

# Record of Telephone Conversation - June 26, 2009

## RECORD OF TELEPHONE CONVERSATION

Submission Type: Original Application Submission ID: 125347/0 Office: OVRR

Product:

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

Applicant:

GlaxoSmithKline Biologicals

Telecon Date/Time: 26-JUN-2009 02:00 PM

Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):

Labeling via FAX/e-mail

Author: JASON HUMBERT

Telecon Summary:

Comments regarding the PI

FDA Participants: Jason Humbert

Jay Slater

Karen Farizo

Non-FDA Participants: Elisa Harkins, GSK

Telecon Body: The following was sent to GSK via e-mail:

Good afternoon Elisa,

Attached are comments related to the Package Insert submitted in the Hiberix BLA.

We request, in response to these items, that the following be submitted:

1. A revised clean version of the package insert,
2. A revised version of the package insert, with changes tracked, and
3. A list of CBER's recommended revisions that were not accepted and the rationale for non-acceptance.

Please do not hesitate to contact me with any questions or concerns.

V/r,

Jason

**Date:** June 26, 2009

**To:** Elisa Harkins, GSK

**From:** Jason Humbert, CBER/OVRR/DVRPA

**Through:** Jay Slater, M.D. Committee Chair

Karen Farizo, M.D., Clinical Reviewer

**Subject:**

### I. Package Insert (draft.proposed.pdf)

**1. General Comment:** We note inconsistent use of *H. influenzae* type b and the abbreviation "Hib", as well as inconsistency in the terminology used to refer to Haemophilus b Conjugate Vaccines. With the next revision of the package insert, we

recommend that you use *H. influenzae* type b rather than Hib throughout the package insert. Please use “Haemophilus b Conjugate Vaccine” to refer to such vaccines.

**2. Page 1 Highlights, Dosage Forms and Strengths:** Please revise as follows: Solution for injection (0.5 mL dose) supplied as vials of lyophilized vaccine . . .prefilled syringes. (3)

**3. Page 1 Highlights, Contraindications:** Please revise as follows: A severe allergic reaction (e.g. anaphylaxis) after a previous dose of any Haemophilus b or tetanus toxoid-containing vaccine or to any ingredient of HIBERIX. (4)

**4. Page 1 Highlights:** Please insert a subsection for WARNINGS AND PRECAUTIONS to include the following:

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give HIBERIX should be based on careful consideration of the potential benefits and possible risks. (5.1)

**5. Page 1 Highlights, Adverse Reactions:** In a subsequent item, we have requested that you delete Study DTPa-IPV-026 from Table 1 (solicited local and general adverse events). Therefore, for consistency with the Full Prescribing Information, please delete injection site swelling from the list of events that occurred at a rate of  $\geq 20\%$ .

**6. Page 1 Highlights, Use in Specific Populations:** Please delete this subsection from Highlights.

**7. Page 2 Lines 4-6:** Please revise as follows:

HIBERIX® is indicated for active immunization as a booster dose for the prevention of invasive disease caused by *Haemophilus influenzae* type b. HIBERIX is approved for use in children 15 months through 4 years of age (prior to fifth birthday). HIBERIX is to be used as a booster dose in children who have received a primary series with a Haemophilus b Conjugate Vaccine that is licensed for primary immunization.

The evaluation of effectiveness of HIBERIX as a booster dose was based on immune responses in children using serological endpoints that predict protection from invasive disease due to *H. influenzae* type b [see *Clinical Pharmacology (12.1) and Clinical Studies (14)*]. These protective antibody levels have not been evaluated in clinical trials in which a booster dose of HIBERIX is compared to a US licensed Haemophilus b Conjugate Vaccine in children who previously received a primary series with a US licensed Haemophilus b Conjugate Vaccine [see *Clinical Studies (14)*].

**8. Page 2, Lines 9-13: Please revise as follows:**

HIBERIX is to be reconstituted only with the accompanying saline diluent. The reconstituted vaccine should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vials containing lyophilized vaccine and the syringes containing diluent also should be inspected visually for cracks prior to administration. If any of these conditions exist, the vaccine should not be administered.

**9. Page 3, Line 22:** Please delete.

**10. Page 3, Lines 23-24:** Please revise as follows:

HIBERIX is to be used as a booster dose in children who have received a primary series with a Haemophilus b Conjugate Vaccine that is licensed for primary immunization [see *Indications and Usage (1)*].

**11. Page 3, Lines 25-27:** Please delete.

**12. Page 3, Lines 33-38:** Please revise as follows:

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any Haemophilus b or tetanus toxoid-containing vaccine or to any ingredient of HIBERIX is a contraindication to administration of HIBERIX [see *Description (11)*].

**13. Page 3, Line 40:** Please insert a subsection as follows:

#### **5.1 Guillain-Barré Syndrome**

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including HIBERIX, should be based on careful consideration of the potential benefits and possible risks.

**14. Page 3, Line 40:** Please change “Antigenuria” to “Interference with Laboratory Tests”.

**15. Page 3, Lines 41-43:** Please revise as follows: Haemophilus b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has been detected in the urine of some vaccinees. New Ref Urine antigen detection may not have diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of HIBERIX.

Suggested New Reference:

Rothstein EP, Madore DV, Giron JA, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. *Pediatr Infect Dis J.* 1991;10:311-4.

**16. Page 3, Line 45:** Please revise as follows:

Safety and effectiveness of HIBERIX in immunosuppressed persons have not been evaluated. If HIBERIX is administered to immunosuppressed persons, including individuals. . .

**17. Page 3, Lines 49-50:** Please revise as follows:

. . . history for possible vaccine hypersensitivity. Epinephrine and other appropriate . . .

**18. Page 3, Line 57 through Page 4, Line 58:** Please delete “As with any vaccine”.

**19. Page 4, Lines 60-67:** Please revise as follows:

In 7 clinical studies, 1,008 children received HIBERIX as a booster dose following primary vaccination with either HIBERIX (N=530), Haemophilus b Conjugate Vaccine manufactured by Sanofi Pasteur SA (N=235), Haemophilus b Conjugate Vaccine manufactured by Merck & Co., Inc. (N=26), or Haemophilus b Conjugate Vaccine manufactured by Wyeth Pharmaceuticals Inc. (no longer licensed in the U.S., N=217). None of the studies included a comparator group that received a booster dose with a US licensed Haemophilus b Conjugate Vaccine. Studies were conducted in Europe, Canada, and Latin America. Across studies, the age of subjects at the time of booster vaccination with HIBERIX ranged from 11 to 25 months (mean age X to X months). Approximately half of subjects were male. Among subjects for whom information on race/ethnicity was available, nearly all subjects were White. In these 7 studies, HIBERIX was administered concomitantly with one of the following vaccines: INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), KINRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine), PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined], or DTaP-HBV (GlaxoSmithKline, not licensed in US). The

formulations of INFANRIX, KINRIX, and PEDIARIX used in these studies differed from the US-licensed formulations only in that they also contained X mg of 2-phenoxyethanol per dose. In these studies, KINRIX and PEDIARIX were administered in dose regimens that are not approved in the US.

**20. Page 4, Lines 68-79 and Page 5, Table 1:**

For the presentation of data on solicited local and general adverse events, we do not view Study DTPa-IPV-026 as sufficiently large to be informative. Therefore, please delete this study from the subsection Solicited Adverse Events.

**21. Page 4, Lines 68-79:** Please revise as follows:

Solicited Adverse Events: In an open-label, multi-center study conducted in Germany, X children received a booster dose of HIBERIX administered concomitantly with PEDIARIX. The mean age at the time of vaccination was X months. X subjects had received a primary series with HIBERIX, X subjects had received a primary series with Haemophilus b Conjugate Vaccine manufactured by Sanofi Pasteur SA, and X subjects had received a primary series with Haemophilus b Conjugate Vaccine manufactured by Wyeth Pharmaceuticals Inc. (no longer licensed in the U.S.). All subjects had previously received three doses of PEDIARIX. Information on adverse events was collected by parents/guardians using standardized forms for 4 consecutive days following vaccination with HIBERIX (i.e., day of vaccination and the next 3 days). The reported frequencies of solicited local and general adverse events are presented in Table 1.

**22. Page 5, Table 1:** Please revise the format of the table to include separate rows for specified events of any intensity and specified events of Grade 3 intensity.

**23. Page 5, Line 87:** Please revise as follows:

Coadministered with Pediarix. In this study Pediarix was given to subjects who had previously received three doses of Pediarix. In the US, Pediarix is approved for use as a three dose primary series; use as a fourth consecutive dose is not approved.

**24. Page 5, Line 97:** Please include a subsection on serious adverse events that occurred in the 31-day period following HIBERIX, across all booster immunization studies.

**25. Page 5, Lines 101-102:** Please revise as follows:

. . .includes serious events and/or events which have a plausible causal connection to HIBERIX. Because these events. . .

**26. Page 5, Lines 103-104:** Please change “the vaccine” to “vaccination”.

**27. Page 6, DRUG INTERACTIONS section:** Please insert a subsection as follows:

**7.X Interference with Laboratory Tests**

Haemophilus b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has been detected in the urine of some vaccinees.<sup>New Ref</sup> Urine antigen detection may not have diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of HIBERIX [see *Warnings and Precautions (5.X)*].

Suggested New Reference:

Rothstein EP, Madore DV, Girone JA, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. *Pediatr Infect Dis J.* 1991;10:311-4.

**28. Page 6, Lines 115-120:** Please revise as follows:

In clinical studies, a booster dose of HIBERIX was administered concomitantly with one of the following vaccines: INFANRIX, KINRIX, PEDIARIX, or DTaP-HBV

(GlaxoSmithKline, not licensed in US). In these studies, KINRIX and PEDIARIX were administered in dose regimens that are not approved in the US. [See *Adverse Reactions (6.1) and Clinical Studies (14)*].

Sufficient data are not available to confirm lack of interference in immune responses to other vaccines administered concomitantly with HIBERIX.

If HIBERIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. HIBERIX should not be mixed with any other vaccine in the same syringe or vial.

**29. Page 7, Line 149:** Please delete “inactivated”.

**30. Page 7, Lines 150-151:** Please revise as follows: The vial stopper and the tip cap and rubber plunger of the prefilled syringes do not contain latex.

**31. Page 7, Lines 155-157:** Please revise “Prior to the . . . most countries worldwide” as follows:

*H. influenzae* type b can cause invasive disease such as sepsis and meningitis.

**32. Page 7, Lines 158-165:** Please revise as follows:

Specific levels of anti-PRP antibody have been shown to correlate with protection against invasive disease due to *H. influenzae* type b. Based on data from passive antibody studies<sup>new ref</sup> and a clinical efficacy study with unconjugated Haemophilus b polysaccharide vaccine,<sup>2</sup> an anti-PRP concentration of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with unconjugated Haemophilus b polysaccharide vaccine indicate that an anti-PRP concentration of  $\geq 1.0$  mcg/mL predicts protection through a 1-year period.<sup>3,4</sup> These antibody levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including HIBERIX.

New reference:

Robbins JB, Parke JC, Schneerson R. Quantitative measurement of “natural” and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res* 1973;7:103-10

**33. Page 7, Lines 171-177:** Please delete.

**34. Page 7, Line 178 through Page 8, Line 203:**

We do not concur with including the immunogenicity results from Study 3 (DTPa-HBV-032) in the package insert. Among the booster immunization studies, this study appears to be an outlier, with unusually high anti-PRP GMC and percentage of subjects with anti-PRP >1.0 mcg/ml prior to booster vaccination. We also note that in this study, only 85 of the 146 subjects who received a fourth dose of HIBERIX were included in the ATP immunogenicity analyses. Therefore, please delete the immunogenicity data from Study DTPa-HBV-032. Instead of the data from Study DTPa-HBV-032, we recommend that you include the immunogenicity data from Study DTPa-HBV-020, which provides the largest number of subjects in the per protocol immunogenicity cohort. Please see next item for specific recommendations for presentation of the immunogenicity data.

**35. Page 7, Line 178 through Page 8, Line 203:** Please revise as follows:

Characteristics of 3 open-label studies that evaluated the immune response to HIBERIX administered as a booster dose are provided in Table 2. None of the studies included a comparator group that received a booster dose with a US licensed Haemophilus b Conjugate Vaccine. <Please insert sentence to describe race/ethnicity of subjects.>

**Table 2. Characteristics of 3 Open-label Booster Immunization Studies of HIBERIX**

	Country	Per Protocol Immunogenicity Cohort N	Priming History	Booster Vaccination with HIBERIX	
				Age at Vaccination	Concomitantly Administered Vaccines <sup>1</sup>
<b>Study 1</b>	Canada	42	PEDIARIX <sup>2</sup> + US licensed Haemophilus b Conjugate vaccine <sup>3</sup> at 2, 4, 6 months	16-18 months	PEDIARIX <sup>2,4</sup>
<b>Study 2</b>	Canada	64	KINRIX <sup>2,5</sup> + HIBERIX at 2, 4, 6 months	16-19 months	KINRIX <sup>2,5</sup>
<b>Study 3</b>	Germany	108	DTPa-HBV <sup>6</sup> + HIBERIX at 3, 4, 5 months	16-23 months	DTPa-HBV <sup>6</sup>

<sup>1</sup>Administered concomitantly with HIBERIX, at a separate site.

<sup>2</sup> Same as US formulation except also contained 2.5 mg 2-phenoxyethanol per dose as preservative.

<sup>3</sup> Haemophilus b Conjugate Vaccine, Sanofi Pasteur SA.

<sup>4</sup> In the US Pediarix is approved for use as a 3-dose series; use as a fourth consecutive dose is not approved.

<sup>5</sup>In the US, KINRIX is approved for use as the fifth dose of DTaP and the fourth dose of IPV in children 4-6 years of age previously primed with an approved regimen of INFANRIX and/or PEDIARIX. The dosing regimen for KINRIX described in the Table is not approved in the US.

<sup>6</sup> DTPa-HBV, GlaxoSmithKline; not licensed in the US.

Antibodies to PRP were measured in sera obtained immediately prior to and 1 month after booster vaccination with HIBERIX. In Study 1, pre-vaccination sera may have been obtained up to one week prior to booster vaccination with HIBERIX. Anti-PRP seroprotection rates and geometric mean concentrations are presented in Table 3.

**Table 3. Anti-PRP GMCs and Seroprotection Rates Prior to and 1 Month Following a Booster Dose of HIBERIX, Per Protocol Immunogenicity Cohort**

	N	Anti-PRP GMC (mcg/mL)		% Anti-PRP <sup>3</sup> 0.15 mcg/mL		% Anti-PRP <sup>3</sup> 1.0 mcg/mL	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
<b>Study 1a</b>	42	0.46	59.07	76.2	100	35.7	97.6
<b>Study 2b</b>	63-64	0.25	47.78	71.4	100	12.7	100
<b>Study 3c</b>	108	0.59	96.12	77.8	100	32.4	100

GMC = geometric mean antibody concentration;

N = number of children for whom serological results were available for the pre- and post-dose immunological evaluations.

Studies 1, 2 and 3 correspond to Studies 1, 2, and 3, respectively, in Table 2.

<sup>a</sup> Canadian study in children 16 to 18 months of age who previously received three doses of PEDIARIX and Haemophilus b Conjugate Vaccine manufactured by Sanofi Pasteur SA. The booster dose of HIBERIX was coadministered with PEDIARIX (a fourth consecutive dose of PEDIARIX is not approved in the US).

<sup>b</sup> Canadian study in children 16 to 19 months of age who previously received three doses of KINRIX and HIBERIX. The booster dose of HIBERIX was coadministered with KINRIX. This KINRIX dosing regimen is not approved in the US.

<sup>c</sup> German study in children 16 to 23 months of age who previously received three doses of DTaP-HBV, GlaxoSmithKline (not licensed in the US) and HIBERIX. The booster dose of HIBERIX was coadministered with DTaP-HBV.

**36. Page 9, Lines 220-221:** You may want to consider revision to clarify that the syringes containing diluent are packaged without needles.

## **II. Carton for Lyophilized Vaccine**

1. After HIBERIX, please insert “For booster only; 15 months through 4 years”.
2. For “Contents: 10 Vials of Lyophilized Vaccine”, please specify that each vial contains one dose.
3. The carton for the lyophilized vaccine includes the statement “See complete prescribing information for reconstitution instructions and dosing”. Please consider a more comprehensive statement such as “See complete prescribing information for additional details.”

## **III. Vial of Lyophilized Vaccine**

1. After HIBERIX, please insert “For booster only; 15 months through 4 years”.

## **IV. Carton for Diluent**

1. Please consider specifying that each syringe contains diluent for reconstitution of one dose of lyophilized vaccine.