActHIB Group (ActHIB + *Infanrix*) 435 subjects, and the Pentacel Group (Pentacel) 400 subjects.

The rates of unsolicited adverse events (AEs) reported across study groups were not different. A similar proportion of subjects in each study group (34.5% - 37.7%) reported at least 1 unsolicited AE within 31 days after the booster dose (Table 21). The most commonly reported unsolicited AEs in the Hiberix group were upper respiratory tract infection (URTI) (6.6%), pyrexia (5.1%) and otitis media (4.9%). In the ActHIB group, pyrexia (9.0%), otitis media (5.5%), cough and URTI (both 5.1%) were reported most commonly. The most commonly reported unsolicited AEs in the Pentacel group were cough (7.8%), pyrexia (6.8%) and URTI (6.5%).

A grade 3 unsolicited AE was reported by 7.8% of subjects both in the Hiberix and Pentacel groups and by 8.5% in the ActHIB group. Grade 3 pyrexia (1.0% - 2.5%) and grade 3 otitis media (0.8% - 1.4%) were reported most frequently in all 3 groups. No deaths were reported in the study.

8. ADVISORY COMMITTEE MEETING

The application was not referred to the Vaccines and Related Biological Products Advisory Committee because the review of information submitted in this supplement did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

No additional relevant issues.

10. LABELING

Review of the submitted prescribing information (PI) required some modifications to the text. After negotiations with the sponsor, it was determined by the committee that the final draft PI for Hiberix received on April 17, 2018, is acceptable. Immunogenicity and safety data from Study Hib-097 were added to the label, and the Pregnancy and Lactation sections of the PI were revised with this efficacy supplement for compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

The Advertising and Promotional Labeling Branch (APLB) found the prescribing information and carton/container labels for the Hiberix Efficacy Supplement (STN 125347/309) to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

The committee recommends approval of this sBLA to include safety and effectiveness data from the booster phase of Study Hib-097 that verify and describe the clinical benefit of Hiberix administered as a booster dose for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b.