A.H.F.S. Category 80:12

Haemophilus b Conjugate Vaccine
(Diphtheria Toxoid-Conjugate)

ProHIBiT®

Caution: Federal (USA) law prohibits dispensing without prescription.

DESCRIPTION

ProHIBiT®, Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate), for intramuscular use, is a sterile solution, prepared from the purified capsular polysaccharide, a polymer of ribose, ribitol and phosphate (PRP) of the Eagen *Haemophilus influenzae* type b strain covalently bound to diphtheria toxoid (D) and dissolved in sodium phosphate buffered isotonic sodium chloride solution. The polysaccharide-protein conjugate molecule is referred to as PRP-D. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. The vaccine is a clear, colorless solution. Each single dose of 0.5 mL is formulated to contain 25 µg of purified capsular polysaccharide and 18 µg of diphtheria toxoid protein.

CLINICAL PHARMACOLOGY

Haemophilus influenzae type b (Haemophilus b) was a leading cause of serious systemic bacterial disease in the United States. Prior to licensure of Haemophilus b Conjugate Vaccines, it was the most common cause of bacterial meningitis, accounting for an estimated 12,000 cases annually, primarily among children under five years of age. The mortality rate was 5%, and neurologic sequelae were observed in as many as 25%-35% of survivors.[1] Most cases of *Haemophilus influenzae* meningitis among children are caused by capsular strains of type b, although this capsular type represents only one of the six types known for this species. In addition to bacterial meningitis, Haemophilus b is responsible for other invasive diseases, including epiglottitis, sepsis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia.[1]

In the United States prior to licensure of Haemophilus b Conjugate Vaccines, approximately one of every 1000 children under five years of age developed systemic Haemophilus b disease each year, and a child's cumulative risk of developing systemic Haemophilus b disease at some time during the first five years of life was approximately one in 200. Attack rates peaked between six months and one year of age and declined thereafter.[1]

Approximately 75%-85% of Haemophilus b disease occurs among children less than 24 months of age.[2,3,4] Incidence rates of Haemophilus b disease are increased in certain high-risk groups, such as native Americans (both American Indian and Eskimos), blacks, individuals of lower socioeconomic status, and patients with asplenia, sickle cell disease, Hodgkin's disease, and antibody deficiency syndromes.[1,4] Recent studies also have suggested that the risk of acquiring primary Haemophilus b disease for children under five years of age appears to be greater for those who attend day-care facilities.[5,6,7,8]

The potential for person-to-person transmission of the 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 contacts under four years of age.[9] Adults can be colonized with *Haemophilus influenzae* type b from children infected with the organism.[10]

In 1974, a randomized controlled trial was conducted in Finland, which allowed the evaluation of clinical efficacy of a non-conjugated Haemophilus type b polysaccharide vaccine in children 3 to 71 months of age.[11] Approximately 98,000 children, half of whom received the Haemophilus b vaccine, were enrolled in the field trial and followed for a four-year period for the occurrence of Haemophilus b disease. Among children 18 to 71 months of age, 90% protective efficacy (95% confidence limits, 55%-98%) was demonstrated for the four-year follow-up period in prevention of all forms of invasive Haemophilus b disease.

Based on evidence from this 1974 Finnish efficacy trial, from passive protection in the infant rat model, and from experience with agammaglobulinemic children, an antibody concentration of ≥ 0.15 µg/mL has been correlated with protection.[11,12,13,14] Antibody levels of ≥ 1 µg/mL were correlated with long-term protection in three-week post-vaccination serum. Anti-capsular antibodies induced by ProHIBiT® in children 18 months of age and older had bactericidal activity, opsonic activity and were also active in passive protection assays.[15,16,17]

The development of stable humoral immunity requires the recognition of foreign material by at least two separate sets of lymphocytes. These sets are the B-lymphocytes which are precursors of antibody forming cells, and the T-lymphocytes which modulate the function of B-cells. Some antigens such as polysaccharides are capable of stimulating B-cells directly to produce antibody (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent).[18]

The manufacturing process utilizes a technology of covalent bonding the capsular polysaccharide of *Haemophilus influenzae* type b to diphtheria toxoid, to produce an antigen which is postulated to convert a T-independent antigen into a T-dependent antigen.[19,20] The protein carries both its own antigenic determinants and those of the covalently bound polysaccharide. As a result of the conjugation to protein, the polysaccharide is presented as a T-dependent antigen resulting in both an enhanced antibody response and an immunologic memory.

In studies conducted with ProHIBiT® in several locations throughout the US, the antibody responses of 18- to 26-month-old children were measured (Table 1).[15] In other studies, the antibody responses to licensed Haemophilus b polysaccharide vaccines were measured in a comparable age group (Table 1).[15] The data shown in Table 1 were obtained from sera tested in one laboratory using a single radioimmunoassay (RIA). Mean antibody levels induced by ProHIBiT® in children 18 to 20 months of age are 30-fold higher than those induced by polysaccharide vaccines in the same age group.[15]

The RIA procedure used by Connaught Laboratories, Inc. to estimate antibody responses to the Haemophilus b vaccines has been shown to correlate with the assay used by the Finland National Public Health Institute.[21] Antibody levels (≥ 1.0 µg/mL) estimated by the Finnish assay were correlated with protection.[11]

TABLE 1[15] **Immunogenicity Studies of ProHIBiT® and Polysaccharide Vaccines***

Vaccine	Age Group	No. of Subjects	Anti-Polysaccharide GMT (µg/mL) Pre	Anti-Polysaccharide GMT (µg/mL) Post	% Subjects Responding with ≥ 1.0 µg/mL**
ProHIBiT®	15 to 17 Mo.	43	0.017	1.12	53%
	18 to 21 Mo.	173	0.025	2.85	75%
	22 to 26 Mo.	37	0.021	2.96	73%
POLYSACCHARIDE	18 to 20 Mo.	51	0.021	0.100	24%
	24 to 27 Mo.	84	0.035	0.520	43%

* Only subjects whose sera had preimmunization levels ≤ 0.60 µg/mL were included in this analysis.

** A subset of these data was obtained from a randomized comparison of the two vaccines, in which the percentage of children 18 to 20 months of age responding with ≥ 1.0 µg/mL was 75% for ProHIBiT® (n=12) and 27% for the polysaccharide (n=11).

Following immunization of 16 to 24-month-old children with a single dose of ProHIBiT®, 89% (109/123) had antibody levels ≥ 0.15 µg/mL 12 months post-immunization, compared to 93% one month post-immunization.[15]

The immunogenicity of ProHIBiT® as a booster vaccination administered to children 12 months of age has been studied in the United States, Finland and Canada.[15]

Based on the study conducted by Drs. Edwards and Decker at Vanderbilt University, it was demonstrated that ProHIBiT® induced booster responses in children immunized with any of four different Hib conjugate vaccines as well as or better than the homologous vaccine.[15]

No impairment of the immune response to ProHIBiT® was observed in a group of 36 patients with sickle cell disease (SS, SC, S-thalassemia), aged 1.5 to 5.0 years (mean 3.3 years).[15,22,23] Satisfactory immune responses were obtained following administration of ProHIBiT® in children 2 to 6 years of age with acute leukemia who had been on chemotherapy < 1 year.[24] However, similar children with chemotherapy > 1 year frequently failed to respond to the vaccine.

INDICATIONS AND USAGE

ProHIBiT® is indicated for immunization against invasive diseases caused by *Haemophilus influenzae* type b.[25,26] ProHIBiT® may be administered as a booster vaccination at 12 to 15 months of age in children who received primary immunization with Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) or Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) as illustrated in Tables 2, 3, 4 and 5. This vaccine also may be administered as primary immunization at 15 months of age in children who have not received primary immunization with any licensed Haemophilus b Conjugate Vaccine.

TABLE 2[15] **ProHIBiT® Booster Induced Anti-PRP Antibody Responses in 12-Month-Old Children Primed with Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)**

	Geometric Mean Titers (GMT)	% of Infants Anti-PRP Antibody Titer ≥ 0.15 µg/mL	% of Infants Anti-PRP Antibody Titer ≥ 1.00 µg/mL
Pre-immunization N=24	0.322	71%	17%
Post-immunization N=24	21.277*	100%	96%**

TABLE 3[15] **ProHIBiT® Booster Induced Anti-PRP Antibody Responses in 15-Month-Old Children Primed with Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)**

	Geometric Mean Titers (GMT)	% of Infants Anti-PRP Antibody Titer ≥ 0.15 µg/mL	% of Infants Anti-PRP Antibody Titer ≥ 1.00 µg/mL
Pre-immunization N=29	0.526	86%	28%
Post-immunization N=29	31.314*	100%	100%**

* Comparison of the booster immunogenicity data at 12 and 15 months showed equivalent antibody titers (p = 0.3115), analysis of variance.
** Comparison of the percentages of 12- and 15-month-old infants who responded with a PRP antibody response ≥ 1.00 µg/mL showed no significant difference (p = 0.267), Chi-square test.

TABLE 4[15] **ProHIBiT® Booster Induced Anti-PRP Antibody Responses in 12-Month-Old Children Primed with Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)**

	Geometric Mean Titers (GMT)	% of Infants Anti-PRP Antibody Titer ≥ 0.15 µg/mL	% of Infants Anti-PRP Antibody Titer ≥ 1.00 µg/mL
Pre-immunization N=29	0.911	93%	34%
Post-immunization N=29	26.062*	100%	97%**

TABLE 5[15] **ProHIBiT® Booster Induced Anti-PRP Antibody Responses in 15-Month-Old Children Primed with Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)**

	Geometric Mean Titers (GMT)	% of Infants Anti-PRP Antibody Titer ≥ 0.15 µg/mL	% of Infants Anti-PRP Antibody Titer ≥ 1.00 µg/mL
Pre-immunization N=32	0.675	86%	40.6%
Post-immunization N=32	44.156*	100%	100%**

* Comparison of the booster immunogenicity data at 12 and 15 months showed equivalent antibody titers (p = 0.1104), analysis of variance.
** Comparison of the percentages of 12 and 15-month-old infants who responded with a PRP antibody response ≥ 1.00 µg/mL showed no significant difference (p = 0.290), Chi-square test.

CHILDREN WITH SYMPTOMATIC HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Immunization with Haemophilus b Conjugate Vaccine is recommended by the American Academy of Pediatrics (Red Book) and Immunization Practices Advisory Committee (ACIP) for children who are immunosuppressed in association with AIDS or any other immunodeficiency disease.[26,27]

ProHIBiT® will not protect against *Haemophilus influenzae* other than type b or other microorganisms that cause meningitis or septic disease.

No impairment of the immune response to the individual antigens was demonstrated when ProHIBiT® and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) were given at the same time in separate syringes at different sites.[15,28]

Limited data are available on concomitant administration of ProHIBiT® with MMR, and OPV (IPV). Fourteen-month-old Finnish children boosted with PRP-D received MMR concomitantly. Pre and 4 weeks post sera from a small subset (11 patients), showed no significant difference in antibody response to Measles, Mumps, or Rubella antigens when compared to a group that received MMR alone. A group of 25 Finnish infants received concomitant DTP, PRP-D, and IPV was compared to a group of 25 receiving DTP and IPV only. No significant difference in response to Type 1, Type 2, or Type 3 polio antigens was noted. Response to oral Polio Vaccine was evaluated in 31 infants immunized with PRP-D who also received OPV concomitantly. No difference in response to Type 1, Type 2, or Type 3 antigens was observed when compared to 22 infants receiving placebo and OPV.[15,29]

ProHIBiT® IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 12 MONTHS OF AGE.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL AND DIPHTHERIA TOXOID, IS A CONTRAINDICATION TO USE OF THIS VACCINE.

WARNINGS

If ProHIBiT® is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

As with any vaccine, vaccination with ProHIBiT® may not protect 100% of susceptible individuals.

PRECAUTIONS

GENERAL

As with the injection of any biological material, Epinephrine Injection (1:1000) should be available for immediate use should an anaphylactic or other allergic reaction occur.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines.

Any febrile illness or infection likely to be accompanied by fever is reason to delay the use of ProHIBiT®, since fever may result occasionally from administration of ProHIBiT® alone.

As reported with Haemophilus b polysaccharide vaccine,[30] cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of protective effects of the vaccine.[15]

Antigenuria has been detected following receipt of Haemophilus b Conjugate Vaccine.[31] Antigen detection may not have diagnostic value in suspected Haemophilus b disease within two weeks of immunization.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of properly.

ALTHOUGH SOME IMMUNE RESPONSE TO THE DIPHTHERIA TOXOID COMPONENT MAY OCCUR, IMMUNIZATION WITH ProHIBiT® DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

ProHIBiT® has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ProHIBiT®. It is also not known whether ProHIBiT® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ProHIBiT® is NOT recommended for use in a pregnant woman.

PEDIATRIC USE

ProHIBiT® IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 12 MONTHS OF AGE.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate). Information sheets are available from the Centers for Disease Control and Prevention (CDC) or the State Health Department.

Prior to administration of Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate), the parent or guardian should be asked about the recent health status of the infant or child to be injected.

The physician should inform the parents or guardian about the significant adverse reactions that have been temporally associated with Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate) administration, informed consent should be obtained and recorded, and the parent should inform the physician if any of these events occur.

As part of the child's immunization record, the date, lot number and manufacturer of the vaccine administered should be recorded.[32,33]

ADVERSE REACTIONS

When ProHIBiT® alone was given to over 1,000 adults and children, no serious adverse reactions were observed.[15,20,25,34] Thrombocytopenia was seen in one adult but a causative relationship was not established.

When ProHIBiT® was given with DTP and Inactivated Poliovirus Vaccine (IPV) to 55,000 Finnish children, the rate and extent of serious adverse reactions were not different from those seen when DTP or IPV were administered alone.[25,35] Allergic reactions such as urticaria were infrequently observed.[15,35]

Adverse reactions following vaccination with ProHIBiT® (without DTP) in subjects 15 to 24 months of age are summarized in Table 6.[34]

TABLE 6[34] **Percentage of Subjects 15 to 24 Months of Age Developing Local or Systemic Reactions to One Dose of Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)**

	No. of Subjects*	Reaction 6 Hours	Reaction 24 Hours	Reaction 48 Hours
Fever >38.3°C	281	1.1	2.1	1.8
Erythema	285	–	2.5	0.4
Induration	285	–	1.0	0.4
Tenderness	285	–	4.6	0.7

* Not all subjects had measurements at all time periods.

Other adverse reactions temporally associated with administration of ProHIBiT® including diarrhea, vomiting, and crying were reported at a frequency of ≤ 1.2%. Fever of 39°C or more occurred in < 1%, while irritability, sleepiness, or anorexia were reported in 16.1%.[34]

Adverse reactions in clinical evaluations among 689 children, 7 to 14 months of age, 24 hours after receiving a single dose of ProHIBiT®, were observed and compared to 139 children who received a saline placebo. There were no significant differences in the reaction rates for fever, erythema, induration, and tenderness between the two groups.[15]

A post-marketing surveillance study was conducted between April 1988 and July 1989 in the United States in 50,007 children 16 to 60 months of age. At Southern California Kaiser Permanente, 29,309 of these children were followed closely to determine the number of systemic and local reactions occurring within 6, 24, and 48 hours post-vaccination with ProHIBiT® alone. These reactions are summarized in Table 7.[15]

TABLE 7[15] **Post-Marketing Surveillance Study in Subjects 16-60 Months of Age Experiencing Adverse Reactions (n=29,309)**

	Reaction % 6 Hours	Reaction % 24 Hours	Reaction % 48 Hours
Fever >38.9°C	2	2	2
Analgesic Given	23	12	8
Irritability	17	14	10
Drowsiness	13	8	5
Unusual Crying	2	2	2
Vomiting/Poor Eating	7	7	7
Redness	2	1	1
Swelling	2	2	1
Tenderness	25	12	5

In 50 children who had received licensed Haemophilis b Conjugate Vaccine in infancy and a booster dose of ProHIBiT® at 12 months of age, the adverse experience profile was similar as summarized in Table 8.[15]

TABLE 8[15] **Adverse Experiences with ProHIBiT® given as a Booster at 12 to 15 Months of Age Primary Series either with Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) or Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (n=50)**

	Reaction % 6 Hours	Reaction % 24 Hours	Reaction % 48 Hours
Fever >38.9°C	0	0	2
Analgesic Given	14	8	6
Irritability	28	18	14
Drowsiness	20	4	6
Unusual Crying	0	0	0
Vomiting/Poor Eating	10	10	6
Hypotonic/Hyporesponsive	0	0	0
Redness	4	6	4
Swelling	4	0	0
Tenderness	4	0	0

Other adverse reactions reported with administration of ProHIBiT® included urticaria, seizure, and renal failure.[15,34] Guillain-Barré syndrome (GBS) rarely has been reported.[36] However, a cause and effect relationship for these adverse events has not been established.

Reporting of Adverse Events
Reporting by parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[32,33,37]

Health-care providers also should report these events to the Director of Medical Affairs, Connaught Laboratories, Inc., a Pasteur Mérieux Connaught Company, Route 611, P. O. Box 187, Swiftwater, PA 18370 or call 1-800-822-2463.

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

The immunizing dose is a single injection of 0.5 mL given intramuscularly in the outer aspect area of the vastus lateralis (mid-thigh) or deltoid.

Each 0.5 mL dose contains 25 µg of purified capsular polysaccharide and 18 µg of conjugated diphtheria toxoid protein.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

DO NOT INJECT INTRAVENOUSLY.

A booster dose of ProHIBiT® should be administered to children 12 to 15 months of age previously immunized with any licensed Hib conjugate vaccine. A single dose of ProHIBiT® should be administered to children 15 months of age and older, not previously immunized with a Hib conjugate vaccine.

HOW SUPPLIED
Vial, 1 Dose (5 per package) – Product No. 49281-541-01
Vial, 5 Dose – Product No. 49281-541-05
Vial, 10 Dose – Product No. 49281-541-10

STORAGE
Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE.

REFERENCES

1. Recommendations of the Immunization Practices Advisory Committee (ACIP). Polysaccharide vaccine for prevention of *Haemophilus influenzae* type b disease. MMWR 34: 201-205, 1985
2. Cochi SL, et al. Immunization of US children with *Haemophilus influenzae* type b polysaccharide vaccine: A cost-effectiveness model of strategy assessment. JAMA 253: 521-529, 1985
3. Murphy TV, et al. Prospective surveillance of *Haemophilus influenzae* type b disease in Dallas County, Texas, and in Minnesota. Pediatr 79: 173-179, 1987
4. Broome CV. Epidemiology of *Haemophilus influenzae* type b infections in the United States. Pediatr Infect Dis J 6: 779-782, 1987
5. Istre GR, et al. Risk factors for primary invasive *Haemophilus influenzae* disease: Increased risk from day care attendance and school-aged household members. J Pediatr 106: 190-195, 1985
6. Redmond SR, et al. *Haemophilus influenzae* type b disease. An epidemiologic study with special reference to day-care centers. JAMA 252: 2581-2584, 1984
7. Murphy TV, et al. County-wide surveillance of invasive Haemophilus infections: Risk of associated cases in Child Care Programs (CCPs). Twenty-third Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #788) 229, 1983
8. Fleming D, et al. *Haemophilus influenzae* b (Hib) disease – secondary spread in day care. Twenty-fourth Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #967) 261, 1984
9. CDC. Prevention of secondary cases of *Haemophilus influenzae* type b disease. MMWR 31: 672-680, 1982
10. Michaels RH, et al. Pharyngeal colonization with *Haemophilus influenzae* type b: A longitudinal study of families with a child with meningitis or epiglottitis due to *H. influenzae* type b. J Infec Dis 136: 222-227, 1977
11. Peltola H, et al. Prevention of *Haemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. N Engl J Med 310: 1561-1566, 1984
12. Smith DH, et al. Responses of children immunized with the capsular polysaccharide of *Haemophilus influenzae*, type b. Pediatr 52: 637-644, 1973
13. Robbins JB, et al. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. Pediatr Res 7: 103-110, 1973
14. Robbins JB, et al. A review of the efficacy trials with *Haemophilus influenzae* type b polysaccharide vaccines. In: Sell, S.H., Wright, P.E. eds. *Haemophilus influenzae*. New York: Elsevier Biomedical. 255-263, 1982
15. Unpublished data available from Connaught Laboratories, Inc.
16. Granoff DM, et al. Immunogenicity of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in adults. J Pediatr 105: 22-27, 1984

17.Cates KL. Serum opsonic activity for *Haemophilus influenzae* type b in infants immunized with polysaccharide-protein conjugate vaccines. J Infec Dis 152: 1076-1077, 1985
18.Benacerraf B, et al. Textbook of Immunology. Cellular interactions. Williams and Wilkins, p 22, 1979
19.Schneerson R, et al. Preparation, characterization, and immunogenicity of *Haemophilus influenzae* type b polysaccharide-protein conjugates. J Exp Med 152: 361-376, 1980
20.Lepow ML, et al. Safety and immunogenicity of *Haemophilus influenzae* type b-polysaccharide diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. J Pediatr 106: 185-189, 1985
21.Greenberg DP, et al. Variability in quantitation of *Haemophilus influenzae* type b anticapsular antibody (anti-PRP) by radioimmunoassay (RIA). Twenty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #209) 133, 1986
22.Frank AL, et al. *Haemophilus influenzae* Type b immunization of children with sickle cell diseases. Pediatr 82: 571-575, 1988
23.Plotkin SA, et al. Vaccines. *Haemophilus influenzae* vaccines. W.B. Saunders Co. p 318, 1988
24.Gigliotti F, et al. Response of children with acute lymphoblastic leukemia (ALL) to *H. influenzae* type b (Hib) conjugate vaccine. The Society for Pediatric Research (Serial #11595), 1988
25.ACIP – Update. Prevention of *Haemophilus influenzae* type b disease. MMWR 37: 13-16, 1988
26.Report of the Committee on Infectious Diseases, ed 22. Elk Grove Village, IL, American Academy of Pediatrics, 1991
27.ACIP. Immunization of children infected with human immunodeficiency virus – Supplementary ACIP statement. MMWR 37: 181-183, 1988
28.Hendley JO, et al. Immunogenicity of *Haemophilus influenzae* type b capsular polysaccharide vaccines in 18-month-old infants. Pediatr 80: 351-354, 1987
29.Eskola J, et al. Simultaneous administration of *Haemophilus influenzae* type b capsular polysaccharide-diphtheria toxoid conjugate vaccine with routine diphtheria-tetanus-pertussis and inactivated poliovirus vaccinations of childhood. Pediatr Infect Dis J 7: 480-484, 1988
30.FDA Workshop on Haemophilus b Polysaccharide Vaccine – A Preliminary Report, MMWR 36: 529-531, 1987
31.Scheifele D, et al. Antigenuria after receipt of Haemophilus b Diphtheria Toxoid Conjugate Vaccine. Pediatr Infect Dis J 8: 887-888, 1989
32.National Childhood Vaccine Injury Act of 1986 (Amended 1987)
33.National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 37: 197-200, 1988
34.Berkowitz CD, et al. Safety and immunogenicity of *Haemophilus influenzae* type b polysaccharide and polysaccharide diphtheria toxoid conjugate vaccines in children 15 to 24 months of age. J Pediatr 110: 509-514, 1987
35.Eskola J, et al. Efficacy of *Haemophilus influenzae* type b polysaccharide diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 317: 717-722, 1987
36.D'Cruz OF, et al. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré Syndrome) after immunization with *Haemophilus influenzae* type b conjugate vaccine. J Pediatr 115: 743-746, 1989
37.Vaccine Adverse Event Reporting System – United States. MMWR 39: 730-733, 1990

Manufactured by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, USA

Product Information
as of July 1992

Printed in USA

PASTEUR MÉRIEUX CONNAUGHT
RHÔNE-POULENC GROUP