Liquid PedvaxHIB®
[Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

DESCRIPTION

PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] is a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) that is covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. The covalent bonding of the PRP to the OMPC which is necessary for enhanced immunogenicity of the PRP is confirmed by quantitative analysis of the conjugate's components following chemical treatment which yields a unique amino acid. The potency of PedvaxHIB is determined by assay of PRP.

Haemophilus influenzae type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

Liquid PedvaxHIB is ready to use and does not require a diluent. Each 0.5 mL dose of Liquid PedvaxHIB is a sterile product formulated to contain: 7.5 mcg of Haemophilus b PRP, 125 mcg of *Neisseria meningitidis* OMPC and 225 mcg of aluminum as amorphous aluminum hydroxyphosphate sulfate (previously referred to as aluminum hydroxide), in 0.9% sodium chloride, but does not contain lactose or thimerosal. Liquid PedvaxHIB is a slightly opaque white suspension.

This vaccine is for intramuscular administration and not for intravenous injection. (See DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY

Prior to the introduction of Haemophilus b Conjugate Vaccines, *Haemophilus influenzae* type b (Hib) 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]

Hib 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 Hib meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation.[5,6] Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis.

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Hib disease occurred in infants less than 6 months of age.[7] The peak incidence of Hib meningitis occurs between 6 to 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.[2,20]

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

- Daycare attendees[8,9]
- Lower socio-economic groups[10]
- Blacks[11] (especially those who lack the Km(1) immunoglobulin allotype)[12]
- Caucasians who lack the G2m(n or 23) immunoglobulin allotype[13]
- Native Americans[14,15,16]
- Household contacts of cases[17]
- Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes[18,19]

An important virulence factor of the Hib bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Hib disease.[3,21] 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 mcg/mL.[22-28]

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier[29] producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen resulting in both an enhanced antibody response and immunologic memory.

Clinical Evaluation of PedvaxHIB

PedvaxHIB, in a lyophilized formulation (lyophilized PedvaxHIB), was initially evaluated in 3,486 Native American (Navajo) infants, who completed the primary two-dose regimen in a randomized, double-blind, placebo-controlled study (The Protective Efficacy Study). At the time of the study, this population had a much higher incidence of Hib disease than the United States population as a whole and also had a lower antibody response to Haemophilus b Conjugate Vaccines, including PedvaxHIB.[14,15,16,30,33]

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 and OPV 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 mcg/mL	% Subjects with >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Lyophilized PedvaxHIB*	416**	Pre-Vaccination	44	10	0.16
	416	Post-Dose 1	88	52	0.95
	416	Post-Dose 2	91	60	1.43
Placebo*	461**	Pre-Vaccination	44	9	0.16
	461	Post-Dose 1	21	2	0.09
	461	Post-Dose 2	14	1	0.08
Lyophilized PedvaxHIB	27†	Prebooster	70	33	0.51
	27	Postbooster††	100	89	8.39

* Post-Vaccination values obtained approximately 1–3 months after each dose.
** The Protective Efficacy Study
† Immunogenicity Trial[34]
†† Booster given at 12 months of age; Post-Vaccination values obtained 1 month after administration of booster dose.

Most subjects were initially followed until 15 to 18 months of age. During this time, 22 cases of invasive Hib 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 primary 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.

At termination of the study, placebo recipients were offered vaccine. All original participants were then followed two years and nine months from termination of the study. During this extended follow-up, invasive Hib disease occurred in an additional seven of the original placebo recipients prior to receiving vaccine and in one of the original vaccine recipients (who had received only one dose of vaccine). No cases of invasive Hib disease were observed in placebo recipients after they received at least one dose of vaccine. Efficacy for this follow-up period, estimated from person-days at risk, was 96.6% (95 C.I., 72.2-99.9%) in children under 18 months of age and 100% (95 C.I., 23.5-100%) in children over 18 months of age.[33]

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.

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. PedvaxHIB was highly immunogenic in all age groups studied.[31,32]

Lyophilized PedvaxHIB induced antibody levels greater than 1.0 mcg/mL in children who were poor responders to nonconjugated PRP vaccines. In a study involving such a subpopulation,[33,34] 34 children ranging in age from 27 to 61 months who developed invasive Hib disease despite previous vaccination with nonconjugated PRP vaccines were randomly assigned to 2 groups. One group (n=14) was vaccinated with lyophilized PedvaxHIB and the other group (n=20) with a nonconjugated PRP vaccine at a mean interval of approximately 12 months after recovery from disease. All 14 children vaccinated with lyophilized PedvaxHIB but only 6 of 20 children re-vaccinated with a nonconjugated PRP vaccine achieved an antibody level of >1.0 mcg/mL. The 14 children who had not responded to revaccination with the nonconjugated PRP vaccine were then vaccinated with a single dose of lyophilized PedvaxHIB; following this vaccination, all achieved antibody levels of >1.0 mcg/mL.

In addition, lyophilized PedvaxHIB has been studied in children at high risk of Hib 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 mcg/mL.

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

TABLE 2
Antibody Responses to Liquid and Lyophilized PedvaxHIB in Infants From the General U.S. Population

Formulation	Age (Months)	Time	No. of Subjects	% Subjects with anti-PRP >0.15 mcg/mL	% Subjects with anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Liquid PedvaxHIB (7.5 mcg PRP)		Pre-Vaccination	487	32	7	0.12
	2-3	Post-Dose 1*	480	94	64	1.55
		Post-Dose 2**	393	97	80	3.22
	12-15	Prebooster	284	80	30	0.49
		Postbooster**	284	99	95	10.23
	24†	Persistence	94	97	55	1.29
Lyophilized PedvaxHIB (15 mcg PRP)		Pre-Vaccination	171	37	6	0.13
	2-3	Post-Dose 1*	169	97	72	1.88
		Post-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 Post-Vaccination
** Approximately one month Post-Vaccination
† Approximately

A booster dose of PedvaxHIB is required in infants who complete the primary two-dose regimen before 12 months of age. This booster dose will help maintain antibody levels during the first two years of life when children are at highest risk for invasive Hib disease. (See TABLE 2 and DOSAGE AND ADMINISTRATION.)

In four United States studies, antibody responses to lyophilized PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 3.)

TABLE 3
Antibody Responses*
After Two Doses of Lyophilized PedvaxHIB Among Infants Initially Vaccinated at 2–3 Months of Age By Racial/Ethnic Group

LYOPHILIZED				
Racial/Ethnic Groups	No. of Subjects	% Subjects With Anti-PRP >0.15 mcg/mL	% Subjects With Anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Native American†	54	96	70	2.47
Caucasian	201	99	82	3.52
Hispanic	76	99	88	3.54
Black	23	100	96	5.40

* One month after the second dose
† Apache and Navajo

In two United States studies, antibody responses to Liquid PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 4.)

TABLE 4
Antibody Responses*
After Two Doses of 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 >0.15 mcg/mL	% Subjects With Anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/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

* One month after the second dose
** Apache and Navajo

Antibodies to the OMPC of *N. meningitidis* have been demonstrated in vaccinee sera, but the clinical relevance of these antibodies has not been established.[33]

Interchangeability of Licensed Haemophilus b Conjugate Vaccines and PedvaxHIB

Published studies have examined the interchangeability of other licensed Haemophilus b Conjugate Vaccines and PedvaxHIB.[42,43,44,45,52] According to the American Academy of Pediatrics, excellent immune responses have been achieved when different vaccines have been interchanged in the primary series. If PedvaxHIB is given in a series with one of the other products licensed for infants, the recommended number of doses to complete the series is determined by the other product and not by PedvaxHIB. PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the booster dose.[52]

Use with Other Vaccines

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)].[33] No impairment of immune response to individual tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

In addition, a PRP-OMPC-containing product, COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.[33]

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS.)

Revaccination

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

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

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

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.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine[36] and another Haemophilus b Conjugate Vaccine[37], cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

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

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.[46]

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

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.[47]

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB;[38] in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen).[49-51] Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB with those of lyophilized PedvaxHIB, 1,699 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 formulations of 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 (>4 hr), 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*

Reaction	Post-Dose 1 (hr)			Post-Dose 2 (hr)			
	No. of Subjects Evaluated	6	24	48	No. of Subjects Evaluated	6	24	48
		Percentage				Percentage		
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 additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.[36,37,39,40,41,49]

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

DOSAGE AND ADMINISTRATION

Liquid PedvaxHIB

FOR INTRAMUSCULAR ADMINISTRATION
DO NOT INJECT INTRAVENOUSLY

If there is an interruption or delay between doses in the primary series, there is no need to repeat the series, but dosing should be continued at the next clinic visit. (See CONTRAINDICATIONS and PRECAUTIONS.)

2 to 14 Months of Age

Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see below and TABLE 6). Infants born prematurely, regardless of birth weight, should be vaccinated at the same chronological age and according to the same schedule and precautions as full-term infants and children.[46]

15 Months of Age and Older

Children 15 months of age and older previously unvaccinated against Hib disease should receive a single 0.5 mL dose of vaccine.

Booster Dose

In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months of age, but not earlier than 2 months after the second dose.

Vaccination regimens for Liquid PedvaxHIB by age group are outlined in TABLE 6.

TABLE 6
Vaccination Regimens for Liquid PedvaxHIB
By Age Groups

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2–10	2 doses, 2 mo. apart	12–15
11–14	2 doses, 2 mo. apart	—
15–71	1 dose	—

Interchangeability

PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the primary and booster doses.[52] (See CLINICAL PHARMACOLOGY.)

Use with Other Vaccines

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)]. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen with the other vaccines when given alone. (See CLINICAL PHARMACOLOGY.)

In addition, a PRP-OMPC-containing product, COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.[33]

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit.

Liquid PedvaxHIB is a slightly opaque white suspension. (See DESCRIPTION.)

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.

Inject 0.5 mL intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm. The buttocks should not be used for active vaccination of infants and children, because of the potential risk of injury to the sciatic nerve.

HOW SUPPLIED

Liquid PedvaxHIB is supplied as follows:

No. 4897 — A box of 10 single-dose vials of liquid vaccine, **NDC** 0006-4897-00.

Storage

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE.

REFERENCES

1. Cochi, S. L., et al: Immunization of U.S. children with *Haemophilus influenzae* type b polysaccharide vaccine: A cost-effectiveness model of strategy assessment. JAMA *253:* 521-529, 1985.
2. Schlech, W. F., III, et al: Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. JAMA *253:* 1749-1754, 1985.
3. 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.
4. Cadoz, M., et al: Etude epidemiologique des cas de meningitis purulentes hospitalises a Dakar pendant la decemie 1970-1979. Bull WHO *59:* 575-584, 1981.
5. Sell, S. H., et al: Long-term Sequelae of *Haemophilus influenzae* meningitis. Pediatr *49:* 206-217, 1972.
6. Taylor, H. G., et al: Intellectual, neuropsychological, and achievement outcomes in children six to eight years after recovery from *Haemophilus influenzae* meningitis. Pediatr *74:* 198-205, 1984.
7. Hay, J. W., et al: Cost-benefit analysis of two strategies for prevention of *Haemophilus influenzae* type b infection. Pediatr *80*(3): 319-329, 1987.
8. Redmond, S. R., et al: *Haemophilus influenzae* type b disease: an epidemiologic study with special reference to daycare centers. JAMA *252:* 2581-2584, 1984.
9. Istre, G. R., et al: Risk factors for primary invasive *Haemophilus influenzae* disease: increased risk from daycare attendance and school age household members. J Pediatr *106:* 190-195, 1985.
10. Fraser, D.W., et al: Risk factors in bacterial meningitis: Charleston County, South Carolina. J Infect Dis *127:* 271-277, 1973.
11. Tarr, P. I., et al: Demographic factors in the epidemiology of *Haemophilus influenzae* meningitis in young children. J Pediatr *92:* 884-888, 1978.
12. Granoff, D. M., et al: Response to immunization with *Haemophilus influenzae* type b polysaccharide-pertussis vaccine and risk of Haemophilus meningitis in children with Km(1) immunoglobulin allotype. J Clin Invest *74:* 1708-1714, 1984.
13. Ambrosino, D. M., et al: Correlation between G2m(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. J Clin Invest *75:* 1935-1942, 1985.
14. Coulehan, J. L., et al: Epidemiology of *Haemophilus influenzae* type b disease among Navajo Indians. Pub Health Rep *99:* 404-409, 1984.
15. Losonsky, G. A., et al: *Haemophilus influenzae* disease in the White Mountain Apaches: molecular epidemiology of a high risk population. Pediatr Infect Dis J *3:* 539-547, 1985.
16. Ward, J. I., et al: *Haemophilus influenzae* disease in Alaskan Eskimos: characteristics of a population with an unusual incidence of disease. Lancet *1:* 1281-1285, 1981.
17. Ward, J. I., et al: *Haemophilus influenzae* meningitis: a national study of secondary spread in household contacts. N Engl J Med *301:* 122-126, 1979.
18. Ward, J., et al: *Haemophilus influenzae* bacteremia in children with sickle cell disease. J Pediatr *88:* 261-263, 1976.
19. Bartlett, A. V., et al: Unusual presentations of *Haemophilus influenzae* infections in immunocompromised patients. J Pediatr *102:* 55-58, 1983.

20. Recommendations of the Immunization Practices Advisory Committee. Polysaccharide vaccine for prevention of *Haemophilus influenzae* type b disease. MMWR *34*(15): 201-205, 1985.

21. Santosham, M., et al: Prevention of *Haemophilus influenzae* type b infections in high-risk infants treated with bacterial polysaccharide immune globulin. N Engl J Med *317:* 923-929, 1987.

22. Siber, G. R., et al: Preparation of human hyperimmune globulin to *Haemophilus influenzae* b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Infect Immun *45:* 248-254, 1984.

23. Smith, D. H., et al: Responses of children immunized with the capsular polysaccharide of *Haemophilus influenzae* type b. Pediatr *52:* 637-645, 1973.

24. Robbins, J. B., et al: Quantitative measurement of 'natural' and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. Pediatr Res *7:* 103-110, 1973.

25. Kaythy, H., et al: The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis *147:* 1100, 1983.

26. Peltola, H., et al: *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatr *60:* 730-737, 1977.

27. Ward, J. I., et al: *Haemophilus influenzae* type b vaccines: Lessons For the Future. Pediatr *81:* 886-893, 1988.

28. Daum, R. S., et al: *Haemophilus influenzae* type b vaccines: Lessons From the Past. Pediatr *81:* 893-897, 1988.

29. Marburg, S., et al: Bimolecular chemistry of macromolecules: Synthesis of bacterial polysaccharide conjugates with *Neisseria meningitidis* membrane protein. J Am Chem Soc *108:* 5282-5287, 1986.

30. Letson, G. W., et al: Comparison of active and combined passive/active immunization of Navajo children against *Haemophilus influenzae* type b. Pediatr Infect Dis J *7*(111): 747-752, 1988.

31. Einhorn, M. S., et al: Immunogenicity in infants of *Haemophilus influenzae* type b polysaccharide in a conjugate vaccine with *Neisseria meningitidis* outer-membrane protein. Lancet *2:* 299-302, 1986.

32. Ahonkhai, V.I., et al: *Haemophilus influenzae* type b Conjugate Vaccine (Meningococcal Protein Conjugate) (PedvaxHIB TM): Clinical Evaluation. Pediatr *85*(4): 676-681, 1990.

33. Data on file at Merck Research Laboratories.

34. Granoff, D. M., et al: Immunogenicity of *Haemophilus influenzae* type b polysaccharide—outer membrane protein conjugate vaccine in patients who acquired Haemophilus disease despite previous vaccination with type b polysaccharide vaccine. J. Pediatr. *114*(6): 925-933, June 1989.

35. Lenoir, A. A., et al: Response to *Haemophilus influenzae* type b (*H. influenzae* type b) polysaccharide *N. meningitidis* outer membrane protein (PS-OMP) conjugate vaccine in relation to Km(1) and G2m(23) allotypes. Twenty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract #216) 133, 1986.

36. Mortimer, E. A.: Efficacy of Haemophilus b polysaccharide vaccine: An enigma. JAMA *260:* 1454, 1988.

37. Meekison, W., et al: Post-marketing surveillance of adverse effects following ProHIBiT vaccine. British Columbia Canada Diseases Weekly Report *15-28:* 143-145, 1989.

38. Goepp, J. G., et al: Persistent urinary antigen excretion in infants vaccinated with *Haemophilus influenzae* type b capsular polysaccharide conjugated with outer membrane protein from *Neisseria meningitidis*. Pediatr Infect Dis J *11*(1): 2-5, 1992.

39. Milstein, J. B., et al: Adverse reactions reported following receipt of *Haemophilus influenzae* type b vaccine: An analysis after one year of marketing. Pediatr *80:* 270, 1987.

40. Black, S., et al: b-CAPSA 1 *Haemophilus influenzae* type b capsular polysaccharide vaccine safety. Pediatr *79:* 321-325, 1987.

41. D'Cruz, O. F., et al: Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) after immunization with *Haemophilus influenzae* type b Conjugate Vaccine. J Pediatr *115:* 743-746, 1989.

42. Recommendations of the Immunization Practices Advisory Committee. Recommendations for use of Haemophilus b Conjugate Vaccines and a combined diphtheria, tetanus, pertussis, and Haemophilus b vaccine. MMWR *42*(RR-13): 1-15, 1993.

43. Daum, R. S., et al: Interchangeability of *Haemophilus influenzae* type b vaccines for the primary series (mix and match): a preliminary analysis [Abstract 976]. Pediatr Res *33:* 166A, 1993.

44. Greenberg, D. P., et al: Enhanced antibody responses in infants given different sequences of heterogenous *Haemophilus influenzae* type b Conjugate Vaccines. J Pediatr *126:* 206-211, 1995.

45. Anderson, E. L., et al: Interchangeability of Conjugated *Haemophilus influenzae* type b Vaccines in Infants. JAMA *273:* 849-853, 1995.

46. Recommendations of the Immunization Practices Advisory Committee. General Recommendations on Immunization. MMWR *43*(RR-1), 1994.

47. Vaccine Adverse Event Reporting System - United States. MMWR *39*(41): 730-733, October 19, 1990.

48. Institute of Medicine Adverse Events Associated With Childhood Vaccines Evidence Bearing on Causality. National Academy Press, Washington, D.C., 260-261, 1994.

49. Keyserling, H.L., et al: Program and Abstracts of the 30th ICAAC, (Abstract #63), 1990.

50. Ward, J.I., et al: Program and Abstracts of the 32nd ICAAC, (Abstract #984), 1992.

51. Lieberman, J.M., et al: Infect Dis, (Abstract #1028), 1993.

52. American Academy of Pediatrics. Recommended Childhood Immunization Schedule - United States, January-December 1998. Pediatr *101*(1): 154-157, 1998.

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