PRODUCT INFORMATION

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

NAME OF THE DRUG
(Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD)

DESCRIPTION

PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD) is a polysaccharide-protein conjugate vaccine prepared from the highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of Haemophilus influenzae type b (Hib, Ross strain). The capsular polysaccharide of Hib is bound covalently to an outer membrane protein complex (OMPC) of the B11 strain of Neisseria meningitidis serogroup B.

Each 0.5 mL dose of liquid PedvaxHIB is formulated to contain 7.5 μg of Haemophilus b polysaccharide, 125 μg of Neisseria meningitidis OMP complex, 35 μg borax and 225 μg of aluminium as aluminium hydroxide in 0.9% sodium chloride.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

CLINICAL PHARMACOLOGY

Immunogenicity

PedvaxHIB is a PRP-conjugate vaccine that overcomes the deficiencies of nonconjugated PRP vaccines in infants and young children.

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. For these vaccines, antibody levels > 0.15 μg/mL were associated with short term protection against Haemophilus influenzae type b disease while levels > 1.0 μg/mL were associated with long term protection. It is expected that these levels associated with short and long term protection are applicable to Hib conjugate vaccines.

Antibody levels fall rapidly during the first eight months following vaccination but levels above 0.15 μg/mL which confer protective immunity may be expected to persist for at least 12 months.

Clinical Trials

The safety and immunogenicity of liquid PedvaxHIB were compared with those of lyophilised 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 1 shows antibody responses from this clinical study in subjects who received their first dose at 2 to 3 months of age.

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### TABLE 1

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Age (Months)</th>
<th>Time</th>
<th>No. of Subjects</th>
<th>% Subjects with anti-PRP</th>
<th>Anti-PRP GMT (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.15 µg/mL</td>
<td>&gt;1.0 µg/mL</td>
</tr>
<tr>
<td>Liquid PedvaxHIB</td>
<td>2-3</td>
<td>Pre-Vaccination</td>
<td>487</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>(7.5 µg PRP)</td>
<td></td>
<td>Post-Dose 1</td>
<td>480</td>
<td>94</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>12-15</td>
<td>Post-Dose 2</td>
<td>393</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebooster</td>
<td>284</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postbooster **</td>
<td>284</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistence</td>
<td>94</td>
<td>97</td>
<td>55</td>
</tr>
<tr>
<td>Lyophilised PedvaxHIB</td>
<td>2-3</td>
<td>Pre-Vaccination</td>
<td>171</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>(15 µg PRP)</td>
<td></td>
<td>Post-Dose 1</td>
<td>169</td>
<td>97</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-Dose 2</td>
<td>133</td>
<td>99</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prebooster</td>
<td>87</td>
<td>71</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postbooster **</td>
<td>87</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistence</td>
<td>37</td>
<td>97</td>
<td>54</td>
</tr>
</tbody>
</table>

*Approximately two months Post-Vaccination.
**Approximately one month Post-Vaccination.
†Approximately 1-3 months after each dose.

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 DOSAGE AND ADMINISTRATION).

### Protective Efficacy

The protective efficacy, safety, and antibody responses to lyophilised PedvaxHIB were evaluated in 3486 Native American (Navajo) infants who completed the primary two-dose regimen in a randomised, 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 PedvaxHIB.

Each infant in this study received two doses of either placebo or lyophilised 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 2).

### Table 2

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. of Subjects</th>
<th>xTime</th>
<th>% Subjects with</th>
<th>Anti-PRP GMT (µg/mL)</th>
</tr>
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<tbody>
<tr>
<td>Lyophilised PedvaxHIB†</td>
<td>416</td>
<td>Prevaccination</td>
<td>44</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>416</td>
<td>Dose 1</td>
<td>88</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>416</td>
<td>Dose 2</td>
<td>91</td>
<td>60</td>
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<tr>
<td>Placebo†</td>
<td>461</td>
<td>Prevaccination</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>461</td>
<td>Dose 1</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>461</td>
<td>Dose 2</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Lyophilised PedvaxHIB**</td>
<td>27</td>
<td>Prebooster</td>
<td>70</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Postbooster ***</td>
<td>100</td>
<td>89</td>
</tr>
</tbody>
</table>

*Postvaccination values obtained approximately 1-3 months after each dose.
†The Protective Efficacy Study.
**Immunogenicity Trial
***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 lyophilised 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 lyophilised PedvaxHIB (see DOSAGE AND ADMINISTRATION, including Booster Dose).

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

In April 1993, the Centre for Disease Control, Territory Health Services, Northern Territory of Australia (NT), began using lyophilised PedvaxHIB for its public Hib vaccination program for all infants born after December 1, 1992. In 1997, a retrospective study was conducted to evaluate the effectiveness of lyophilised PedvaxHIB in the NT population. Overall, the incidence of invasive Hib disease in children under five years of age declined from 141/100,000 child-years prior to the public Hib vaccination program to 19/100,000 child-years following institution of the program. The incidence in the group at highest risk (Aboriginal infants 4 to 11 months of age) declined from 1,315 to 185 / 100,000 child-years. For infants and children who had received at least two doses of lyophilised PedvaxHIB in the first year of life, or one dose of lyophilised PedvaxHIB if the regimen was begun in the second year of life, the overall effectiveness of lyophilised PedvaxHIB was 97.5%.

INDICATIONS

Liquid PedvaxHIB is indicated for active immunisation 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 Haemophilus influenzae other than type b or against other microorganisms that cause meningitis or sepsis.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

If the child is suffering from any acute illness, vaccination should be postponed until the child has recovered. Minor infections, without fever or systemic upset, are not reasons to postpone vaccination.

Vaccination should not proceed in children who have had a severe local reaction or a general reaction which can be confidently related to a preceding Hib vaccination. Note that when Hib vaccine has been given with DTP, generalised reactions are far more likely to have been caused by the DTP vaccine.

PRECAUTIONS

General

Adequate treatment facilities, including adrenaline, should be available for immediate use should an anaphylactoid or anaphylactic reaction occur.
The expected immune response may not be obtained when liquid PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised.

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

As with other vaccines, approximately 30 days are required for protective levels of antibody to be achieved.

As with any vaccine, vaccination with liquid PedvaxHIB may not result in a protective antibody response in 100 percent of susceptible persons given the vaccine.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccine.

There is insufficient evidence that liquid PedvaxHIB given immediately after exposure to natural Haemophilus influenza 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.

**Pregnancy  (Category B2)**

It is not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Liquid PedvaxHIB is not recommended therefore for use in a pregnant woman.

**Use in Lactation**

It is not known whether PedvaxHIB is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when liquid PedvaxHIB is administered to breast feeding females.

**Paediatric 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 under the age of 2 months because of poor antibody response and possible interference with response to vaccine doses within the next few months. 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.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

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

**Interactions with Other Drugs**

The expected immune response may not be obtained when liquid PedvaxHIB is used in persons receiving immunosuppressive therapy.

**Use With Other Vaccines**

Liquid PedvaxHIB may be administered on the same day as any of the other standard childhood vaccines (DTP, OPV, MMR, or hepatitis B). When DTP and Liquid PedvaxHIB are administered on the same day, they should be injected in different limbs, using separate syringes.
Effects on 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 lyophilised PedvaxHIB. In clinical studies with lyophilised PedvaxHIB, children with this antigenuria demonstrated a normal immune response to the vaccine.

ADVERSE EFFECTS

In clinical studies, the type and frequency of adverse reactions with liquid PedvaxHIB were similar to those seen with lyophilised PedvaxHIB. (For full details of adverse reactions with the lyophilised formulation, please refer to the product information for PedvaxHIB®.)

In a multicenter clinical study (n=903) comparing the effects of liquid PedvaxHIB with those of lyophilised PedvaxHIB, 1699 doses of liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general US 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 3, in decreasing order of frequency were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤2.5cm diameter, see also Table 3), injection site swelling/induration (≤2.5cm diameter, see also Table 3), unusual high-pitched crying, prolonged crying (>4hr.), diarrhoea, 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 summarised in Table 3.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. of Subjects Evaluated</th>
<th>Post-Dose 1 (hr)</th>
<th>Post-Dose 2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Fever**</td>
<td>Percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;38.3°C</td>
<td>Rectal</td>
<td>222</td>
<td>18.1</td>
</tr>
<tr>
<td>Erythema &gt;2.5 cm diameter</td>
<td></td>
<td>674</td>
<td>2.2</td>
</tr>
<tr>
<td>Swelling &gt;2.5 cm diameter</td>
<td></td>
<td>674</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*DTP and OPV were administered concomitantly to most subjects

**Fever was also measured by the axillary method or reported as normal for an additional 346 infants after dose 1 and an additional 249 infants after dose 2; however, these data are 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.
Post Marketed Experience

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

**Haemic and Lymphatic System**: Lymphadenopathy

**Hypersensitivity**: Angioedema

**Nervous System**: Seizures (including febrile seizures)

**Skin**: Sterile injection site abscess, pain at the injection site

Potential Adverse Reactions

During studies with *Haemophilus influenzae* type b polysaccharide vaccines, convulsions, early onset Haemophilus b disease and Guillain Barre syndrome have occurred rarely. However, a cause and effect relationship between these side effects and the vaccination was not established.

**DOSAGE AND ADMINISTRATION**

For intramuscular administration, do not inject intravenously.

**2-14 MONTHS OF AGE**

Infants 2-14 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).

**15 MONTHS OF AGE AND OLDER**

Children 15 months of age or older previously unvaccinated against Haemophilus b disease should receive a single 0.5mL dose of vaccine.

**BOOSTER DOSE**

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

Parenteral drug products should be inspected visually for extraneous particulate matter and discolouration prior to administration. Liquid PedvaxHIB is a slightly opaque white suspension.

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.

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 0.5mL intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.
OVERDOSAGE

There is no data with regard to overdosage. Contact the poisons information center for management of overdose.

PRESENTATION AND STORAGE

Liquid PedvaxHIB is a sterile suspension for intramuscular use and is available as a single dose vial. Available in single packs and packs of 10.

STORAGE

The vaccine must be maintained at 2-8° C during shipment to ensure that there is no loss of potency.

Store vaccine at 2-8°C.

DO NOT FREEZE.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty. Limited,
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South Granville, N.S.W. 2142

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DISTRIBUTOR

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This document was approved by the Therapeutic Goods Administration on 20 July 1999
Date of most recent amendment 22 December 2010.