INDICATIONS AND USAGE

ActHIB® [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] Solution for Intramuscular Injection

Initial U.S. Approval: 1993

RECENT MAJOR CHANGES

Warnings and Precautions, Syncope (5.7) 7/2022

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

For intramuscular administration only

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 (35° to 46°F) and administer within 24 hours. Stored vaccine should be re-agitated prior to injection.

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:

• 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)
• In children 15-20 months of age tenderness (20%) was the most common local reaction following a single dose. (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-VAC-CINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

ActHIB® is a vaccine indicated for the prevention of invasive disease caused by Haemophilus influenzae (H. influenzae) type b. ActHIB is approved for use in children 2 months through 5 years of age.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only

2.1 Immunization Series

ActHIB vaccine is administered as a four-dose series (0.5 mL per dose) as:

• A primary three-dose series of a single dose at 2, 4, and 6 months of age.
• A single booster dose at 15 to 18 months of age.

2.2 Reconstitution

ActHIB vaccine is a solution for injection supplied as single-dose vials of lyophilized vaccine (vial 1 of 2) to be reconstituted only with the accompanying saline diluent (0.4% Sodium Chloride) (vial 2 of 2). To reconstitute ActHIB vaccine, withdraw 0.6 mL of saline diluent and inject into the vial of lyophilized ActHIB vaccine. Agitate the vial to ensure complete reconstitution. The reconstituted ActHIB vaccine will appear clear and colorless. Withdraw a 0.5-mL dose of the reconstituted vaccine and inject intramuscularly. After reconstitution, ActHIB vaccine is not administered promptly store at 2° to 8°C (35° to 46°F) and administer within 24 hours. Stored vaccine should be re-agitated prior to injection. Refer to Figures 1, 2, 3, and 4.

2.3 Administration

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any Haemophilus 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

Instructions for Reconstitution of ActHIB Vaccine with Saline Diluent (0.4% Sodium Chloride)

Figure 1. Disinfect the diluent vial stopper, inject the needle and withdraw 0.6 mL of 0.4% Sodium Chloride diluent as indicated.

Figure 2. Cleanse the ActHIB vaccine stopper, insert the syringe needle into the vial, and inject the total volume of diluent.

Figure 3. Agitate vial thoroughly.

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

14 CLINICAL PHARMACOLOGY

14.1 Immunogenicity of ActHIB Vaccine in Children 2, 4 and 6 Months of Age

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

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
AcHIB vaccine is administered as a single dose (0.5 mL) by intramuscular injection into the anterolateral aspect of the thigh or deltoid. Discard unused portion. Do not administer this product intravenously, intradermally, or subcutaneously.

AcHIB vaccine should not be mixed in the same syringe with other parenteral products.

3. DOSAGE FORMS AND STRENGTHS

AcHIB vaccine is a solution for injection supplied as a single-dose vial of lyophilized powder to be reconstituted with the supplied 0.4% Sodium Chloride diluent. A single dose, after reconstitution is 0.5 mL.

4. CONTRAINDICATIONS

4.1 Hypersensitivity

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 AcHIB vaccine [see DESCRIPTION (11)].

5. WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine and other appropriate agents must be available should an acute anaphylactic reaction occur.

5.2 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 AcHIB vaccine, should be based on careful consideration of the potential benefits and possible risks.

5.3 Altered Immunocompetence

In immunosuppressed persons, including those receiving immunosuppressive therapy, the expected antibody responses may not be obtained.

5.4 Limitations of Vaccine Effectiveness

Vaccination with AcHIB vaccine may not protect 100% of individuals.

5.5 Tetanus Immunization

Immunization with AcHIB vaccine does not substitute for routine tetanus immunization.

5.6 Interference with Laboratory Tests

Urine antigen detection may not have a diagnostic value in suspected disease due to Haemophilus influenzae type b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has been detected in the urine of some vaccinees. Urine antigen detection may not have a diagnostic value in suspected disease due to H. influenzae type b or tetanus toxoid-containing vaccine, including AcHIB vaccine [see DRUG INTERACTIONS (7.3)].

5.7 Syncope

Syncope (fainting) has been reported following vaccination with AcHIB. Procedures should be in place to avoid injury from fainting.

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 the 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 AcHIB vaccine during US clinical trials. Of these, 1,064 subjects 12 to 24 months of age who received AcHIB vaccine during US clinical trials. Of these, 1,064 subjects 12 to 24 months of age who received AcHIB vaccine and may not reflect the rates observed in practice.

The incidence of selected solicited injection site and systemic adverse reactions which occurred within 48 hours following immunization with AcHIB vaccine is shown in Table 1.

Table 1: Local and Systemic Reactions at 6, 24, and 48 Hours Following Immunization with AcHIB Vaccine in Children 15 to 20 months old (2)

<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>N=110</td>
<td>N=110</td>
<td>N=110</td>
</tr>
<tr>
<td>Tenderness</td>
<td>20.0</td>
<td>8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Induration</td>
<td>5.5</td>
<td>3.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Swelling</td>
<td>3.6</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Systemic (%)</td>
<td>N=103-110</td>
<td>N=105-110</td>
<td>N=104-110</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;38.0°C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;39.5°C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent cry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unusual cry</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Induration is defined as hardness with or without swelling.

In a US trial (P3070), 1,454 children were enrolled and received one dose of AcHIB vaccine at 2 months of age and subsequent doses administered at 4 and 6 months of age (concomitantly with DAPTACEL + IPOL + ActHIB; a US-licensed diphtheria, tetanus and pertussis vaccine) and POKV [Pneumococcal conjugate vaccine, 7-valent] vaccines at 2, 4, and 6 months of age and hepatitis B vaccine at 2 and 6 months of age. At 15-16 months of age, 418 children received a 4th dose of AcHIB and DAPTACEL vaccines. The most frequent systemic reactions following any dose (>50% of participants) were decreased activity/lethargy, fussiness/ irritability, and inconsolable crying.

Table 2: Number (Percentage) of Children with Selected Solicited Systemic Adverse Reactions by Severity Occurring within 0-3 Days After Vaccination in Study P3070

<table>
<thead>
<tr>
<th>Systemic Reactions</th>
<th>DAPTACEL + IPOL + AcHIB Vaccines</th>
<th>DAPTACEL + ActHIB Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Dose 1 N=1,300-1,406</td>
<td>Dose 2 N=1,246-1,360</td>
</tr>
<tr>
<td>≥38.0°C</td>
<td>9.3</td>
<td>16.1</td>
</tr>
<tr>
<td>≥39.5°C</td>
<td>1.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased Activity/Lethargy</td>
<td>Any</td>
<td>51.1</td>
</tr>
<tr>
<td>Moderate or Severe</td>
<td>24.3</td>
<td>15.8</td>
</tr>
<tr>
<td>Severe</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Inconsolable Crying</td>
<td>Any</td>
<td>58.5</td>
</tr>
<tr>
<td>≥1 hour</td>
<td>16.4</td>
<td>16.0</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>2.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Fussiness/Irritability</td>
<td>Any</td>
<td>75.8</td>
</tr>
<tr>
<td>≥1 hour</td>
<td>33.3</td>
<td>30.5</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>5.6</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Note. - Ages of study participants ranged from 1.3 to 19.5 months.

*Fever is based upon actual temperatures recorded with no adjustments to the measurement route.

†Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 44.8%, 54.0%, 1.0%, and 0.1%, respectively.

Following Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 61.1%, 36.6%, 1.7%, and 0.5%, respectively.

‡Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

In Study P3070, within 30 days following any of Doses 1-3 of DAPTACEL + IPOL + AcHIB vaccines, 50 of 1,455 (3.4%) participants experienced a serious adverse event (SAE). One SAE of seizure with apnea occurring on the day of vaccination with the first dose of the three vaccines was determined by the investigators as possibly related. Within 30 days following Dose 4, four of 418 (1.0%) participants who received DAPTACEL + AcHIB vaccines experienced a serious adverse event. None was assessed by the investigators as related to the study of vaccines.

6.2 Postmarketing Experience

The following events have been spontaneously reported during the post-approval use of AcHIB vaccine. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

- Immune system disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- Nervous system disorders: Convulsions, syncope
- General disorders and administration site conditions: Extensive limb swelling, peripheral edema, pruritus, rash (including generalized rash)

7. DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In clinical trials, AcHIB vaccine was administered, at separate sites, concomitantly with one or more of the following vaccines: DTaP, Measles, Mumps and Rubella vaccine (MMR), Hepatitis B vaccine, and Inactivated Poliovirus Vaccine (IPV). No impairment of the antibody response to the individual antigens was demonstrated when AcHIB vaccine was given at the same time but separate sites with these vaccines.(2)

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to AcHIB vaccine [see WARNINGS AND PRECAUTIONS (5.6)].
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

ActHIB is not approved for use in individuals 6 years of age and older. No human or animal data are available to assess vaccine-associated risks in pregnancy.

8.2 Lactation

ActHIB is not approved for use in individuals 6 years of age and older. Human or animal data are not available to assess the impact of ActHIB on milk production, its presence in breast milk, or its effects on the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of ActHIB have not been established in infants below the age of 6 weeks and children and adolescents 6 years of age and older [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 Haemophilus influenzae type b capsular polysaccharide (polysorbil-1,2,3,4-tetraol-phosphate, PRP), a high-molecular-weight polymer prepared from H. influenzae strain 1482 grown in a semisynthetic medium, covalently bound to tetanus toxoid. (4) The lyophilized ActHIB vaccine powder and saline diluent contain no preservative. The tetanus toxoid is prepared by extraction, ammonium sulfate purification, and formalin inactivation of the toxoid from Clostridium tetani (Harvard strain) grown in a modified Mueller and Miller medium. (9) The culture medium contains milk-derived raw materials (casein derivatives). Further manufacturing process steps reduce residual formaldehyde to levels below 0.5 micrograms (mcg) per dose by calculation. The toxoid is filter sterilized prior to the conjugation process. In the final formulated vaccine, pH is adjusted using hydrochloric acid. Potency of ActHIB vaccine is specified on each lot by limits on the content of PRP polysaccharide and protein in each dose and the proportion of polysaccharide and protein in the vaccine that is characterized as high molecular weight conjugate. When ActHIB is reconstituted with saline diluent (0.4% Sodium Chloride), each 0.5-mL dose is formulated to contain 10 mcg of purified capsular polysaccharide conjugated to 24 mcg of inactivated type b capsular polysaccharide vaccine. (5) The vaccine was demonstrated in serum after immunization and correlated with the anti-PRP antibody response induced by ActHIB vaccine. (1)

Antibody titers to H. influenzae capsular polysaccharide (anti-PRP) of >1.0 mcg/mL following vaccination with unconjugated PRP vaccine correlated with long-term protection against invasive Haemophilus influenzae type b disease in children older than 24 months of age. (7) Although the relevance of this threshold to clinical protection after immunization with conjugate vaccines is not known, particularly in light of the induced, immunologic memory, this level continues to be considered as indicative of long-term protection. (9) In clinical studies, ActHIB vaccine induced, on average, anti-PRP levels ≥1.0 mcg/mL in 90% of infants after the primary series (2, 4, and 6 months) and in more than 98% of infants following a booster dose given at 15 to 19 months of age. (1)

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenicity

No evidence of carcinogenicity was demonstrated in any of ActHIB vaccine studies in races, sex, or age groups. The local irritant associated with ActHIB vaccine is protein derived from egg. (2) Human and animal data are not available to assess the impact of ActHIB on milk production, its presence in breast milk, or its effects on the breastfed infant.

14 CLINICAL STUDIES

14.1 Immunogenicity of ActHIB Vaccine in Children 2, 4, and 6 Months of Age

Two clinical trials supported by the National Institutes of Health (NIH) have compared the anti-PRP antibody responses to three Haemophilus influenzae type b conjugate vaccines in racially mixed populations of children. These studies were done in Tennessee (Table 3) and in Minnesota, Missouri, and Texas (10) (Table 4) in infants immunized with ActHIB vaccine and other Haemophilus influenzae type b conjugate vaccines. In all studies, ActHIB vaccine-induced antibody responses to PRP were comparable to those induced by other Haemophilus influenzae type b conjugate vaccines. These studies were done in racially mixed populations of children. These studies were done in Tennessee (Table 3) and in Minnesota, Missouri, and Texas (Table 4) in infants immunized with ActHIB vaccine and other Haemophilus influenzae type b conjugate vaccines. In all studies, ActHIB vaccine-induced antibody responses to PRP were comparable to those induced by other Haemophilus influenzae type b conjugate vaccines. In the studies comparing ActHIB vaccine with other Haemophilus influenzae type b conjugate vaccines, the laboratory results demonstrated that 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.

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 vaccine 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. (2)

15 REFERENCES

1 Data on file, Sanofi Pasteur SA.
2 Data on file, Sanofi Pasteur Inc.
14 CDC. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 37:197-200, 1988.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Single-dose, lyophilized vaccine vial (vial 1 of 2) (NDC 49281-547-58) packaged with single-dose diluent vial (vial 2 of 2) (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° to 8°C (35° to 46°F). DO NOT FREEZE. Discard unused portion.

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 guardians 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. (13) (14) (15) 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, DAPTACEL and IPOL are registered trademarks of Sanofi Pasteur Inc.
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HibTITER is a registered trademark of Nuron Biotech.

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