PRODUCT MONOGRAPH

Liquid PedvaxHIB®

[Haemophilus b conjugate vaccine
(meningococcal protein conjugate), MSD Std.]

Suspension for Injection

THERAPEUTIC CLASSIFICATION

Active Immunizing Agent

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

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Vaccine for immunization against Haemophilus influenzae type b.

ACTION AND CLINICAL PHARMACOLOGY

DISEASE EPIDEMIOLOGY

Prior to the introduction of Haemophilus b conjugate vaccines, *Haemophilus influenzae* type b (Haemophilus b) was the most frequent cause of bacterial meningitis and a leading cause of serious systemic bacterial disease in young children worldwide.[1,2,3,4]

Haemophilus b disease occurred primarily in children under 5 years of age in the United States prior to the initiation of a vaccine program and was estimated to account for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which were meningitis. The mortality rate from Haemophilus b meningitis is about 5%. In addition, up to 35% of survivors develop neurological sequelae

including convulsions, deafness, and mental retardation.[5,6] Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis. Since the introduction and widespread use of Haemophilus b conjugate vaccines in the United States, the incidence of invasive Haemophilus b disease has declined 95% among children aged less than 5 years.[7]

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Haemophilus b disease occurred in infants less than 6 months of age.[8] The peak incidence of Haemophilus b meningitis occurs between 6 and 11 months of age. Forty-seven percent of all cases occur by one year of age with the remaining 53% of cases occurring over the next four years.[2,9]

Among children under 5 years of age, the risk of invasive Haemophilus b disease is further increased in certain populations including the following:

- Day-care attendees[10,11]
- Lower socio-economic groups[12]
- Blacks[13] (especially those who lack the Km(1) immunoglobulin allotype)[14]
- Caucasians who lack the G2m(n or 23) immunoglobulin allotype[15]
- Native Americans[16-18]
- Household contacts of cases[19]
- Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes[20,21]

IMMUNOLOGY OF HAEMOPHILUS B DISEASE

An important virulence factor of the Haemophilus b bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Haemophilus b disease.[3,22] While the anti-PRP level associated with protection using conjugated vaccines has not yet been determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from >0.15 to >1.0 μg/mL.[23-29]

Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] is a PRP-conjugate vaccine that overcomes the deficiencies of nonconjugated PRP vaccines in infants and young children. Conjugation of a carbohydrate to a protein carrier[30] enhances antibody responses to the carbohydrate, a process that is thought to convert the T-independent antigen (PRP alone) into a T-dependent antigen which results in both an enhanced antibody response and immunologic memory.

The protective efficacy, safety, and antibody responses to another formulation of PedvaxHIB® (lyophilized PedvaxHIB®) were evaluated in 3486 Native American (Navajo) infants who completed the primary two-dose regimen in a randomized, double-blind, placebo-controlled study (The Protective Efficacy Study). This population has a much higher incidence of Haemophilus b disease than the United States population as a whole and also has a lower antibody response to Haemophilus b conjugate vaccines, including lyophilized PedvaxHIB®.[16-18,31,32]

Each infant in this study received two doses of either placebo or lyophilized PedvaxHIB® with the first dose administered at a mean of 8 weeks of age and the second administered approximately two months later; DTP (Diphteria-Tetanus-Pertussis) and OPV (Oral Polio Virus) were administered concomitantly. Antibody levels were measured in a subset of each group (Table 1).

TABLE 1

Antibody Responses in Navajo Infants

Vaccine	No. of Subjects	Time	% Subjects with >0.15 µg/mL	% Subjects with >1.0 µg/mL	Anti-PRP GMT[#] (µg/mL)
Lyophilized PedvaxHIB® *┤	416	Prevaccination	44	10	0.16
	416	Dose 1	88	52	0.95
	416	Dose 2	91	60	1.43
Placebo*┤	461	Prevaccination	44	9	0.16
	461	Dose 1	21	2	0.09
	461	Dose 2	14	1	0.08
Lyophilized PedvaxHIB® **	27	Prebooster	70	33	0.51
	27	Postbooster ***	100	89	8.39

[#] Geometric Mean Titers
* Postvaccination values obtained approximately 1-3 months after each dose.
┤ The Protective Efficacy Study.
** Immunogenicity Trial[34]
*** Booster given at 12 months of age; postvaccination values obtained 1 month after administration of booster dose.

In this study, 22 cases of invasive Haemophilus b disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the recommended two-dose regimen, the protective efficacy of lyophilized PedvaxHIB® was calculated to be 93% with a 95% confidence interval of 57%-98% (p = 0.001, two-tailed). In the two months between the first and second doses, the difference in number of cases of disease between placebo and vaccine recipients (8 vs 0 cases, respectively) was statistically significant (p = 0.008, two-tailed); however, a primary two-dose regimen is required for infants 2-14 months of age. A subset of 1368 infants from this study was followed to 15 months of age with no additional cases of invasive Haemophilus b disease occurring after the primary two-dose regimen of lyophilized PedvaxHIB® .

Since protective efficacy with lyophilized PedvaxHIB® was demonstrated in such a high risk population, it would be expected to be predictive of efficacy in other

populations.

CLINICAL EVALUATION

The safety and immunogenicity of lyophilized PedvaxHIB® were evaluated in infants and children in other clinical studies that were conducted in various locations throughout the United States. Lyophilized PedvaxHIB® was highly immunogenic in all age groups studied.[33,34]

Antibody responses from these clinical studies (excluding Native Americans) are shown in Table 2.[32]

TABLE 2

Antibody Responses* to lyophilized PedvaxHIB® in Other Clinical Studies

Age (months)	Time	No. of Subjects	% Subjects Responding with >0.15 μg/mL	>1.0 μg/mL	Post-Vaccination Anti-PRP GMT (μg/mL)
2-3	Dose 1**	113	97	81	2.48
	Dose 2***	113	98	88	4.60
4-14	Dose 1**	252	98	75	2.53
	Dose 2***	252	100	92	6.04
15-17	Single Dose***	59	100	83	3.11
18-23	Single Dose***	59	98	97	7.43
24-71	Single Dose***	52	98	92	10.55

* Only subjects with prevaccination anti-PRP 0.15 μg/mL are included in this table (excluding Native Americans).
** Two months postvaccination.
*** One month postvaccination.

In addition, lyophilized PedvaxHIB® has been studied in children 2-17 months of age at high risk of Haemophilus b disease because of genetically-related deficiencies

(Blacks who were Km (1) allotype negative and Caucasians who were G2m (23) allotype negative) and are considered hyporesponsive to nonconjugated PRP vaccines on this basis.[35] The hyporesponsive children had anti-PRP responses comparable to those of allotype positive children of similar age range when vaccinated with lyophilized PedvaxHIB®. All children achieved anti-PRP levels of >1.0 1g/mL.

The safety and immunogenicity of Liquid PedvaxHIB® were compared with those of lyophilized PedvaxHIB® in a clinical study involving 903 infants 2 to 6 months of age from the general U.S. population.[32,36] DTP and OPV were administered concomitantly to most subjects. The antibody responses induced by lyophilized PedvaxHIB® and Liquid PedvaxHIB® were similar. Table 3 shows antibody responses in subjects who received their first dose at 2 to 3 months of age.[32]

TABLE 3

Antibody Responses to Liquid PedvaxHIB® and lyophilized PedvaxHIB® in Infants From the General U.S. Population

Formulation	Age (months)	Time	No. of Subjects	% Subjects with >0.15 1g/mL	% Subjects with >1.0 1g/mL	Anti-PRP GMT (1g/mL)
		Prevaccination	487	32	7	0.12
Liquid	2-3	Dose 1*	480	94	64	1.55
PedvaxHIB®		Dose 2**	393	97	80	3.22
(7.5 1g PRP)	12-15	Prebooster	284	80	30	0.49
		Postbooster	284	99	95	10.23
	24┤	Persistence	94	97	55	1.26
Lyophilized		Prevaccination	171	37	6	0.13
PedvaxHIB®	2-3	Dose 1*	169	97	72	1.88
(15 1g PRP)		Dose 2**	133	99	81	2.69
	12-15	Prebooster	87	71	28	0.39
		Postbooster**	87	99	91	7.64
	24┤	Persistence	37	97	54	1.10

* Approximately two months postvaccination.
** Approximately one month postvaccination.
┤ Approximately.

Since the magnitude of initial antibody response is lower among younger infants, a booster dose is required in infants who complete the primary two-dose regimen before 12 months of age (see DOSAGE AND ADMINISTRATION).

The antibody responses with lyophilized PedvaxHIB® and Liquid PedvaxHIB® were compared in two randomized clinical studies.[32,36] Table 4 shows similar responses in several subgroups of infants vaccinated at 2 to 3 months of age.

TABLE 4
Antibody Responses
After Two Doses of lyophilized PedvaxHIB® and Liquid PedvaxHIB® Among Infants Initially Vaccinated at 2 ┌3 Months of Age By Racial/Ethnic Group

LIQUID

Racial/Ethnic Groups	No. of Subjects	% Subjects With Anti-PRP		Anti-PRP GMT (μg/mL)
		>0.15 μg/mL	>1.0 μg/mL	
Native American┤	90	97	78	2.76
Caucasian**	143	94	72	2.16
Hispanic**	184	98	85	4.34
Black**	18	100	94	7.58

LYOPHILIZED*

Racial/Ethnic Groups	No. of Subjects	% Subjects With Anti-PRP		Anti-PRP GMT (μg/mL)
		>0.15 μg/mL	>1.0 μg/mL	
Native American*┤	10	100	80	3.82
Caucasian**	46	100	74	2.30
Hispanic**	60	98	87	3.30
Black**	5	100	100	1.93

* One month after the second dose
** One to two months after the second dose
┤ Apache and Navajo

Antibody Persistence

Persistence of antibody at 36 months of age was studied in 134 children following 3 doses of Liquid PedvaxHIB® (last dose [booster] given when 12-15 months old).[32,36] In those children 98% had antibody titers > 0.15 μg/mL, and 58% had antibody titers > 1.0 μg/mL. Anti-PRP geometric mean titers (GMTs) were 1.5 μg/mL.

INDICATIONS AND CLINICAL USE

Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 59 months of age.

As with other vaccines, several days following administration of Liquid PedvaxHIB® are required for protective levels of antibody to be achieved.

Liquid PedvaxHIB® will not protect against *Haemophilus influenzae* other than type b or against other microorganisms that cause meningitis or sepsis.

REVACCINATION

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

USE WITH OTHER VACCINES

Studies have been conducted in which Liquid PedvaxHIB® has been administered concomitantly with the primary vaccination series and/or booster doses of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps and Rubella Virus Vaccine Live attenuated, MSD Std.) (using separate sites and syringes).[32] No impairment of immune response to individual tested antigens was demonstrated. The type, frequency and severity of adverse experiences observed in these studies were similar to those seen when the individual vaccines were given alone.*

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

WARNINGS

The expected immune response may not be obtained when Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised.

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* NOTE: The National Advisory Committee on Immunization (NACI) recommends administration on a single day of all vaccines (i.e., DTP, IPV (or OPV), M-M-R® II and *Haemophilus influenzae* type b conjugate vaccine), appropriate to the patient's age and previous vaccination status, if the patient is unlikely to return for further vaccination.[37] If this is done, separate sites and syringes should be used for the injectable vaccines: Liquid PedvaxHIB®, M-M-R® II, DTP, IPV and DTP-IPV.

PRECAUTIONS

GENERAL

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

As with any vaccine, vaccination with Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] may not result in a protective antibody response in 100% of susceptible persons given the vaccine.

As reported with Haemophilus b polysaccharide vaccine[38] and another Haemophilus b conjugate vaccine,[39] cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence showing that Liquid PedvaxHIB® given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

Any acute infection or febrile illness is reason for delaying use of Liquid PedvaxHIB® except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

An immunogenic response to the carrier protein (*N. meningitidis*) has been demonstrated but its clinical benefit has not been established.

USE IN OBSTETRICS

Animal reproduction studies have not been conducted with Liquid PedvaxHIB®. These products are not recommended for use in individuals six years of age or older.

USE IN CHILDREN

Safety and effectiveness in infants below the age of two months and in children six years of age and older have not been established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Liquid PedvaxHIB® has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

LABORATORY TESTS

Sensitive tests, e.g., Latex Agglutination Kits, may detect PRP derived from the vaccine in the urine of some vaccinees for at least 30 days following vaccination with Hib conjugate vaccines.[40]

ADVERSE REACTIONS

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB® with those of lyophilized PedvaxHIB®, 1699 doses of Liquid PedvaxHIB® were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both lyophilized PedvaxHIB® and Liquid PedvaxHIB® were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB® in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in Table 5, in decreasing order of frequency, were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤ 2.5 cm diameter, see also Table 5), injection site swelling/induration (≤ 2.5 cm diameter, see also Table 5) unusual high-pitched crying, prolonged crying (>4hr.), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB® are summarized in

Table 5.

TABLE 5

Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB®*

	LIQUID							
		Post-Dose 1 (hr)				Post-Dose 2 (hr)		
Reaction	No. of Subjects Evaluated	6	24	48	No. of Subjects Evaluated	6	24	48
		%				%		
Fever** >38.3°C (101°F) Rectal	222	18.1	4.4	0.5	206	14.1	9.4	2.8
Erythema >2.5 cm diameter	674	2.2	1.0	0.5	562	1.6	1.1	0.4
Swelling >2.5 cm diameter	674	2.5	1.9	0.9	562	0.9	0.9	1.3

* DTP and OPV were administered concomitantly to most subjects.

* Fever was also measured by another method or reported as normal for an add infants after dose 1 and for an additional 249 infants after dose 2: however, the not included in this table.

Adverse reactions reported during a three-day period following administration of the

booster dose were generally similar in type and frequency to those seen following primary vaccination.

During clinical trials with another formulation of PedvaxHIB®, a few adverse reactions were reported that have not been seen in clinical studies with Liquid PedvaxHIB®: nausea, urticaria, thrombocytopenia, and tracheitis.

Post-Marketing Experience

As with any vaccine, there is the possibility that broad use of Liquid PedvaxHIB® could reveal adverse reactions not observed in clinical trials. The following additional adverse reactions have been reported:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Seizures (including febrile seizures)

Skin

Sterile injection site abscess; pain at the injection site

POTENTIAL SIDE EFFECTS

The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: convulsions, early onset Haemophilus b disease, Guillain Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.[38,39,41-44]

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION
DO NOT INJECT INTRAVENOUSLY OR INTRADERMALLY.

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration. Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningocaccal protein conjugate)] is a slightly opaque white suspension.

Inject 0.5 mL intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm. Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

2 - 6 MONTHS OF AGE

Infants beginning immunization at 2 - 6 months of age should receive two doses of vaccine (0.5 mL per dose) 2 months apart with a booster dose at 12 months of age.

7 - 11 MONTHS OF AGE

Unvaccinated children 7 - 11 months of age should receive two doses (0.5 mL per dose) 2 months apart with a booster dose at 15 - 18 months of age (or as soon as possible thereafter) and not less than 2 months after the second dose.

12 - 17 MONTHS OF AGE

Unvaccinated children 12 - 17 months of age should receive a single dose (0.5 mL) of vaccine as soon as possible and an additional dose at, or after 18 months of age, and at least two months after the first dose.

18 - 59 MONTHS OF AGE

Children 18 - 59 months of age who have not previously received the vaccine should receive a single dose (0.5 mL) of vaccine.

PHARMACEUTICAL INFORMATION

COMPOSITION

Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] is a polysaccharide-protein conjugate vaccine which has been shown to produce antibody to the capsular polysaccharide of *Haemophilus influenzae* type b. The vaccine is prepared from the highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Hib, Ross strain). By a unique chemical reaction, the capsular polysaccharide of Hib is bound covalently to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. The process involves independent modifications of the PRP and OMPC to give derivatives that will react to yield a conjugate vaccine with covalently bound components. The covalent bonding of the PRP to the OMPC, which is necessary for enhanced immunogenicity of the PRP, can be substantiated by intentional chemical separation of the conjugate's components which yields a unique amino acid. This amino acid is found only if covalent bonding occurred.

Each 0.5 mL dose of Liquid PedvaxHIB® is formulated to contain 7.5 μg of Haemophilus b PRP, 125 μg of *Neisseria meningitidis* OMPC as the active ingredients, 225 μg of aluminum as amorphous aluminum hydroxyphosphate sulphate (previously referred to as aluminium hydroxide), 35 μg sodium borate USP/NF and 0.9% sodium chloride as non-medicinal ingredients. Liquid

PedvaxHIB® does not contain lactose and is preservative-free.

STABILITY AND STORAGE RECOMMENDATIONS

The vaccine must be maintained at 20C - 80C during shipment to ensure that there is no loss of potency.

Store vaccine at 20C - 80C.

DO NOT FREEZE.

AVAILABILITY OF DOSAGE FORMS

Liquid PedvaxHIB® [Haemophilus b conjugate vaccine (meningococcal protein conjugate)] is supplied as a box of five 0.5 mL single-dose vial of liquid vaccine.

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