HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HIBERIX safely and effectively. See full prescribing information for HIBERIX.
HIBERIX [Haemophilus b Conjugate Vaccine (Tetanus ToxoidConjugate)] for injection, for intramuscular use

Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 04/2018

---------- INDICATIONS AND USAGE----------
HIBERIX is a vaccine indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b. HIBERIX is approved for use in children aged 6 weeks through 4 years (prior to fifth birthday). (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular administration only.

A 4-dose series (0.5-mL each) given by intramuscular injection (2.3):
- Primary series: One dose each at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age.
- Booster: One dose at 15 through 18 months of age.

Do not mix HIBERIX with any other vaccine in the same syringe or vial. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Solution for injection supplied as a vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 mL. (3)

---------- CONTRAINDICATIONS ----------
Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b- or tetanus toxoid-containing vaccine or any component of HIBERIX. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give HIBERIX should be based on potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including HIBERIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including HIBERIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.3)

---------- ADVERSE REACTIONS ----------
Common solicited adverse reactions (≥20%) were pain and redness at the injection site, irritability, drowsiness, fever, loss of appetite, fussiness, and restlessness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HIBERIX is indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* (*H. influenzae)* type b. HIBERIX is approved for use in children aged 6 weeks through 4 years (prior to fifth birthday).

The evaluation of effectiveness of HIBERIX 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), Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Reconstitution

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. If either of these conditions exists, the vaccine should not be administered.

Figure 1. Cleanse both vial stoppers. Withdraw 0.6 mL of saline diluent from accompanying vial.

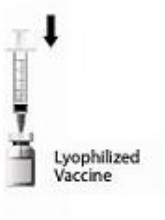

Figure 2. Transfer 0.6 mL saline diluent into lyophilized vaccine vial.

Figure 3. Shake the vial well.

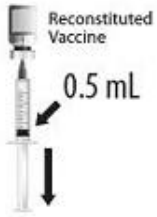

Figure 4. After reconstitution, withdraw 0.5 mL of reconstituted vaccine and administer **intramuscularly**.

Use a separate sterile needle and sterile syringe for each individual.

After reconstitution, administer HIBERIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and administer within 24 hours. If the vaccine is not administered immediately, shake the solution well again before administration.

2.2 Administration

For intramuscular use only.

HIBERIX is administered as a single dose (0.5 mL) by intramuscular injection into the anterolateral aspect of the thigh or deltoid.

Do not administer this product intravenously, intradermally, or subcutaneously.

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.

2.3 Dose and Schedule

HIBERIX is administered as a 4-dose series (0.5-mL each dose) given by intramuscular injection. The series consists of a primary immunization course of 3 doses administered at 2, 4, and 6 months of age, followed by a booster dose administered at 15 through 18 months of age. The first dose may be given as early as 6 weeks of age.

3 DOSAGE FORMS AND STRENGTHS

HIBERIX is a solution for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 mL.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b- or tetanus toxoid-containing vaccine or any component of the vaccine is a contraindication to administration of HIBERIX *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred 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.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including HIBERIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including HIBERIX, to infants born prematurely should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination.

5.4 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine hypersensitivity. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

5.5 Altered Immunocompetence

Safety and effectiveness of HIBERIX in immunosuppressed children have not been evaluated. If HIBERIX is administered to immunosuppressed children, including children receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.6 Interference with Laboratory Tests

Urine antigen detection may not have a diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of a *H. influenzae* type b-containing vaccine, including HIBERIX *[see Drug Interactions (7.1)]*.

5.7 Tetanus Immunization

Immunization with HIBERIX does not substitute for routine tetanus immunization.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of HIBERIX could reveal adverse reactions not observed in clinical trials.

Across clinical trials, common solicited adverse reactions (≥20%) were pain and redness at the injection site, irritability, drowsiness, fever, loss of appetite, fussiness, and restlessness.

Study 1: In a randomized, controlled clinical trial conducted in the U.S., children were vaccinated with HIBERIX (n = 2,963), a U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 520), or a U.S.-licensed combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate Vaccine (DTaP-IPV/Hib) (Sanofi Pasteur Ltd.) (n = 520) at 2, 4, and 6 months of age. HIBERIX and Control PRP-T (Sanofi Pasteur SA) were administered concomitantly with PEDIARIX (DTaP-HBV-IPV) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] and Pneumococcal 13-valent Conjugate Vaccine (PCV13) (Wyeth Pharmaceuticals Inc.) with Doses 1, 2, and 3 and ROTARIX [Rotavirus Vaccine, Live, Oral] with Doses 1 and 2. DTaP-IPV/Hib was administered concomitantly with PCV13 and ENGERIX-B [Hepatitis B Vaccine (Recombinant)] with Doses 1, 2, and 3 and ROTARIX with Doses 1 and 2. If a birth dose of hepatitis B vaccine was received, ENGERIX-B was given with Doses 1 and 3. In the total population, 51.2% were male; 61% were white, 8% were Asian, 9% were black, and 22% were other racial/ethnic groups.

In Study 1, children received a booster dose of either HIBERIX (n = 2,336), a Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 435), or a combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate Vaccine (DTaP-IPV/Hib) (Sanofi Pasteur Ltd.) (n = 400) at 15 to 18 months of age (mean age: 15.6 months) following primary vaccination at 2, 4, and 6 months of age with the same vaccine. The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur

SA) was administered concomitantly with INFANRIX (DTaP) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

In 7 additional clinical studies, 1,008 children received HIBERIX as a booster dose following primary vaccination with either HIBERIX (n = 530), Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 235), Haemophilus b Conjugate Vaccine (Merck & Co., Inc.) (n = 26), or Haemophilus b Conjugate Vaccine (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 U.S.-licensed Haemophilus b Conjugate Vaccine. Studies were conducted in Europe, Canada, and Latin America. Across these studies, the mean age of subjects at the time of booster vaccination with HIBERIX ranged from 16 to 19 months. At the time of vaccination, 172 (17.1%) subjects were aged 11 to 14 months, 642 (63.7%) subjects were aged 15 to 18 months, and 194 (19.2%) subjects were aged 19 to 25 months. Approximately half of the 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 non-U.S. formulations (containing 2.5 mg 2-phenoxyethanol per dose as preservative) of one of the following U.S.-licensed vaccines: INFANRIX (DTaP) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed], KINRIX (DTaP-IPV) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine], or PEDIARIX (DTaP-HBV-IPV). In the studies, DTaP-IPV and DTaP-HBV-IPV were administered in dosing regimens not approved in the U.S. Some subjects received DTaP-HBV (GlaxoSmithKline Biologicals, not licensed in U.S.) concomitantly with HIBERIX.

Solicited Adverse Reactions

The reported frequencies of solicited local reactions and general adverse reactions from Study 1 after primary and booster vaccination are presented in Table 1 and Table 2, respectively.

Table 1. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Primary Series Vaccination[a] (at 2, 4, and 6 Months of Age) with HIBERIX[b], Control PRP-T[b], or DTaP-IPV/Hib[c], Total Vaccinated Cohort[d]

	HIBERIX %			Control PRP-T %			DTaP-IPV/Hib %		
	Dose			Dose			Dose		
Adverse Reactions	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Local[e]									
n	**2,828**	**2,668**	**2,553**	**498**	**481**	**463**	**492**	**469**	**443**
Pain	49	45	43	57	53	48	58	50	49
Pain, Grade 3[f]	4	3	2	9	5	4	9	3	3
Redness	19	25	29	24	32	30	26	31	37
Redness, >20 mm	1	1	1	2	1	0	2	2	2
Swelling	13	15	19	19	22	20	20	24	24
Swelling, >20 mm	2	1	1	4	3	1	4	2	2
General									
n	**2,830**	**2,669**	**2,553**	**499**	**480**	**463**	**492**	**469**	**443**
Irritability	69	70	67	76	71	67	73	67	69
Irritability, Grade 3[g]	4	6	5	8	8	5	6	5	3
Drowsiness	60	54	49	66	56	50	61	52	50
Drowsiness, Grade 3[h]	2	3	2	4	2	1	4	3	3
Loss of appetite	29	28	28	33	32	27	34	24	24
Loss of appetite, Grade 3[i]	1	2	2	2	1	0	1	0	1
Fever	14	19	19	16	19	16	12	11	18
Fever, Grade 3[j]	0	1	1	0	0	1	0	0	1

n = All subjects for whom safety data were available.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] Each dose (Doses 1, 2, and 3) of HIBERIX or Control PRP-T (Sanofi Pasteur SA) was concomitantly administered with PEDIARIX (DTaP-HBV-IPV) and PCV13. Doses 1 and 2 were concomitantly administered with ROTARIX.

[c] Each dose (Doses 1, 2, and 3) of DTaP-IPV/Hib was concomitantly administered with PCV13 and ENGERIX-B with Doses 1, 2, and 3 and ROTARIX with Doses 1 and 2. If a birth dose of hepatitis B vaccine was received, ENGERIX-B was given with Doses 1 and 3.

[d] Study 1: NCT01000974.

[e] Local reactions at the injection site for HIBERIX, Control PRP-T, or DTaP-IPV/Hib.

[f] Grade 3 pain defined as cried when limb was moved/spontaneously painful.

[g] Grade 3 irritability defined as crying that could not be comforted/prevented normal activity.

[h] Grade 3 drowsiness defined as prevented normal daily activity.

[i] Grade 3 loss of appetite defined as did not eat at all.

[j] Fever defined as ≥100.4°F (≥38.0°C) rectally; Grade 3 fever defined as >103.1°F (>39.5°C) rectally.

Table 2. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Booster Vaccination[a] (Dose 4 at 15 through 18 Months of Age) with HIBERIX[b], Control PRP-T[b], or DTaP-IPV/Hib, Total Vaccinated Cohort[c]

Adverse Reactions	HIBERIX %		Control PRP-T %		DTaP-IPV/Hib%	
	Any	Grade 3[d]	Any	Grade 3[d]	Any	Grade 3[d]
Local[e]	**n = 2,224**		**n = 416**		**n = 379**	
Pain	41	1	43	1	43	2
Redness	30	0	31	1	30	3
Swelling	18	1	20	1	20	3
General	**n = 2,225**		**n = 416**		**n = 379**	
Irritability	58	2	60	5	53	2
Drowsiness	39	1	39	3	31	0
Loss of appetite	28	1	34	2	22	1
Fever[f]	15	1	14	1	18	1

n = All subjects for whom safety data were available.

Subjects received primary vaccination at 2, 4, and 6 months of age with the same vaccine as the booster dose.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur SA) was concomitantly administered with INFANRIX (DTaP).

[c] Study 1: NCT01000974.

[d] Grade 3 pain defined as cried when limb was moved/spontaneously painful.

Grade 3 redness, swelling defined as >20 mm.

Grade 3 irritability defined as crying that could not be comforted/prevented normal activity.

Grade 3 drowsiness defined as prevented normal daily activity.

Grade 3 loss of appetite defined as did not eat at all.

Grade 3 fever defined as >102.2°F (>39.0°C) axillary.

[e] Local reactions at the injection site for HIBERIX, Control PRP-T, or DTaP-IPV/Hib.

[f] Fever defined as ≥99.5°F (≥37.5°C) axillary.

In an open-label, multicenter study conducted in Germany (Study 2), 371 children received a booster dose of HIBERIX administered concomitantly with DTaP-HBV-IPV. The mean age at the time of vaccination was 16 months. Subjects in this study had previously received a primary series with either HIBERIX (n = 92), Control PRP-T (Sanofi Pasteur SA) (n = 96), or Haemophilus b Conjugate Vaccine (Wyeth Pharmaceuticals Inc.) (no longer licensed in the U.S.)

(n = 183). All subjects previously received 3 doses of DTaP-HBV-IPV. The reported frequencies of solicited local reactions and general adverse reactions are presented in Table 3.

Table 3. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Booster Vaccination[a] (Dose 4) with HIBERIX[b] Coadministered with DTaP-HBV-IPV[c], Intent-to-Treat Cohort (n = 371)

Adverse Reactions	% Any	% Grade 3
Local[d]		
Redness	25	2[e]
Pain	21	1[f]
Swelling	15	2[e]
General		
Fever[g]	35	4
Fussiness	26	1[h]
Loss of appetite	23	1[i]
Restlessness	22	1[i]
Sleepiness	20	1[i]
Diarrhea	15	1[i]
Vomiting	5	1[i]

n = All subjects for whom safety data were available.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] In this study, 92 subjects previously received 3 doses of HIBERIX, 96 subjects previously received 3 doses of a Control PRP-T (Sanofi Pasteur SA), and 183 subjects previously received 3 doses of a Haemophilus b Conjugate Vaccine that is no longer licensed in the U.S.

[c] In this study, DTaP-HBV-IPV was given to subjects who previously received 3 doses of DTaP-HBV-IPV. In the U.S., PEDIARIX is approved for use as a 3-dose primary series; use as a fourth consecutive dose is not approved in the U.S.

[d] Local reactions at the injection site for HIBERIX.

[e] Grade 3 redness or swelling defined as >20 mm.

[f] Grade 3 pain defined as causing crying when limb moved.

[g] Fever defined as ≥100.4°F (≥38.0°C) rectally or ≥99.5°F (≥37.5°C) axillary, oral, or tympanic; Grade 3 fever defined as >103.1°F (>39.5°C) rectally or >102.2°F (>39.0°C) axillary, oral, or tympanic.

[h] Grade 3 fussiness defined as persistent crying and could not be comforted.

[i] Grade 3 for these symptoms defined as preventing normal daily activity.

Serious Adverse Reactions

In Study 1, one of 2,963 subjects who received HIBERIX and coadministered vaccines given at 2, 4, and 6 months of age experienced a serious adverse reaction which was in temporal association with vaccination and had no alternative plausible causes (convulsion on Day 14 after Dose 1). One of 2,336 subjects who received a booster dose of HIBERIX concomitantly with

INFANRIX experienced a serious adverse reaction which was in temporal association with vaccination and had no alternative plausible causes (new onset febrile seizure on Day 1 after Dose 4).

In the 7 additional studies, 2 of 1,008 subjects reported a serious adverse reaction that occurred in the 31-day period following booster immunization with HIBERIX. One subject developed bilateral pneumonia 9 days post-vaccination and one subject experienced asthenia following accidental drug ingestion 18 days post-vaccination.

6.2 Postmarketing Experience

In addition to reports in clinical trials for HIBERIX, the following adverse reactions have been identified during postapproval use of HIBERIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccination.

General Disorders and Administration Site Conditions

Extensive swelling of the vaccinated limb, injection site induration.

Immune System Disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema.

Nervous System Disorders

Convulsions (with or without fever), hypotonic-hyporesponsive episode (i.e., sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis), somnolence, syncope, or vasovagal responses to injection.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea *[see Warnings and Precautions (5.3)]*.

Skin and Subcutaneous Tissue Disorders

Rash, urticaria.

7 DRUG INTERACTIONS

7.1 Interference with Laboratory Tests

Haemophilus b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has been detected in the urine of some vaccinees.[1] Urine antigen detection may not have a diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of a *H. influenzae* type b-containing vaccine, including HIBERIX *[see Warnings and Precautions (5.6)]*.

7.2 Concomitant Vaccine Administration

In clinical studies, HIBERIX was administered concomitantly with routinely recommended

pediatric vaccines *[see Clinical Studies (14.2)]*.

7.3 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to HIBERIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

HIBERIX is not approved for use in individuals aged 5 years and older. No human or animal data with HIBERIX are available to assess vaccine-associated risks in pregnancy.

8.2 Lactation

HIBERIX is not approved for use in individuals aged 5 years and older. No human or animal data are available to assess the impact of HIBERIX on milk production, its presence in breast milk, or its effects on the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of HIBERIX in children younger than 6 weeks and in children aged 5 to 16 years have not been established.

11 DESCRIPTION

HIBERIX [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] is a solution for intramuscular injection, supplied as a sterile, lyophilized powder which is reconstituted at the time of use with the accompanying saline diluent. HIBERIX contains Haemophilus b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]), a high molecular weight polymer prepared from the *H. influenzae* type b strain 20,752 grown in a synthetic medium that undergoes heat inactivation and purification. The tetanus toxin, prepared from *Clostridium tetani* grown in a semi-synthetic medium, is detoxified with formaldehyde and purified. The capsular polysaccharide is covalently bound to the tetanus toxoid. After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. The diluent for HIBERIX is a sterile saline solution (0.9% sodium chloride) supplied in vials.

After reconstitution, each 0.5-mL dose is formulated to contain 10 mcg of purified capsular polysaccharide conjugated to approximately 25 mcg of tetanus toxoid, 12.6 mg of lactose, and ≤0.5 mcg of residual formaldehyde.

HIBERIX does not contain a preservative.

The lyophilized vaccine and saline diluent vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

H. influenzae is a gram-negative coccobacillus. Most strains of *H. influenzae* that cause invasive disease are type b. *H. influenzae* type b can cause invasive disease such as sepsis and meningitis.

Specific levels of antibodies to polyribosyl-ribitol-phosphate (anti-PRP) have been shown to correlate with protection against invasive disease due to *H. influenzae* type b. Based on data from passive antibody studies[2] and a clinical efficacy study with unconjugated *Haemophilus* b polysaccharide vaccine[3], 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 ≥1.0 mcg/mL predicts protection through at least a 1-year period.[4,5] These antibody levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including HIBERIX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

HIBERIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Immunological Evaluation

Primary Series Vaccination (Doses 1, 2, and 3)

The immunogenicity of HIBERIX was evaluated in a randomized, controlled trial (Study 1). HIBERIX or control vaccines were administered concomitantly with U.S.-licensed vaccines *[see Adverse Reactions (6.1)]*.

Anti-PRP geometric mean concentrations (GMCs) and seroprotection rates 1 month following Dose 3 of HIBERIX, Control PRP-T (Sanofi Pasteur SA), or DTaP-IPV/Hib are presented in Table 4.

Table 4. Anti-PRP GMCs and Seroprotection Rates 1 Month following 3 Doses of HIBERIX, Control PRP-T[a], or DTaP-IPV/Hib[b] Administered at 2, 4, and 6 Months of Age, ATP Cohort for Immunogenicity[c]

Vaccine	n	Anti-PRP GMC (mcg/mL) (95% CI)	% Anti-PRP ≥0.15 mcg/mL (95% CI)	% Anti-PRP ≥1.0 mcg/mL (95% CI)
HIBERIX	1,590	5.19 (4.77, 5.66)	96.6 (95.6, 97.4)	81.2 (79.2, 83.1)
Control PRP-T	274	6.74 (5.59, 8.13)	96.7[d] (93.9, 98.5)	89.8[e] (85.6, 93.1)
DTaP-IPV/Hib	253	3.64 (2.89, 4.58)	92.5[f] (88.5, 95.4)	78.3[f] (72.7, 83.2)

[a] U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

[b] U.S.-licensed DTaP-IPV/Hib Vaccine (Sanofi Pasteur Ltd.).

[c] Study 1: NCT01000974.

[d] HIBERIX was non-inferior to Control PRP-T for percent of subjects achieving anti-PRP ≥0.15 mcg/mL (lower limit of 95% CI on difference of HIBERIX minus Control PRP-T ≥ predefined limit of -5%).

[e] The non-inferiority criterion was not met (lower limit of 95% CI for the difference in the percentages of subjects with anti-PRP ≥1.0 mcg/mL between two groups [HIBERIX minus Control PRP-T] was -12.28%, which was lower than the predefined limit of -10%).

[f] Analyses of anti-PRP immune responses following DTaP-IPV/Hib vaccination were exploratory.

Booster Vaccination (Dose 4)

The immunogenicity of HIBERIX administered as a booster dose at 15 to 18 months of age was evaluated in a subset of children from Study 1 (n = 336) in comparison with U.S.-licensed vaccines following primary vaccination at 2, 4, and 6 months of age *[see Adverse Reactions (6.1)]*. The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur SA) was administered concomitantly with INFANRIX.

Antibodies to PRP were measured in sera obtained immediately prior to and 1 month after booster vaccination with HIBERIX or the control vaccines. Anti-PRP GMCs and seroprotection rates are presented in Table 5.

Table 5. Anti-PRP GMCs and Seroprotection Rates prior to and 1 Month following a Booster Dose (Dose 4 at 15 through 18 Months of Age) of HIBERIX, Control PRP-T[a], or DTaP-IPV/Hib[b], ATP Cohort for Immunogenicity[c]

Vaccine	n	Anti-PRP GMC (mcg/mL) (95% CI)		% Anti-PRP ≥0.15 mcg/mL (95% CI)		% Anti-PRP ≥1.0 mcg/mL (95% CI)	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
HIBERIX	329-336	0.50 (0.42, 0.59)	48.78 (42.0, 56.66)	75.1 (70.0, 79.7)	100.0 (98.9, 100.0)	32.2 (27.2, 37.6)	99.1 (97.4, 99.8)
Control PRP-T	226-236	0.47 (0.38, 0.57)	40.29 (33.39, 48.63)	76.1 (70.0, 81.5)	99.6 (97.7, 100.0)	27.0 (21.3, 33.3)	97.9[d] (95.1, 99.3)
DTaP-IPV/Hib	175-186	0.38 (0.30, 0.48)	37.54 (30.53, 46.16)	66.3 (58.8, 73.2)	100.0 (98.0, 100.0)	25.1 (18.9, 32.2)	98.9[e] (96.2, 99.9)

[a] U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

[b] U.S.-licensed DTaP-IPV/Hib Vaccine (Sanofi Pasteur Ltd.).

[c] Study 1: NCT01000974.

[d] HIBERIX was non-inferior to Control PRP-T for percent of subjects achieving anti-PRP ≥1.0 mcg/mL (lower limit of 97.5% CI on difference of HIBERIX minus Control PRP-T ≥predefined limit of -10%) at 1 month following the booster dose.

[e] Analyses of anti-PRP immune responses following DTaP-IPV/Hib vaccination were exploratory.

In 6 additional clinical studies, the immune response to HIBERIX administered as a booster dose was evaluated in a total of 415 children aged 12 to 23 months. At the time of vaccination, 30 children were aged 12 to 14 months, 316 children were aged 15 to 18 months, and 69 children were aged 19 to 23 months. Among subjects, 43% to 60% were male. Among subjects for whom information on race/ethnicity was available, nearly all subjects were white. None of the studies included a comparator group that received a booster dose with a U.S.-licensed Haemophilus b Conjugate Vaccine. Characteristics of 3 of these studies are presented in Table 6.

Table 6. Characteristics of 3 Open-Label Booster Immunization Studies of HIBERIX

Study	Country	Per-Protocol Immunogenicity Cohort n	Priming History	Booster Vaccination with HIBERIX	
				Age at Vaccination (months)	Concomitantly Administered Vaccine[a]
3	Canada	42	DTaP-HBV-IPV[b] + Haemophilus b Conjugate Vaccine[c] at 2, 4, and 6 months of age	16-18	DTaP-HBV-IPV[b]
4	Canada	64	DTaP-IPV[d] + HIBERIX at 2, 4, and 6 months of age	16-19	DTaP-IPV[d]
5	Germany	108	DTaP-HBV[e] + HIBERIX at 3, 4, and 5 months of age	16-23	DTaP-HBV[e]

[a] Administered at a separate site.

[b] Non-U.S. formulation equivalent to PEDIARIX with the exception of containing 2.5 mg 2-phenoxyethanol per dose as preservative. In the U.S., PEDIARIX is approved for use as a 3-dose primary series; use as a fourth consecutive dose is not approved in the U.S.

[c] U.S.-licensed Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

[d] Non-U.S. formulation equivalent to KINRIX with the exception of containing 2.5 mg 2-phenoxyethanol per dose as preservative. In the U.S., KINRIX is approved for use as the fifth dose of DTaP and the fourth dose of IPV in children aged 4 to 6 years previously primed with approved dosing regimens of INFANRIX and/or PEDIARIX. The DTaP-IPV dosing regimen is not approved in the U.S.

[e] Manufactured by GlaxoSmithKline Biologicals (not licensed in the U.S.).

Antibodies to PRP were measured in sera obtained immediately prior to and 1 month after booster vaccination with HIBERIX. Geometric mean concentrations and anti-PRP seroprotection rates are presented in Table 7.

Table 7. Anti-PRP GMCs and Seroprotection Rates prior to and 1 Month following a Booster Dose of HIBERIX, Per-Protocol Immunogenicity Cohort

Study	n	Anti-PRP GMC (mcg/mL)		% Anti-PRP ≥0.15 mcg/mL		% Anti-PRP ≥1.0 mcg/mL	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
3[a]	42	0.46	59.07	76.2	100	35.7	97.6
4[b]	63-64	0.25	47.78	71.4	100	12.7	100
5[c]	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 3, 4, and 5 correspond to Studies 3, 4, and 5, respectively in Table 6.

[a] Canadian study in children aged 16 to 18 months who previously received 3 doses of DTaP-HBV-IPV and Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA). The booster dose of HIBERIX was coadministered with DTaP-HBV-IPV (a fourth consecutive dose of PEDIARIX is not approved in the U.S.). In this study, pre-vaccination sera may have been obtained up to 1 week prior to booster vaccination with HIBERIX.

[b] Canadian study in children aged 16 to 19 months who previously received 3 doses of DTaP-IPV and HIBERIX. The booster dose of HIBERIX was coadministered with DTaP-IPV. The DTaP-IPV dosing regimen is not approved in the U.S.

[c] German study in children aged 16 to 23 months who previously received 3 doses of DTaP-HBV (GlaxoSmithKline Biologicals, not licensed in the U.S.) and HIBERIX. The booster dose of HIBERIX was coadministered with DTaP-HBV.

14.2 Concomitant Vaccine Administration

Primary Series Vaccination (Doses 1, 2, and 3)

In U.S. Study 1, subjects who received HIBERIX concomitantly with PEDIARIX (DTaP-HBV-IPV) and PCV13 at 2, 4, and 6 months of age had no evidence for reduced antibody responses relative to the response in control subjects administered Control PRP-T (Sanofi Pasteur SA) concomitantly with PEDIARIX (DTaP-HBV-IPV) and PCV13, to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, and pertactin), diphtheria toxoid (antibody levels ≥0.1 IU/mL), tetanus toxoid (antibody levels ≥0.1 IU/mL), poliovirus types 1, 2, and 3 (antibody levels ≥1:8 to each virus), PCV13 (antibody levels ≥0.2 mcg/mL and GMC to each serotype), or hepatitis B (anti-hepatitis B surface antigen ≥10 mIU/mL). The immune responses to PEDIARIX (DTaP-HBV-IPV) and PCV13 were evaluated 1 month following Dose 3. Subjects in both groups received ROTARIX at 2 and 4 months of age.

Booster Vaccination (Dose 4)

In U.S. Study 1, subjects who received a booster dose of HIBERIX concomitantly with INFANRIX at 15 to 18 months of age had no evidence for reduced antibody responses to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, and pertactin), diphtheria

toxoid (antibody levels ≥0.1 IU/mL), and tetanus toxoid (antibody levels ≥0.1 IU/mL), relative to the responses in control subjects administered Control PRP-T (Sanofi Pasteur SA) concomitantly with INFANRIX.

In 7 additional studies, a booster dose of HIBERIX was administered concomitantly with non-U.S. formulations of INFANRIX, KINRIX, and PEDIARIX. Non-U.S. formulations of KINRIX and PEDIARIX were administered in dosing regimens not approved in the U.S.

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

15 REFERENCES

1. Rothstein EP, Madore DV, Girone JAC, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. *Pediatr Infect Dis J.* 1991;10:311-314.
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3. Peltola H, Käythy H, Sivonen A, et al. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: A double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics.* 1977;60:730-737.
4. Käythy H, Peltola H, Karanko V, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis.* 1983;147:1100.
5. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis.* 1984;149:1034.

16 HOW SUPPLIED/STORAGE AND HANDLING

HIBERIX is available in single-dose vials of lyophilized vaccine, accompanied by vials containing 0.85 mL of saline diluent (packaged without syringes or needles).

Supplied as package of 10 doses (NDC 58160-818-11):

NDC 58160-816-01 Vial of lyophilized vaccine in Package of 10: NDC 58160-816-05

NDC 58160-817-01 Vial of saline diluent in Package of 10: NDC 58160-817-05

16.1 Storage before Reconstitution

Lyophilized vaccine vials: Store refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light.

Diluent: Store refrigerated or at controlled room temperature between 2° and 25°C (36° and 77°F). Do not freeze. Discard if the diluent has been frozen.

16.2 Storage after Reconstitution

Administer within 24 hours of reconstitution. After reconstitution, store refrigerated between 2° and 8°C (36° and 46°F). Discard the reconstituted vaccine if not used within 24 hours. Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

- Inform parents or guardians of the potential benefits and risks of immunization with HIBERIX.
- Inform parents or guardians about the potential for adverse reactions that have been temporally associated with administration of HIBERIX or other vaccines containing similar components.
- Give parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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