ActHIB® Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
Solution for Intramuscular Injection
Initial U.S. Approval: 1993

---------------------------------RECENT MAJOR CHANGES ---------------------------------
Warnings and Precautions, Latex (5.2) – Removed [3/2016]

-----------------------------------INDICATIONS AND USAGE ----------------------------------
• ActHIB is a vaccine indicated for the prevention of invasive disease caused by Haemophilus influenzae type b. ActHIB vaccine is approved for use as a four dose series in infants and children 2 months through 5 years of age (1)

------------------------------ DOSAGE AND ADMINISTRATION -----------------------------
Four dose series (0.5 mL each) by intramuscular injection:
• A three dose primary series administered at 2, 4 and 6 months of age. (2.1)
• A single booster dose administered at 15-18 months of age. (2.1)

----------------------------DOSAGE FORMS AND STRENGTHS ---------------------------
• Solution for injection: lyophilized powder to be reconstituted in supplied 0.4% Sodium Chloride 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 ActHIB vaccine. (4)

------------------------------ WARNINGS AND PRECAUTIONS -----------------------------
• If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the potential benefits and risks of giving ActHIB vaccine must be evaluated. (5.2)

------------------------------------ ADVERSE REACTIONS ------------------------------------
• Following administration of ActHIB vaccine in children 2-20 months of age, rates of adverse reactions varied by dose number and age of recipients:
  • In children 15-20 months of age tenderness (20%) was the most common local reaction following a single dose. (6.1)
  • The most frequent systemic reactions after any dose for children 2 months to 16 months of age were fussiness/irritability (75%), inconsolable crying (58%) and decreased activity/lethargy (51%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

Revised: April 2016
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 to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

More than 7,000 infants and young children (≤2 years of age) have received at least one dose of ActHIB vaccine during US clinical trials. Of these, 1,064 subjects 12 to 24 months of age who received ActHIB vaccine alone reported no serious or life threatening adverse reactions. (5) (6)

Adverse reactions associated with ActHIB vaccine generally subsided after 24 hours and did not persist beyond 48 hours after immunization.

In a US trial, the safety of ActHIB vaccine was evaluated in 110 children 15 to 20 months of age. All children received three doses of Haemophilus influenzae type b conjugate vaccine (ActHIB vaccine or a previously licensed Haemophilus b conjugate vaccine) at approximately 2, 4, and 6 months of age. The incidence of selected solicited injection site and systemic adverse reactions which occurred within 48 hours following the dose of ActHIB vaccine is shown in Table 1.

Table 1: Local and Systemic Reactions at 6, 24, and 48 Hours Following Immunization with ActHIB Vaccine in Children 15 to 20 months old (6)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>6 Hrs. Post-dose</th>
<th>24 Hrs. Post-dose</th>
<th>48 Hrs. Post-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local (%)</td>
<td>Total N = 110</td>
<td>Total N = 110</td>
<td>Total N = 110</td>
</tr>
<tr>
<td>Fever (&gt;102.2°F) (39.0°C)</td>
<td>0.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Numbness</td>
<td>0.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Sensation</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Injection Site</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Induration</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Crying</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Persistent Crying</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Urinary Crying</td>
<td>1.9</td>
<td>1.9</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Adverse events were generally mild in severity. The most frequent adverse events reported were injection site reactions (e.g., induration, swelling, erythema, injection site pain). Systemic reactions were generally self-limited and of short duration. The most frequent systemic reactions following any dose (>50% of participants) were injection site pain, redness, swelling, and induration. Systemic reactions generally resolved within 24 hours of administration and were not considered to be related to the vaccine.

Table 2: Number (Percentage) of Children with Selected Solicited Systemic Adverse Reactions by Severity Occurring within 0-3 Days After Vaccination in Study P3T06

<table>
<thead>
<tr>
<th>Systemic Reaction</th>
<th>Dose 1: N = 1,390-1,406</th>
<th>Dose 2: N = 1,346-1,360</th>
<th>Dose 3: N = 1,301-1,312</th>
<th>Dose 4: N = 379-381</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38.5°C</td>
<td>9.3%</td>
<td>16.1%</td>
<td>15.8%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Decreased Activity/ Lethargy ≤20%</td>
<td>51.1%</td>
<td>37.4%</td>
<td>31.2%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Inconsolable Crying</td>
<td>24.3%</td>
<td>15.8%</td>
<td>12.7%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Fussiness/ Irritability</td>
<td>12.7%</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Note: Ages of study participants ranged from 1.3 to 19.5 months.
The response to ActHIB vaccine is typical of a T-dependent immune response to antigens.

The prominent isotype of anti-capsular PRP antibody induced by ActHIB vaccine is IgG.

Antibody titers to \( H. influenzae \) type b conjugate vaccines were administered concomitantly with OPV and whole-cell DTP vaccines at separate sites. Neither OPV nor whole-cell DTP vaccines are licensed or distributed in the US currently.

### 7.1 Concomitant Administration with Other Vaccines

In clinical trials, ActHIB vaccine was administered, at separate sites, concomitantly with one or more of the following vaccines: DTPa; Measles, Mumps and Rubella vaccine (MMR); Hepatitis B vaccine; and Inactivated Poliovirus Vaccine (IPV). No immunity of the antibody response to the individual antigens was demonstrated when ActHIB vaccine was given at the same time but separate sites with these vaccines. (6)

### 7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimitobolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to ActHIB vaccine. [See Altered Immunocompetence (5.3)]

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy category C

Animal reproduction studies have not been conducted with ActHIB vaccine. It is also not known whether ActHIB vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

#### 8.4 Pediatric Use

Safety and effectiveness of ActHIB vaccine in infants below the age of 6 weeks have not been established. [See Dosage and Administration (2.1)]

### 11 DESCRIPTION

ActHIB vaccine is a sterile, lyophilized powder to be reconstituted with saline diluent (0.4% Sodium Chloride) for intramuscular administration only. The vaccine consists of the \( H. influenzae \) type b conjugate vaccines were administered concomitantly with OPV and whole-cell DTP vaccines at separate sites. Neither OPV nor whole-cell DTP vaccines are licensed or distributed in the US currently.

### Table 3: Anti-PRP Antibody Responses Following a Two or Three Dose Series of a \( H. influenzae \) type b Conjugate Vaccine (T etanus T oxoid Conjugate)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Geometric Mean Concentration (GMC) (mcg/mL)</th>
<th>Post Third Immunization % ≥1.0 mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-Tb (ActHIB vaccine)</td>
<td>65</td>
<td>0.10</td>
<td>83%</td>
</tr>
<tr>
<td>PRP-OMPc (PedvaxHIB)</td>
<td>64</td>
<td>0.11</td>
<td>50%</td>
</tr>
<tr>
<td>HbOCf (HibTITER®)</td>
<td>61</td>
<td>0.07</td>
<td>75%</td>
</tr>
</tbody>
</table>

#### Table 4: Anti-PRP Antibody Responses Following a Two or Three Dose Series of a \( H. influenzae \) type b Conjugate Vaccine (Meningococcal Protein Conjugate)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Geometric Mean Concentration (GMC) (mcg/mL)</th>
<th>Post Third Immunization % ≥1.0 mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-Tb (ActHIB vaccine)</td>
<td>142</td>
<td>0.25</td>
<td>97%</td>
</tr>
<tr>
<td>PRP-OMP (PedvaxHIB)</td>
<td>149</td>
<td>0.18</td>
<td>85%</td>
</tr>
<tr>
<td>HbOCf (HibTITER®)</td>
<td>167</td>
<td>0.17</td>
<td>90%</td>
</tr>
</tbody>
</table>

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

\( H. influenzae \) is a gram-negative cocobacillus. Most strains of \( H. influenzae \) that cause invasive disease (e.g., sepsis and meningitis) are \( H. influenzae \) type b. The response to ActHIB vaccine is typical of a T-dependent immune response to antigens.
Native American populations have had high rates of *H. influenzae* type b disease and have been observed to have low immune responses to *Haemophilus influenzae* type b conjugate vaccines. In a clinical study enrolling Alaskan Native Americans, following the administration of a three dose series of ActHIB vaccine at 6 weeks, 4 months, and 6 months of age, 75% of subjects achieved an anti-PRP antibody titer of ≥1.0 mcg/mL at 7 months of age (1 month after the last vaccination). (17)

14.2 Immunogenicity of ActHIB Vaccine in Children 12 to 24 Months of Age

In four separate studies, children 12 to 24 months of age who had not previously received *Haemophilus influenzae* type b conjugate vaccination were immunized with a single dose of ActHIB vaccine (Table 5). Geometric Mean Concentration (GMC) of anti-PRP antibody responses were 5.12 mcg/mL (90% responding with ≥1.0 mcg/mL) for children 12 to 15 months of age and 4.4 mcg/mL (82% responding with ≥1.0 mcg/mL) for children 17 to 24 months of age. (6)

Table 5: Anti-PRP Antibody Responses in 12- to 24-month-old Children Immunized with a Single Dose of ActHIB

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Pre-Immunization</th>
<th>Post Immunization</th>
<th>% Subjects With</th>
<th>GMC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 to 15 months</td>
<td>256</td>
<td>0.06</td>
<td>5.12</td>
<td>1.6</td>
<td>90.2</td>
</tr>
<tr>
<td>17 to 24 months</td>
<td>81</td>
<td>0.10</td>
<td>4.40</td>
<td>3.7</td>
<td>81.5</td>
</tr>
</tbody>
</table>

a N = Number of children

b Post immunization responses measured at approximately 1 month after vaccination

ActHIB vaccine has been found to be immunogenic in children with sickle cell anemia, a condition that may cause increased susceptibility to *Haemophilus influenzae* type b disease. Following two doses of ActHIB vaccine given at two-month intervals, 89% of these children (mean age 11 months) had anti-PRP antibody titers of ≥1.0 mcg/mL. This is comparable to anti-PRP antibody levels demonstrated in normal children of similar age following two doses of ActHIB vaccine. (18)

15 REFERENCES


5. Data on file, Sanofi Pasteur SA.

6. Data on file, Sanofi Pasteur Inc.


16 HOW SUPPLIED-STORAGE AND HANDLING

16.1 How Supplied

Single-dose, lyophilized vaccine vial (NDC 49281-547-58) packaged with single-dose diluent vial (NDC 49281-546-58). Supplied as package of 5 vials each (NDC 49281-545-03).

The vial stoppers for ActHIB vaccine and diluent are not made with natural rubber latex.

16.2 Storage and Handling

Store lyophilized ActHIB vaccine packaged with saline diluent (0.4% Sodium Chloride) at 2°C to 8°C (35°F to 46°F). DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the patient, parent, or guardian.

Inform the patients, parents, or guardians about the potential benefits and risks of the vaccine and importance of completing the immunization series unless a contraindication to further immunization exists. In addition to this, parents and guardian must be informed about the potential for adverse reactions that have been temporarily associated with the administration of ActHIB vaccine or other vaccines containing similar ingredients. Prior to administration of ActHIB vaccine healthcare providers should ask parents or guardians about the recent health status of the infant or child to be immunized. As part of the child's immunization record, the date, lot number, and manufacturer of the vaccine administered should be recorded. (7) (8) (19) Vaccine recipients and guardians must report any adverse reactions upon administration of the vaccine to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

ActHIB is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:
Sanofi Pasteur SA
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Distributed by:
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