

## Summary for Basis of Approval

Reference Number:  
90-0689

Drug Licensed Name:  
Haemophilus b Conjugate Vaccine  
(Tetanus Toxoid Conjugate)

Manufacturer:  
Pasteur Merieux Serums & Vaccins, S.A.

Drug Trade Name:  
ActHIB™

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™, is composed of the purified capsular polysaccharide isolated from *Haemophilus influenzae* type b covalently attached to tetanus toxoid prepared from the inactivated toxin of *Clostridium tetani*.

### I. INDICATIONS AND USAGE

ActHIB™ is indicated for the active immunization of infants and children 2 months through [REDACTED] of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b.

Levels of antibody associated with protection may not be achieved earlier than two weeks following the last recommended dose.

*As with any vaccine, vaccination with ActHIB™ may not protect 100% of susceptible individuals.*

### II. DOSAGE AND ADMINISTRATION:

The vaccine is a sterile, lyophilized powder which is to be reconstituted just before use with the supplied saline diluent (0.4% sodium chloride). Each 0.5 mL dose of ActHIB is formulated to contain 10 µg of purified capsular polysaccharide conjugated to approximately 24 µg of tetanus toxoid. The vaccine also contains 8.5% sucrose. The vaccine and diluent contain no preservatives. The vaccine when reconstituted is colorless and should be injected intramuscularly in the outer aspect of the vastus lateralis (mid thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve tract. In the event of [REDACTED] ActHIB may be given [REDACTED] in the lateral aspect of the thigh.

Infants between 2 and 6 months of age should receive three 0.5 mL doses at 6 to 8 week intervals, followed by a booster at 15 to 18 months of age. Infants 7 to 11 months of age who have not been previously immunized should receive two 0.5 mL doses at 6 to 8 week intervals, followed by a booster dose at 15 to 18 months of age. Children 12 to 14 months of age who have not been previously immunized should receive one 0.5 mL dose, followed by a booster at 15 to 18 months of age, but not less than 2 months

after the previous dose. Children 15 to [redacted] months of age who have not been previously immunized should receive a single 0.5 mL dose. ActHIB™ is packaged in single dose vials with a [redacted] 0.6 mL syringe containing 0.4% sodium chloride diluent.

The recommended immunization schedule is summarized as follows:

Age at First Dose (months)	Primary Series	Booster
2 to 6	3 Doses, 6 to 8 weeks apart	1 Dose, 15 to 18 months
7 to 11	2 Doses, 6 to 8 weeks apart	1 Dose, 15 to 18 months
12 to 14	1 Dose	1 Dose, 15 to 18 months
15 to [redacted]	1 Dose	None

The current recommendation of the Advisory Committee on Immunization Practices (ACIP) is for routine immunization of all children with Haemophilus b conjugate vaccine beginning at 2 months of age.

### III. MANUFACTURING AND CONTROLS

#### A. Manufacturing and Control testing:

Haemophilus b Polysaccharide: The organism, *H. influenzae* type b strain [redacted] is grown in a chemically defined [redacted] medium. The capsular polysaccharide is [redacted] from the [redacted] medium by the addition of [redacted] [redacted] and the product is purified by [redacted] [redacted] The purified polysaccharide is assayed for [redacted] protein and [redacted] content. [redacted] and identity [redacted] tests are also performed.

The [redacted] polysaccharide is obtained from the purified polysaccharide by reaction with [redacted] and [redacted]. The [redacted] is then tested for [redacted] content, [redacted] and [redacted]

Carrier protein: The tetanus toxin is prepared from cultures of *Clostridium tetani* grown in a modified Mueller and Miller medium. Tetanus toxin is purified, [redacted] and filter-sterilized to obtain tetanus toxoid. Assays for [redacted]

[REDACTED] percentage of [REDACTED] and [REDACTED] are performed.

Conjugation and purification: Tetanus toxoid and the [REDACTED] polysaccharide are conjugated using [REDACTED]. The conjugate is purified by [REDACTED] to eliminate [REDACTED] and [REDACTED] conjugate. The [REDACTED] bulk is sterilized by [REDACTED] filtration. Assays are performed for [REDACTED] and [REDACTED] content, [REDACTED]. The potency test for this vaccine is a combination of two physical-chemical assays; percentage of HMWC and the protein to polysaccharide ratio.

Final vaccine: The final bulk vaccine is obtained from the concentrated bulk by [REDACTED] in [REDACTED], pH [REDACTED] containing 8.5% sucrose, sterilized by [REDACTED] filtration and then filled into vials and lyophilized. The lyophilized product is tested for identity, polysaccharide content, general safety, sterility, pyrogenicity, pH, residual moisture, sucrose, percentage of HMWC, and [REDACTED]. The release specifications are shown in Table 1.

The manufacturer submitted three lots of vaccine, S2440, S2441 and S2468, for demonstration of manufacturing consistency as well as two later lots for release testing, H1025 and H0990. These lots met the specifications shown in Table 1.

#### B. Stability studies:

The recommended storage temperature of the lyophilized vaccine and [REDACTED] syringe containing diluent is +2° to + 8° C (35° - 46° F). Stability of the vaccine was monitored by the evaluation of [REDACTED] and [REDACTED]. Following storage of the vaccine at the recommended temperature range for [REDACTED] months (three vaccine lots) and at higher temperatures, the product was shown to be stable. Based on results from these stability studies, the dating period is [REDACTED] months at +2° to +8° C from the date of initiation of the final container potency tests (% HMWC and polysaccharide:protein ratio). Pasteur Merieux serums & Vaccins has made a commitment to an ongoing stability program.

C. Validation:

The major equipment used in the manufacture and filling of the vaccine have been validated. In addition, appropriate specifications have been established for monitoring environmental conditions for each critical work area of the manufacturing facilities located in [REDACTED], near Lyon, France.

D. Labeling: The package insert is in compliance with the appropriate sections, 610.60, 610.61, 610.62, 201.56, and 201.57, of 21 CFR and contains statements concerning use, contraindications, warnings, immunogenicity, experience, precautions, adverse reactions, dosage and administration, how supplied, and information on storage of the vaccine.

The primary label used on the vials of **HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate)** states the following: the proper name and the trade name, **HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) ActHIB™**; a statement referring to the package insert for dosage information; storage statements, **DO NOT FREEZE. Store at 2° – 8°C (35° – 46°F)**; a caution stating to **SHAKE WELL after reconstitution**; space for adding lot number and expiration date at the time of packaging; the NDC number; Mfd. by: **PASTEUR MERIEUX Serums & Vaccins S.A., Lyon, France**, US. Lic. No. 384.

The primary label used on the vial of **DILUENT FOR HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate)** states the following: contents of vial, **0.6 mL**; contains **(0.4% Sodium Chloride)**; space for adding a lot number and the expiration date at the time of labeling vials; Mfd. by **PASTEUR MERIEUX Serums & Vaccins S.A., Lyon, France**

The label on the unit carton for **HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate)** states the following: the proper name and the trade name, **HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) ActHIB™**; contents of vials **(1 dose)**; storage conditions, **Store between 2° – 8°C (35° – 46°F)**; the caution statement concerning the federal dispensing law; a caution to **SHAKE WELL after reconstitution**; a statement referring to the package insert for indications and directions; a space for adding lot number and expiration date at the time of packaging; the NDC number; Mfd. by **PASTEUR MERIEUX Serums & Vaccins S.A.,**

Lyon, France, US. License No. 384, and distributed by Connaught Laboratories, Inc., Swiftwater, PA.

**E. Establishment Inspection:**

The facilities were inspected by the FDA on two separate occasions. The first preliminary inspection was done in June, 1991. The most recent pre-license inspection was on February 5-7, 1992. The facilities, manufacturing protocols, quality control laboratory, storage conditions, record keeping, and other aspects of conjugate manufacturing were considered to be satisfactory and in compliance with applicable regulatory requirements.

**F. Environmental Assessment**

Production of this product occurs entirely in France. Substances toxic to the environment are not released into the environment. Environmental assessment was filed, reviewed and a Finding of No Significant Impact was prepared for this product approval for Pasteur Merieux Serums et Vaccins. The company has stated that they are in compliance with all state, local or governmental requirements of the country in which production occurs.

**IV. PHARMACOLOGY:**

The manufacturer's labeling is adequate with respect to pharmacology. For additional information see the clinical pharmacology section of the attached package insert.

**V. MEDICAL**

**A. General information:**

For many years *H. influenzae* type b (Haemophilus b) has been the leading cause of invasive bacterial diseases, such as meningitis, septicemia and epiglottitis, in young children in the United States. Ninety-five percent of invasive Haemophilus b disease among children <5 years of age is caused by organisms with the type b polysaccharide capsule. Before effective vaccines were introduced, it was estimated that 1/200 children developed invasive Haemophilus b disease by 5 years of age. Sixty percent of these children had meningitis, with a 3% to 6% mortality rate. Permanent sequelae, ranging from mild hearing loss to mental retardation, affects 20% to 30% of survivors of Haemophilus b meningitis. Approximately two-thirds of all cases of invasive

Haemophilus b disease occur in infants and children <15 months of age, a group for which a vaccine was not available until 1990.<sup>1,2</sup>

It has been shown by a number of investigators that the *H. influenzae* type b capsule is a major virulence factor. Antibodies to the capsular polysaccharide are bactericidal and opsonize the bacteria for phagocytic killing. Studies in the United States showed that the peak incidence of Haemophilus b disease occurs in children between 6 and 12 months of age, a time period in which the lowest antibody levels to the organism are found. In a field trial performed in Finland in 1974, the presence of antibodies induced by an Haemophilus b polysaccharide vaccine was shown to correlate with protection. Thus protection against Haemophilus b disease is correlated with the presence of antibody to the Haemophilus b polysaccharide.

An anti-PRP antibody titer  $\geq 1.0 \mu\text{g/mL}$  following vaccination with unconjugated PRP vaccine was associated with long-term protection against invasive Haemophilus b disease. Although the relevance of this antibody threshold to clinical protection after immunization with a conjugate vaccine is not known, this level continues to be considered as indicative of long-term protection.

The incidence of invasive Haemophilus b disease is higher in Native Americans, Eskimos, children of lower socioeconomic status and those with asplenia, sickle cell disease, Hodgkin's disease, or immunodeficiency syndromes. Studies also have suggested that the risk of acquiring primary invasive Haemophilus b disease under 5 years of age appears to be higher for children attending day-care facilities.

The potential for person-to-person transmission of the Haemophilus b organism among susceptible individuals has been recognized. Studies of secondary spread of disease in household contacts of index patients have shown a substantially increased risk among exposed household members under 4 years of age.

The characteristics of an immune response depend on the type of cells producing the response and the antigens stimulating the response. Proteins induce B lymphocytes to produce antibody aided by thymus derived lymphocytes called T helper (TH) cells. Such antigens are called thymus-dependent or TD antigens. These antigens induce long lasting responses in young infants that prime for a booster type response on reexposure to the antigen. In contrast, polysaccharides stimulate B cells without TH

cell help, producing a response of both IgG and IgM antibodies that does not prime for a booster type response. These antigens are called thymus-independent or TI antigens. TI antigens are poorly immunogenic at best in young infants. Chemical linkage of the Haemophilus b polysaccharide or smaller oligosaccharides to a protein carrier such as tetanus toxoid apparently converts the TI saccharide to a TD antigen. This results in an enhanced antibody response, especially in infants, to the polysaccharide that is long-lasting, and is predominantly of the IgG isotype. The conjugate importantly primes for an anamnestic response on reexposure to the polysaccharide.

**B: Brief description of clinical studies:**

Overview: ActHIB™ has been administered to more than 200,000 infants worldwide during the program of clinical trials and over 500,000 infants in France following approval in that country. Few serious adverse reactions have been reported and, when given with DTP vaccine, the adverse experience profile is not different from that ordinarily seen when DTP is administered alone. Immunogenicity has been evaluated in more than 1,500 infants. After the primary three dose immunization series, ActHIB™ induces PRP antibody levels  $\geq 1.0 \mu\text{g/mL}$  in approximately 90% of infants as measured by [REDACTED]

Safety: Using the US immunization schedule at 2, 4, and 6 months of age and route of immunization, ActHIB™ has been evaluated for safety in over 7,400 children with in excess of 20,000 doses. Numbers of studies and age groups involved are summarized in Table 2. Most children under 12 months of age also received DTP and oral polio vaccines at the same visit. In a multicenter (GA, MS, OH, PA, UT) study 365 infants were followed for 72 hours after IM administration of ActHIB™ and DTP at separate sites. Data were collected after 6, 24, 48 and 72 hours and the reaction rates at 24 hours are shown in Table 3 (see also package insert Table 5). The rates of reactions were not different from those expected following administration of DTP alone. All reaction rates declined with time and by 72 hours most had resolved. In other studies approximately 1,450 doses of ActHIB™ were administered to 12 to 24 month-old children without any serious adverse events.

During an efficacy trial initiated in Southern California, 4,300 children received ActHIB™ and DTP at the same time in separate legs at approximately 2, 4 and 6 months of age. Of these, approximately 3,000 children were followed for 30 days for

both common and less common adverse reactions temporally associated with vaccine administration. A similar number of children received Hepatitis B vaccine in place of ActHIB™. The rates of adverse reactions were not significantly different for both groups. Less common events occurring within 30 days of immunization were monitored. After 13,000 doses of ActHIB™, 5 SIDS and 5 febrile seizures were seen in the ActHIB group, compared to 4 SIDS and 2 febrile seizures in the Hepatitis B group.

Additional safety data with ActHIB™ are available from the efficacy studies conducted in North Carolina (820 infants), in Oxford, England (26,600 infants, see reference 6), and in Finland (107,000 infants). In each of these studies the vaccine was well tolerated and no serious adverse reactions were reported.

Efficacy: Efficacy of ActHIB™ was evaluated based upon fulfillment of a series of immunological surrogates (described below). Approval of this vaccine was based primarily upon the immunological surrogates, because (1) two other Haemophilus b conjugate vaccines were approved for routine use infants in 1990, (2) the English trial did not use the US immunization schedule, and (3) because once an effective vaccine was approved in the US it becomes very difficult to conduct an acceptable controlled clinical trial to demonstrate efficacy of another vaccine for the same indication. The surrogate data are supported by a published report of efficacy in a field trial in England using a different immunization schedule than that recommended in the US.

Approval of the first Haemophilus b conjugate vaccine for use in infants in October, 1990, resulted in termination of two ongoing efficacy trials with ActHIB™ in approximately 12,000 subjects, half of whom received ActHIB™. It can be noted that at the time the studies were terminated no cases of Haemophilus b disease had occurred in subjects receiving the full three dose immunization series.

Some immunologic surrogates of an effective Haemophilus b conjugate vaccine are presented in Table 4. Studies of four different Haemophilus b conjugate vaccines have shown a number of common features that clearly differentiate the immune responses to conjugate vaccines from those to the unconjugated Haemophilus b polysaccharide. These include induction of antibodies in infants at an age when they do not respond to the free polysaccharide, induction of higher levels of IgG relative to IgM, and priming of infants for a booster response to the native polysaccharide. However, conjugate vaccines differ from one another in the magnitude and duration of

the initial response after the recommended 2 or 3 dose immunization series. Protection against *Haemophilus b* disease is associated with opsonic and bactericidal antibodies directed against the capsular polysaccharide. It is likely that opsonic activity alone is sufficient because individuals with deficiencies in the late complement components appear not to be at increased risk of *Haemophilus b* disease, as they are for neisserial disease. Bactericidal and opsonic antibody levels to *H. influenzae* type b have been shown to correlate with one another. It was the opinion of the FDA Vaccines and Related Biological Products Advisory Committee in September 1991, that immunological criteria, as shown in Table 4, could be used as the basis for demonstrating clinical efficacy of a new *Haemophilus b* conjugate vaccine. This was confirmed again by the Committee a year later. These immunological surrogates were therefore used to demonstrate immunological equivalence between ActHIB and the two licensed *Haemophilus b* conjugate vaccines approved for administration to infants.

Immune surrogates for efficacy: It was important to determine whether ActHIB™ induced similar amounts of anti-*Haemophilus b* polysaccharide antibody and seroconversion rates to 1 ug/mL, compared to the other licensed vaccines. The immunogenicity of HibTITER®, PedVaxHib™, and ActHIB™ was compared in a randomized trial in 458 US. infants. All sera were blindly assayed at the Pediatric Division of Infectious Diseases, [REDACTED] Results show that 97% of ActHIB recipients had a PRP antibody concentration  $\geq 1.0$   $\mu\text{g}/\text{mL}$  after the third dose, with a geometric mean titer of 6.37  $\mu\text{g}/\text{mL}$  (see Figure 1). By comparison, the values for HibTITER®, and PedVaxHib™ after the primary immunization series were 90% (6.31  $\mu\text{g}/\text{mL}$ ) and 85% (4.00  $\mu\text{g}/\text{mL}$ ) respectively. The antibody concentrations after the final dose of the primary series were not significantly different among the three groups.

A randomized comparative trial at Vanderbilt University School of Medicine (TN) compared the immunogenicity of two *Haemophilus b* conjugate vaccines (HibTITER®, and PedVaxHib™ ) to ActHIB™, given at 2, 4 and 6 months concomitantly with DTP vaccine. All sera were blindly assayed at Vanderbilt University Pediatric Infectious Disease Laboratory. Results showed that 83% of ActHIB™ recipients had a PRP antibody concentration  $\geq 1.0$   $\mu\text{g}/\text{mL}$  after the third dose, with a geometric mean titer of 3.64  $\mu\text{g}/\text{mL}$  (see Figure 1). The comparable values for HibTITER®, and PedVaxHib™ were 75% (3.08  $\mu\text{g}/\text{mL}$ )

and 55% (1.14 ug/mL) respectively. After the recommended two dose series for PedVaxHib the geometric mean titer was 0.84  $\mu$ g/mL and 50% had  $\geq 1.0 \mu$ g/mL.

Antibody persistence to the age of the recommended booster dose (15 to 18 months) was examined in 141 French children, after immunization at 3, 4, and 5 months of age. After the primary immunization series the GMT for anti-PRP antibody was 4.31  $\mu$ g/mL, and 88.2% had  $\geq 1 \mu$ g/mL. At 18 months immediately prior to booster immunization the antibody level was 1.22  $\mu$ g/mL and 54% had  $\geq 1 \mu$ g/mL. Similar results were observed in the comparative trial in Tennessee, where the GMT was 0.55  $\mu$ g/mL at 15 months of age and 21.49  $\mu$ g/mL 1 month later after the booster.

It is important to know that the conjugate vaccine will induce a memory type response in infants, so that upon exposure to the native polysaccharide a rapid antibody response may occur. This also helps confirm the T-cell dependent nature of the response. Administration of pure polysaccharide vaccine at 14 months of age after the primary immunization series at 4 and 6 months of age in Finnish children confirmed that ActHIB™ had primed for an anamnestic response to the polysaccharide. In 24 Finnish children the anti-Haemophilus b polysaccharide antibody levels at 14 and 15 months were 1.8 and 29.4  $\mu$ g/mL with 66.7 and 95.7 percent of the children having  $\geq 1.0 \mu$ g/mL before and after immunization with the polysaccharide respectively.

Studies of the isotype distribution showed that IgG Haemophilus b antibody is increasingly predominant after the second and third doses of ActHIB™, attesting to the T-dependent characteristics of ActHIB™, and that [redacted] antibody is the predominant subclass after the primary three dose immunization series.

ActHIB™ vaccine-induced antibody is functionally effective. Complement mediated bactericidal and opsonic activity were present in serum after vaccination. Post-immunization bactericidal and PRP antibody titers were statistically correlated. In comparative assays, bactericidal activity of ActHIB™ induced antibody was found to be similar to that reported with the two other US. vaccines licensed for infants. In studies by Schlesinger et al. (1992) they found that the mean avidity of antibodies induced by ActHIB was somewhat lower than for HibTITER,  $1.9 \text{ nM}^{-1}$  ( $28\% \geq 2.50 \text{ nM}^{-1}$ ) versus  $2.6 \text{ nM}^{-1}$  ( $52\% \geq 2.50 \text{ nM}^{-1}$ ), and the bactericidal titers were directly correlated with the avidity. Sera with avidities of  $\geq 2.50 \text{ nM}^{-1}$  required 6.6 fold less antibody for similar bactericidal activity.

Immunogenicity in toddlers: In three US trials in children 12 to 15 months of age and in one trial in 17 to 24 month-olds, a single dose of ActHIB™ produced an antibody response comparable to that achieved by the 3 dose primary immunization series in infants. In 256 children 12 to 15 months of age the mean antibody levels increased from 0.06 to 5.12 ug/mL. Ninety percent of these children had  $\geq 1$  ug/mL of anti-polysaccharide antibody after immunization.

C. Advisory Committee Considerations: Data regarding the manufacture, immunogenicity and safety of Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) were discussed at length at two meetings of the Vaccines and Related Biological Products Advisory Committee on September 5, 1991 and October 28, 1992. It was the consensus of the Committee at the 1991 meeting that immune surrogates could be used to show clinical potency in infants. At the 1992 meeting it was the Committee's opinion that Pasteur Merieux had satisfactorily demonstrated safety and effectiveness of the ActHIB™ vaccine using these surrogates.

D. Adequacy of labeling: The labeling for the Pasteur Merieux Haemophilus b conjugate vaccine is appropriate for the product and indication.

#### VI. APPROVED PACKAGE INSERT:

The package insert is attached.

Carl E. Frasch, Ph.D.  
Chairman

Bascom F. Anthony, M.D.

Jane L. Halpern, Ph.D.

Kathryn Stein, Ph.D.

Ann Sutton, M.A., MPH

Willie F. Vann, Ph.D.

**Key references:**

1. S.B. Black, H.R. Shinefield, B. Fireman, R. Halt, M. Polen, E. Vittinghoff, and North CA Kaiser Perm Vaccine Sty Ctr, Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61 080 children, Pediatr. Infect. Dis. J., **10**:97 (1991).
2. M. Santosham, M. Wolff, R. Reid, M. Hohenboken, M. Bateman, J. Goepp, M. Cortese, D. Sack, J. Hill, W. Newcomer, L. Capriotti, J. Smith, M. Owen, S. Gahagan, D. Hu, R. Kling, L. Lukacs, R.W. Ellis, P.P. Vella, G. Calandra, H. Matthews, and V. Ahonkhai, The efficacy in Navajo infants of a conjugate vaccine consisting of *Haemophilus influenzae* type b polysaccharide and *Neisseria meningitidis* outer-membrane protein complex, N. Engl. J. Med., **324**:1767 (1991).
3. C. Chu, R. Schneerson, J. B. Robbins, S. C. Rastogi, Further studies on the immunogenicity of *Haemophilus influenzae* type b and pneumococcal type 6A polysaccharide-protein conjugates, Infect. Immun., **40**: 245, (1983).
4. D.M. Granoff, E.L. Anderson, M.T. Osterholm, S.J. Holmes, J.E. McHugh, R.B. Belshe, F. Medley, and T.V. Murphy, Differences in the immunogenicity of three *Haemophilus influenzae* type b conjugate vaccines in infants, J. Pediatr., **121**:187 (1992).
5. M.D. Decker, K.M. Edwards, R. Bradley, and P. Palmer, Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines, J. Pediatr., **120** :184 (1992).
6. R. Body, E.R. Moxon, J.A. MacFarlane, R.T. Mayon-White, and M.P.E. Slack, Efficacy of *Haemophilus influenzae* type b conjugate vaccine in Oxford region. Lancet **340**:847, 1992.
7. Schlesinger, Y. D.M. Granoff, and the Vaccine Study Group: Avidity and bactericidal activity of antibody elicited by different *Haemophilus influenzae* type b conjugate vaccines. JAMA **267**:1489, 1992

**Table 1. Release specifications for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Pasteur Mérieux**

1. Haemophilus b polysaccharide determined on			
2. Tetanus toxoid			
3. Bulk conjugate			
4. Final container	Sterility Identity General safety Pass rabbit pyrogen test Residual moisture  /dose Sucrose/dose		

**Table 2. Summary of studies for safety pertaining to use of ActHIB™ in the United States**

Study	Age (mo)	Other vaccines	Total subjects receiving ActHIB™				Route	Country
			Combined *	Separate *	Alone	Total		
CLI-1	12	none	0	0	36	36	IM	USA
CLI-2	12 to 15	none	0	0	256	256	IM	USA
CLI-3	15 to 17	none	0	0	50	50	IM	USA
CLI-4	17 to 24	none	0	0	134	134	IM	USA
NIH, TN	2	DTP	0	65	0	65	IM	USA
UCLA, efficacy	2	DTP	0	5212	0	5212	IM	USA
NC efficacy	2	DTP	0	760 **	60 **	820	IM	USA
Multicenter	2	DTP	0	365	0	365	IM	USA
CLI-5	2	DTP	152	148	0	300	IM	USA
CLI-6	2	DTP	45	45	0	90	IM	USA
Canada	2	DTP	220	222	0	442	IM	Canada #
Chile	2	DTP	94	92	0	186	SC	Chile #
Totals:			511	6909	536	7956		

\* ActHIB™ was in most studies administered at a separate site from DTP, but four studies included some individuals who received ActHIB™ combined in the same syringe with Connaught Laboratories, Inc. DTP, a formulation not currently approved.

\*\* In the NIH sponsored trial in North Carolina, for each adverse reaction, the number of individuals examined varied, and thus the numbers shown are approximate.

# Children in Canada and Chile received vaccine using the USA immunization schedule at 2, 4, and 6 months of age at separate sites from DTP, excepting those who received a combined vaccine.

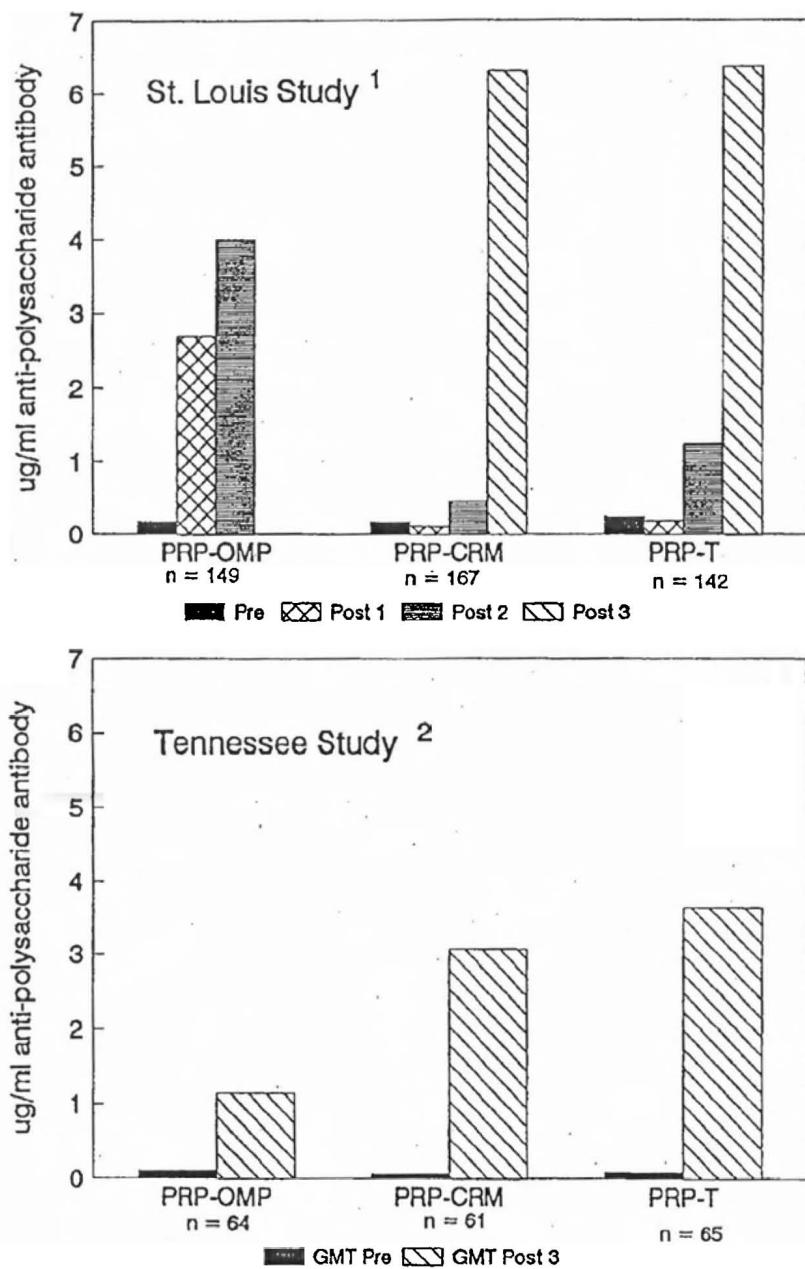
**Table 3. Multicenter evaluation of ActHIB™ given simultaneously with DTP for safety and immunogenicity - Percent local and systemic reactions observed 24 hours after immunization**

Number:	Dose 1	Dose 2	Dose 3
	365	364	365
<b>Local Reactions</b>			
Redness:			
Any	4.1	5.8	6.9
> 1 inch	0	0.8	0.8
Swelling	6.3	4.7	3.8
Tenderness	11.5	7.4	6
<b>Systemic Reactions</b>			
Temperature			
100.8-102	1.1	5.5	8.0
>102.0	0.3	1.1	0.8
Irritability	21.9	25	25.2
Drowsiness	29.9	18.1	13.4
Anorexia	5.8	5	4.9
Diarrhea	6.6	4.7	6.3
Vomiting	4.1	3.3	2.7
Rhinorrhea	5.5	12.1	11.8
Cough	6.9	9.4	5.2
Rash	0.3	0	0.8

Table 4. Some items including immunological surrogates used in evaluation of the Pasteur Merieux Haemophilus b Conjugate Vaccine

- 
1. Demonstration of safety.
  2. Randomized comparative study with currently licensed vaccines in infants for demonstration of comparable immunogenicity. The primary comparison would be seroconversion rates to 0.15  $\mu\text{g}/\text{ml}$  and 1.0  $\mu\text{g}/\text{ml}$  after the primary immunization series. The antibody assays should be done in the same laboratory.
  3. Examination of antibody persistence to the age of the recommended booster dose.
  4. Demonstration that the vaccine primes the infants for a subsequent booster response to the native polysaccharide. The polysaccharide should be given 6 months or more after completion of the primary immunization series.
  5. Determination of the IgG, IgM, and IgG subclass response following primary immunization series.
  6. Demonstration of functional capacity of conjugate-induced antibodies by opsonic or bactericidal assay in young children.

**Figure 1.**  
**Comparative antibody responses to three different Haemophilus b conjugate vaccines**



PRP-OMP = PedVaxHib, Merck      PRP-CRM = HibTITER, Praxis Biologics  
 PRP-T = ActHIB, Pasteur Mérieux

1. Granoff et al. J. Pediatr. 121:187, 1992

2. Decker et al. J. Pediatr. 120:184, 1992