SUMMARY FOR BASIS OF APPROVAL

Reference Number:
90-0217

Drug Licensed Name:
Haemophilus b Conjugate Vaccine
(Diphtheria CRM_{197} Protein Conjugate)

Manufacturer:
Praxis Biologics, Inc

Drug Trade name:
HibTITER®

I. INDICATIONS AND USAGE:

HibTITER® Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) is indicated for the immunization of children 2 months to 5 years of age against invasive diseases caused by *Haemophilus influenzae* type b.

II. DOSAGE AND ADMINISTRATION:

Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) is indicated for children 2 months to 5 years of age for the prevention of invasive Haemophilus b disease. **For infants 2 to 6 months of age, the** immunizing dose is three separate injections of 0.5 ml given at approximately 2-month intervals intramuscularly, preferably in the outer aspect of the vastus lateralis (mid-thigh). Previously unvaccinated infants from 7 through 11 months of age should receive two separate intramuscular injections as described at approximately 2-month intervals. Children from 12 through 14 months of age not previously vaccinated receive one intramuscular injection as described above. All vaccinated children receive a single booster dose at 15 months of age or older, but not less than two months after the previous dose. Previously unvaccinated children 15 to 60 months of age receive a single intramuscular injection of HibTITER® as described or in the deltoid muscle.

Age at first Immunization (mos.)	No. of Doses	Booster
2-6	3	Yes
7-11	2	Yes
12-14	1	Yes
15 and over	1	No

The current recommendation of the Immunization Practices Advisory Committee (ACIP) is for routine immunization of all children at 15 months of age. **The ACIP has not yet reviewed the new indication for** children less than 15 months of age.

Each dose of 0.5 ml is formulated to contain 10 μg of purified Haemophilus b saccharide and approximately 25 μg of CRM_{197} protein.

III. MANUFACTURING AND CONTROLS:

See the Summary for Basis of Approval, dated February, 1989 for the manufacture and control of the Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate).

Environmental Impact Analysis: An environmental impact assessment, amended to address the expanded use of the vaccine to infants, was submitted on September 24, 1990 and October 2, 1990. Increased use of the product is not expected to have any significant effect on the environment. Original assessment was based on the plant at full scale production capacity. A finding of no significant impact is attached.

IV. PHARMACOLOGY:

The manufacture's labeling is adequate with respect to pharmacology. For additional information see the Summary for Basis of Approval, dated February, 1989.

V. MEDICAL:

A. General information: *H. influenzae* type b (Haemophilus b) is the most frequent cause of bacterial meningitis, epiglottitis, and other invasive infections in young children, and is recognized as a major pediatric health problem. It is estimated that approximately 20,000 cases of invasive Haemophilus disease occur annually in the United States. Approximately 55% of systemic disease occurs in children 6-18 months of age. The disease causes significant morbidity, mortality, and post-meningitis sequelae. The case fatality rate for meningitis is approximately 5% and up to 38% of survivors may have some sequelae. Haemophilus b meningitis is a leading cause of acquired mental retardation and deafness in children.

It has been shown by a number of investigators that the *H. influenzae* type b capsule is a major virulence factor and that most of the *H. influenzae* strains that cause systemic disease in young children have the type b capsule. Antibodies to the capsular polysaccharide can be bactericidal and opsonize the organism for phagocytic killing. In a field trial performed in Finland in 1974, the presence of antibodies induced by an Haemophilus b Polysaccharide Vaccine was shown to correlate with protection in children 18 months of age and older. Other studies in the United States have shown that the peak incidence of Haemophilus b disease occurs in children 6 to 12 months of age, a period during which one finds the lowest antibody levels to the organism. Thus, protection against disease can be correlated with presence of antibody to Haemophilus b polysaccharide.

Some studies indicate that the risk of developing Haemophilus b disease is higher among children under 5 years of age who attend day-care than those who do not. The incidence of invasive disease is also increased in certain groups, such as Native Americans, blacks, and those with medical conditions, such as asplenia, sickle-cell disease, and antibody deficiency syndromes. The risk of Haemophilus b disease is increased

somewhat for children with malignancies associated with immunosuppression.

The characteristics of an immune response depend on the type of cells producing the response and the antigens stimulating the process. Certain antigens, such as proteins, induce B lymphocytes to produce antibody aided by thymus derived lymphocytes called T helper (TH) cells. These antigens are called thymus-dependent or TD antigens. The immune response is long lasting, boostable, and IgG antibody predominates. In contrast, polysaccharide antigens stimulate B cells without T cell help, producing a non-boostable response of both IgG and IgM antibodies. These antigens are known as thymus-independent or TI antigens. Linkage of Haemophilus b saccharides to a protein converts the TI saccharide to a TD antigen and results in an enhanced antibody response to the saccharide that is boostable and predominantly of the IgG isotype.

B. Brief description of clinical studies:

Efficacy: For background information on the basis for the initial approval of HibTITER® in December 1988 see the Summary for Basis of Approval dated February 1989.

Efficacy of HibTITER® was evaluated in a large scale clinical trial in northern California. The multi-ethnic composition of the children in the California study was representative of the general population in northern California. The study was conducted from February 1988 through June 1990. 30,884 infants less than 6 months of age were vaccinated with HibTITER® of whom 22,124 received 3 doses at about 2, 4 and 6 months of age simultaneously with DTP but at a separate injection site. A control group of 30,558 infants received DTP alone. The control group consisted of those infants offered the vaccine who refused and a smaller group not offered the vaccine due to birth dates falling initially within the first 5, later the first 6, and finally the first 7 days of the month.

After more than 24,000 person years of follow up, there have been no (0) cases of Haemophilus b disease in infants who received 3 doses of HibTITER® and 12 cases of Haemophilus b disease (6 cases of meningitis) in the control group (Table 1). The rates of Haemophilus b disease were 0 and 105 per 100,000 in the vaccinated and control infants, respectively. The estimate of efficacy is 100% ($p = 0.0002$); 95% Confidence Intervals (C.I.), 2 tailed, 68%, 100%. When the data was corrected for age and seasonality, there were 0 cases among vaccinated infants and 18 cases in the control group. Efficacy is 100% ($p = 0.0001$); 95% C.I., 71%, 100%. There has also been 5,445 person-years of follow up among infants after two doses of vaccine which is predominantly time between the second and third doses. There have been no (0) cases of Haemophilus b disease in this group whereas, among similarly aged control subjects, there were eight cases; the rates of disease were therefore 0 and 149 cases/100,000 in vaccinees and controls respectively. There was one case of Haemophilus b disease after one dose of the Praxis Haemophilus b Conjugate Vaccine, defined as occurring > 21 days after immunization. There were two other cases

of Haemophilus b disease which occurred prior to day 21. There were five cases among similarly aged control subjects. The rates of disease were therefore 21 and 123 cases per 100,000 in the vaccinated and control populations, respectively.

In Finland, approximately 53,000 infants received HibTITER® at 4 and 6 months of age and a booster dose at 14 months in a comparative trial conducted from January 1988 through June 1990. Only two children developed Haemophilus b disease after receiving the 2 dose primary vaccination schedule. One child became ill at 15 months of age and the other at 18 months of age; neither child received their scheduled booster at 14 months of age. No vaccine failure has been reported in children who received the 2-dose primary series and the booster dose at 14 months of age. Based on more than 32,000 person years of follow-up time, the estimate of efficacy is about 95% when compared to historical control groups followed between 1985 and 1988. Historical controls were used since all infants received one of two Haemophilus b conjugate vaccines during the period of the trial. The results of this trial support those obtained in the pivotal study carried out in Northern California.

Clinical studies for safety: Adverse reactions associated with the Praxis Haemophilus b Conjugate Vaccine have been evaluated in 401 infants vaccinated initially at 1 to 6 months of age with 1118 doses independent of DTP vaccine. Observations were made during the day of vaccination and days 1 and 2 postvaccination. A temperature > 38.3°C was recorded at least once during the observation period following 2% of the vaccinations. Local erythema, warmth or swelling (> 2 cm) was observed following 3.3% of vaccinations. The incidence of temperature > 38.3°C was greater during the first postvaccination day than during the day of vaccination or the second postvaccination day. The incidence of local erythema, warmth or swelling was similar during the day of vaccination and the first postvaccination day; it was lower during the second postvaccination day. All side effects have been infrequent, mild and transient with no serious sequelae (see Table 2 of Package insert). No differences in the rates of these complaints were reported after dose 1, 2, or 3.

Additional safety data with HibTITER® are available from the efficacy studies conducted in young infants. 79,483 doses were given to 30,844 infants at approximately 2, 4, and 6 months of age in California usually at the same time as DTP (but at a separate injection site) and oral polio vaccine; approximately 100,000 doses have been given to 53,000 infants at 4 and 6 months in Finland at the same time as a combined DTP and inactivated polio (IPV) vaccine but at a separate injection site. The rates and types of reactions associated with the vaccinations were not different from those seen when DTP or DTP-IPV was administered alone. These included fever, local reactions, rash and one hyporesponsive episode with a single seizure.

The safety of HibTITER® was also evaluated in the California study by direct phone questioning of the parents or guardians of 6,887 vaccine recipients and by analysis of emergency room (ER) visits and of hospitalizations following vaccination. The rates and types of side

effects reported within 24 hours of vaccination were similar to those cited in Table 2 of the package insert. All ER visits during the 30 days after receipt of 23,800 doses of HibTITER® were tabulated by 16 diagnostic categories, and the results compared to vaccinated subjects during any other time period and to all non-vaccinated infants. There was no increase in age-adjusted rates of any type of ER visit by vaccine recipients; indeed, overall ER utilization and febrile illnesses were significantly reduced in the 30-day post vaccination group. A similar analysis was conducted for any hospitalizations during the 60 days following the 23,800 vaccinations studied. The overall rate of hospitalizations was significantly reduced in the 60-day post vaccination group.

For details of the side effects associated with a single vaccination of HibTITER® given (without DTP) to infants of 15-23 months of age see the Summary for Basis of Approval dated February 1989 and the package insert.

Similar results have been observed in the analysis of 2,285 subjects of 18-60 months of age, vaccinated as part of a post-marketing safety study of HibTITER®. These data were collected by telephone survey 24-48 hours after vaccination. Additional observations included irritability, restless sleep and GI symptoms (diarrhea, vomiting and loss of appetite) in the group that received the Praxis Haemophilus b Conjugate Vaccine alone.

Clinical studies for immunogenicity: The immunogenicity of the Praxis Haemophilus b Conjugate Vaccine was evaluated in infants vaccinated initially at 1 to 6 months of age in 10 centers in the United States. Infants received three doses at approximately 2-month intervals. Total anti-Haemophilus b polysaccharide (HbPs) antibody levels were determined by a standardized radioimmunoassay in one laboratory whose results correlate with the assay used by the National Public Health Institute of Finland. Anti-HbPs antibody levels $\geq$ 1 μg/mL were attained by more than 90% of infants of all ages after two doses and by more than 98% after three doses (Table 2). One month after the third vaccination, the geometric mean antibody level was 22.4 μg/ml. Long-term persistence of the antibody response was observed. More than 80% of 235 infants who received three doses of vaccine had an anti-HbPs antibody level $\geq$ 1 μg/mL at 2 years of age.

A two dose immunization schedule in children from 7 through 11 months of age induced higher geometric mean antibody levels and comparable seroconversion rates compared to the three dose schedule in younger infants (Table 2). Children between 12 and 14 months of age responded similarly.

The vaccine generated an immune response characteristic of a protein antigen: IgG anti-HbPs antibodies of IgG1 subclass predominated and the immune system was primed for a booster response to the vaccine or the native polysaccharide as presumably would occur by natural antigenic exposure. When evaluated in an *in vitro*, complement-mediated bactericidal (BC) assay, none of the prevaccination sera of the 1-6 month old infants killed *H. influenzae* type b. Two months after the

second dose of vaccine, 95% of the infants' sera had BC activity; and one month after the third dose, 98% of the sera had BC activity.

These data may be compared to the response to a single dose of HibTITER® administered to 377 children 15-23 months of age: geometric mean antibody levels of 10.8 and 12.2 μg/mL were generated in 15-17 and 18-23 month olds respectively, and more than 97% had anti-HbPs antibody levels ≥ 1 μg/mL (Table 2).

In one study, immunogenicity of HibTITER® was evaluated in 26 children 22 months to 5 years of age who had not responded to earlier vaccination with Haemophilus b Polysaccharide Vaccine. One dose of HibTITER® was immunogenic in all 26 children and generated titers of > 1 μg/mL in 25 of the 26 infants. The vaccine has also been found to be immunogenic in children with sickle-cell disease, a disease associated with increased susceptibility to Haemophilus b disease. In 20 infants aged 2 to 6 months with sickle-cell disease, three doses of HibTITER® given at 2-month intervals generated a geometric mean anti-HbPs antibody level of 22.1 μg/mL and 100% of the subjects had a level > 1 μg/mL one month after the third dose. 90% of the infants had a level > 1 μg/mL 18 months after the initial vaccination. The vaccine has also been shown to be immunogenic in native American infants. A group of 50 infants in Alaska received three doses at 2, 4, and 6 months of age. One month after the third vaccination, the geometric mean was 15.1 μg/mL and 95% of infants had levels > 1 μg/mL. Antibody levels > 1 μg/mL were observed in 71% of these infants at 15-18 months of age. These levels are comparable to those seen in healthy U.S. infants who received their first dose at 1 to 2 months of age and subsequent doses at 4 and 6 months of age.

Other Studies: Antigenuria was studied in 10 children, 15-18 months of age, immunized with HibTITER®. Urine specimens obtained from each child on days 1, 3, 5 and 7 following immunization were tested and all were found to be negative for the Haemophilus polysaccharide antigen throughout the 7 day follow up.

C. Advisory Committee considerations: Date regarding the safety, immunogenicity, and efficacy of Haemophilus b Conjugate Vaccines have been presented to a number of the Vaccines and Related Biological Products Advisory Committee meetings. Data on immunogenicity and efficacy of HibTITER® (Diphtheria CRM_{197} Protein Conjugate) were presented at the meeting held on August 20, 1990. The committee concluded that in their opinion the Praxis vaccine was safe and effective when administered to infants beginning at 2 months of age.

D. Adequacy of labeling: The labeling for HibTITER® (Diphtheria CRM_{197} Protein Conjugate) is appropriate and adequate for the product. See attached package insert.

TABLE 1

Clinical efficacy of the Praxis Biologics Haemophilus b Conjugate Vaccine in Northern California Kaiser Permanente Health Plan after three doses#

Study group	No. infants	Person years follow-up	Mean follow-up /child +	No. cases	Incidence/10^5 subjects
Vaccinated	21,120	13,021	7.4 mo.	0	0 *
Nonvaccinated	19,329	11,429	7.1	12	105 *
Refused	13,509	8,291	7.4	5	60
Not offered	5,820	3,138	6.5	7	223

Doses were given at 2, 4, and 6 months of age. In 5,445 person years of follow-up (2.5 mo./ infant) between the second and third doses there were no cases, compared to 8 cases after 5,445 person years in unvaccinated infants.

\+ The maximum follow-up for most children would be upto 15-18 months of age or 9-12 months of follow-up.

* The efficacy was 100% with the lower limit of the 95% confidence interval equal to 68% (two-tailed).

TABLE 2

Comparison of antibody levels and seroconversion rates following immunization with the Praxis Biologics Haemophilus b Conjugate Vaccine following different immunization schedules

Age at initial immunization (months)*	n=	Post immunization values, μg/ml Dose 1 GMT	Dose 1 % ≥ 1	Dose 2 GMT	Dose 2 % ≥ 1	Dose 3 GMT	Dose 3 % ≥ 1
1-6	423	0.45	27.9	8.49	90.3	22.4	99.2
7	87	1.95	72.4	28.53	98.5		
8	25	2.24	76.0	27.55	100		
9	54	3.13	81.5	26.04	100		
10	53	3.13	84.9	27.45	100		
11	54	5.95	90.7	29.44	100		
12	49	5.51	89.8	33.39	100		
13	52	7.89	94.2	32.80	100		
14	58	5.94	86.2	30.39	100		
15-17	236	10.8	97.9				
18-23	141	12.3	97.2				

* The doses were spaced approximately 2 months apart.

Carl E. Frasch, Ph.D.
Chairperson

Kathryn E. Stein, Ph.D.

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