HAEMOPHILUS b CONJUGATE VACCINE
(Diphtheria CRM_{197} Protein Conjugate)
HibTITER®

Rx only

DESCRIPTION

Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) HibTITER is a sterile solution of a conjugate of oligosaccharides of the capsular antigen of *Haemophilus influenzae* type b (Haemophilus b) and diphtheria CRM_{197} protein (CRM_{197}) dissolved in 0.9% sodium chloride. The oligosaccharides are derived from highly purified capsular polysaccharide, polyribosylribitol phosphate, isolated from Haemophilus b strain Eagan grown in a chemically defined medium (a mixture of mineral salts, amino acids, and cofactors). The oligosaccharides are purified and sized by diafiltrations through a series of ultrafiltration membranes, and coupled by reductive amination directly to highly purified CRM_{197}.[1,2] CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* C7 (β197) grown in a casamino acids and yeast extract-based medium that is ultrafiltered before use. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography to high purity. The conjugate is purified to remove unreacted protein, oligosaccharides, and reagents; sterilized by filtration; and filled into vials. HibTITER is intended for intramuscular use.

The vaccine is a clear, colorless solution. Each single dose of 0.5 mL is formulated to contain 10 µg of purified Haemophilus b saccharide and approximately 25 µg of CRM_{197} protein. The potency of HibTITER is determined by chemical assay for polyribosylribitol.

CLINICAL PHARMACOLOGY

For several decades *Haemophilus influenzae* type b (Haemophilus b) was the most common cause of invasive bacterial disease, including meningitis, in young children in the United States. Although nonencapsulated *H. influenzae* are common and six capsular polysaccharide types are known, strains with the type b capsule caused most of the invasive Haemophilus diseases.[3]

Haemophilus b diseases occurred primarily in children under 5 years of age prior to immunization with *Haemophilus influenzae* type b vaccines. In the US, the cumulative risk of developing invasive Haemophilus b disease during the first 5 years of life was estimated to be about 1 in 200. Approximately 60% of cases were meningitis. Cellulitis, epiglottitis, pericarditis, pneumonia, sepsis, or septic arthritis made up the remaining 40%. An estimated 12,000 cases of Haemophilus b meningitis occurred annually prior to the routine use of conjugate vaccines in toddlers.[3,4] The mortality rate can be 5%, and neurologic sequelae have been observed in up to 38% of survivors.[5]

The incidence of invasive Haemophilus b disease peaks between 6 months and 1 year of age, and approximately 55% of disease occurs between 6 and 18 months of age.[3] Interpersonal transmission of Haemophilus b occurs and risk of invasive disease is increased in children younger than 4 years of age who are exposed in the household to a primary case of disease. Clusters of cases in children in day care have been reported and recent studies suggest that the rate of secondary cases may also be increased among children exposed to a primary case in the daycare setting.[3,6]

The incidence of invasive Haemophilus b disease is increased in certain children, such as those who are native Americans, black, or from lower socioeconomic status, and those with medical conditions such as asplenia, sickle cell disease, malignancies associated with immunosuppression, and antibody deficiency syndromes.[3,4,6]

The protective activity of antibody to Haemophilus b polysaccharide was demonstrated by passive antibody studies in animals and in children with agammaglobulinemia or with Haemophilus b disease[7] and confirmed with the efficacy study of Haemophilus b polysaccharide (HbPs) vaccine.[8] Data from passive antibody studies indicate that a preexisting titer of antibody to HbPs of 0.15 µg/mL correlates with protection.[9] Data from a Finnish field trial in children 18 to 71 months of age indicate that a titer of > 1.0 µg/mL 3 weeks after vaccination is associated with long-term protection.[10,11]

Linkage of Haemophilus b saccharides to a protein such as CRM_{197} converts the saccharide (HbO) to a T-dependent (HbOC) antigen, and results in an enhanced antibody response to the saccharide in young infants that primes for an anamnestic response and is predominantly of the IgG class.[12] Laboratory evidence indicates that the native state of the CRM_{197} protein and the use of oligosaccharides in the formulation of HibTITER enhances its immunogenicity.[13–15]

Prior to licensure, the immunogenicity of HibTITER was evaluated in US infants and children.[15] Infants 1 to 6 months of age at first immunization received three doses at approximately 2-month intervals.[16] Children 7 to 11 and 12 to 14 months of age received 2 doses at the same interval.[15] Children 15 to 23 months of age received a single dose.[17] HibTITER was highly immunogenic in all age groups studied, with 97% to 100% of 1,232 infants attaining titers of ≥ 1 µg/mL and 92% to 100% for bactericidal activity.[15–17]

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 ≥ 1 µg/mL at 2 years of age.[18]

The vaccine generated an immune response characteristic of a protein antigen. IgG anti-HbPs antibodies of IgG_1 subclass predominated and the immune system was primed for a booster response to HibTITER. There is some evidence suggesting natural increases in antibody levels over time after vaccination, most probably the result of contact with Haemophilus type b organisms or cross-reactive antigens.[18] These studies were carried out at a time when significant levels of Haemophilus b disease were still present in the community.

Antibody generated by HibTITER has been found to have high avidity, a measure of the functional affinity of antibody to bind to antigen. High-avidity antibody is more potent than low-avidity antibody in serum bactericidal assays.[19] The contribution to clinical protection is unknown.

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.[20] HibTITER has been found to be immunogenic in children with sickle cell disease, a condition that may cause increased susceptibility to Haemophilus b disease.[21] HibTITER has

also been shown to be immunogenic in native American infants, such as the group of 50 studied in Alaska who received three doses at 2, 4, and 6 months of age.[20] Antibody levels achieved were comparable to those seen in healthy US infants who received their first dose at 1 to 2 months of age and subsequent doses at 4 to 6 months of age.[15,16,20]

Postlicensure surveillance of immunogenicity was conducted during the distribution of the first 30 million doses of HibTITER and during the time period over which Haemophilus b disease in children has been decreasing significantly in areas of extensive vaccine usage.[20,22–29] After three doses, titers ranged from 2.37 to 8.45 μg/mL with 67% to 94% attaining ≥ 1 μg/mL.[20,24,25]

Persistence of antibody was examined in several cohorts of subjects that received either a selected commercial lot or that were part of the initial efficacy trial in northern California. Geometric mean titers for these cohorts were between 0.51 and 1.96 just prior to boosting at 15 to 18 months. These lots not only induced persistent antibody but also provided effective priming for a booster dose with commercial lots, with postboosting titers greater than 1.0 μg/mL in 80% to 97% of subjects.[20]

HibTITER (HbOC) was shown to be effective in a large-scale controlled clinical trial in a multiethnic population in northern California carried out between February 1988 and June 1990.[30,31] There were no (0) vaccine failures in infants who received three doses of HibTITER and 12 cases of Haemophilus b disease (6 cases of meningitis) in the control group. The estimate of efficacy is 100% (P= .0002) with 95% confidence intervals of 68% to 100%. Through the end of 1991, with an additional 49,000 person-years of follow-up, there were still no cases of Haemophilus b disease in fully vaccinated infants less than 2 years of age.[22,23] One case of disease has been reported in a 3 1/2-year-old child who did not receive a booster dose as recommended.

A comparative clinical trial was performed in Finland where approximately 53,000 infants received HibTITER at 4 and 6 months of age and a booster dose at 14 months in a trial conducted from January 1988 through December 1990. Only two children developed Haemophilus b disease after receiving the two-dose primary immunization schedule. One child became ill at 15 months of age and the other at 18 months of age; neither child received the scheduled booster at 14 months of age. No vaccine failure has been reported in children who received the two-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.[20] Historical controls were used since all infants received one of two Haemophilus b conjugate vaccines during the period of the trial.

Evidence of efficacy postlicensure includes significant reductions in Haemophilus b disease that are closely associated with increases in the net doses of Haemophilus b Conjugate Vaccine distributed in the US.[20,22–29] In the northern California Kaiser Permanente there has been a 94% decrease in Haemophilus disease incidence in 1991 for children younger than 18 months of age, compared to 1984-1988, when HibTITER was not available for this age group.[22,23] Furthermore, active surveillance by the Centers for Disease Control and Prevention (CDC) has shown a 71% decrease in Haemophilus b disease in children less than 15 months old, between 1989 and 1991, which corresponds temporally and geographically with increases in net doses of

Haemophilus b conjugate vaccine distributed in the US.[26] As with all vaccines, this conjugate vaccine cannot be expected to be 100% effective. There have been rare reports to the Vaccine Adverse Event Reporting System (VAERS) of Haemophilus b disease following full primary immunization.

INDICATIONS AND USAGE

Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) HibTITER is indicated for the immunization of children 2 months to 71 months of age against invasive diseases caused by *H. influenzae* type b.

As with any vaccine, HibTITER may not protect 100% of individuals receiving the vaccine.

The American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP) encourage the routine simultaneous administration of *Haemophilus influenzae* type b vaccines with other currently recommended vaccines, but at different sites (see **DRUG INTERACTIONS**).[32,33,34,35]

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to the use of HibTITER.

The occurrence of an allergic or anaphylactic reaction following a prior dose of HibTITER is a contraindication to the use of HibTITER.

WARNINGS

HibTITER WILL NOT PROTECT AGAINST *H. INFLUENZAE* OTHER THAN TYPE b STRAINS, NOR WILL HibTITER PROTECT AGAINST OTHER MICROORGANISMS THAT CAUSE MENINGITIS OR SEPTIC DISEASE.

AS WITH ANY INTRAMUSCULAR INJECTION, HibTITER SHOULD BE GIVEN WITH CAUTION TO INFANTS OR CHILDREN WITH THROMBOCYTOPENIA OR ANY COAGULATION DISORDER, OR TO THOSE RECEIVING ANTICOAGULANT THERAPY (SEE **DRUG INTERACTIONS**).

ANTIGENURIA HAS BEEN DETECTED FOLLOWING RECEIPT OF HAEMOPHILUS b CONJUGATE VACCINE[36] AND THEREFORE ANTIGEN DETECTION IN URINE MAY NOT HAVE DIAGNOSTIC VALUE IN SUSPECTED HAEMOPHILUS b DISEASE WITHIN 2 WEEKS OF IMMUNIZATION.

The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected into persons with known or possible latex sensitivity.

PRECAUTIONS

GENERAL

1. CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

2. PRIOR TO ADMINISTRATION OF ANY DOSE OF HibTITER, THE PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE HEALTH CARE PROVIDER SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATION IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH HibTITER AND TO ALLOW AN ASSESSMENT OF BENEFITS AND RISKS.

3. BEFORE THE INJECTION OF ANY BIOLOGICAL, THE HEALTH CARE PROVIDER SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER SIDE REACTIONS. This should include: a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1,000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.

4. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization procedures.[37,38] Deferral of administration of vaccine may be considered in individuals receiving immunosuppressive therapy.[37] Other groups should receive this vaccine according to the usual recommended schedule.[37–39] (See **DRUG INTERACTIONS**.)

5. Minor illnesses, such as mild respiratory infection with or without low-grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. The administration of HibTITER® should be postponed in subjects suffering from acute severe febrile illness.

6. This product is not contraindicated based on the presence of human immunodeficiency virus infection.[40]

7. As reported with Haemophilus b polysaccharide vaccine, cases of Haemophilus b disease may occur prior to the onset of the protective effects of the vaccine.[3,41]

8. The vaccine should not be injected intradermally, subcutaneously, or intravenously since the safety and immunogenicity of these routes have not been evaluated. The vaccine should be given intramuscularly.

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

10. Special care should be taken to prevent injection into a blood vessel.

11. The vaccine is to be administered immediately after being drawn up into a syringe. Single dose 0.5 mL vial contains no preservative. Use one dose per vial; do not re-enter vial. Discard unused portions.

12. As with any vaccine, HibTITER® may not protect 100% of individuals receiving the vaccine.

ALTHOUGH SOME ANTIBODY RESPONSE TO DIPHTHERIA TOXIN OCCURS, IMMUNIZATION WITH HibTITER DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected into persons with known or possible latex sensitivity.

INFORMATION FOR PATIENT

PRIOR TO ADMINISTRATION OF HibTITER, HEALTH CARE PERSONNEL SHOULD INFORM THE PARENT, GUARDIAN OR OTHER RESPONSIBLE ADULT, OF THE RECOMMENDED IMMUNIZATION SCHEDULE FOR PROTECTION AGAINST HAEMOPHILUS b DISEASE AND THE BENEFITS AND RISKS TO THE CHILD RECEIVING THIS VACCINE. GUIDANCE SHOULD BE PROVIDED ON MEASURES TO BE TAKEN SHOULD ADVERSE EVENTS OCCUR, SUCH AS, ANTIPYRETIC MEASURES FOR ELEVATED TEMPERATURES AND THE NEED TO REPORT ADVERSE EVENTS TO THE HEALTH CARE PROVIDER. Parents should be provided with vaccine information pamphlets at the time of each vaccination, as stated in the National Childhood Vaccine Injury Act.[42]

PATIENTS, PARENTS, OR GUARDIANS SHOULD BE INSTRUCTED TO REPORT ANY SERIOUS ADVERSE REACTIONS TO THEIR HEALTH CARE PROVIDER.

DRUG INTERACTIONS

Children receiving therapy with immunosuppressive agents (large amounts of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.[37,38,39] (See **PRECAUTIONS, GENERAL**.)

As with other intramuscular injections, HibTITER should be given with caution to children on anticoagulant therapy.

No impairment of the antibody response to the individual antigens was demonstrated when HibTITER was given at the same time but at separate sites as diphtheria tetanus pertussis vaccine (DTP) plus oral polio vaccine (OPV) to children 2 to 20 months of age or measles-mumps-rubella (MMR) to children 15 ± 1 month of age.[20,43,44]

There are no clinical studies where a direct comparison of the immune responses to HibTITER was compared with the concurrent administration of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), hepatitis B vaccine (Hep B), inactivated poliovirus vaccine (IPV), 7-valent Conjugate Vaccine-Diphtheria CRM_{197} Protein (Prevnar), or Varicella vaccine. However, in clinical trials where HibTITER and DTaP or HibTITER, DTaP, IPV, and Hep B vaccines were administered concurrently with or without Prevnar in children at 2, 4, and 6 months of age, the percentage of children achieving Hib antibody levels of ≥0.15 or ≥1.0 μg/mL were similar.[45,46] In one study where children 12-15 months of age were administered a booster dose of HibTITER concurrently with DTaP and Prevnar, some suppression of the Hib antibody response was observed, but over 97% of children achieved titers of ≥1.0 μg/mL.[47,48] However, in another study where a booster dose of HibTITER was administered to children at 12-15 months of age concurrently with or without Prevnar the percentage of children achieving Hib antibody levels of ≥0.15 or ≥1.0 μg/mL was found to be similar.[49,50]

HibTITER and DTaP administered concurrently with and without Prevnar at 2, 4, and 6, and 12-15 months of age did not impair immune responses to the seven Pneumococcal vaccine serotypes in Prevnar.[47,48,51,52]

There are no clinical trials where the local and systemic reactogenicity of HibTITER was directly compared with the concurrent administration of DTaP, Hep B, IPV, Prevnar, or Varicella vaccines.

The American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP) encourage routine simultaneous administration of DTaP, IPV, *Haemophilus influenzae* type b vaccine, pneumococcal conjugate vaccine, measles-mumps-rubella (MMR), varicella vaccine and hepatitis B vaccine for children who are the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit, unless, in the judgment of the provider, complete vaccination of the child will not be compromised by administering different vaccines at different visits. Simultaneous administration is particularly important if the child might not return for subsequent vaccinations.[32,33,34,35]

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
HibTITER has not been evaluated for its carcinogenic, mutagenic potential, or impairment of fertility.

PREGNANCY
REPRODUCTIVE STUDIES— PREGNANCY CATEGORY C

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

GERIATRIC USE
This vaccine is NOT recommended for use in adult populations.

PEDIATRIC USE
The safety and effectiveness of HibTITER in children below the age of 6 weeks have not been established.

ADVERSE REACTIONS
Adverse reactions associated with HibTITER have been evaluated in 401 infants who were vaccinated initially at 1 to 6 months of age and were given 1,118 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 (Table 1). No difference in the rates of these complaints was reported after dose 1, 2, or 3.

TABLE 1 Number of Subjects (Percent) Manifesting Side Effects Associated with HibTITER Administered Independently from DTP* (Infants Vaccinated Initially at 1-6 Months of Age)

	Dose 1 n = 401			Dose 2 n = 383			Dose 3 n = 334		
Symptoms	Same Day As Vacc.	+1 Day	+2 Days	Same Day As Vacc.	+1 Day	+2 Days	Same Day As Vacc.	+1 Day	+2 Days
Temp > 38.3°C	0	2	2	2	3	2	2	6	5
	-	< 1%	< 1%	< 1%	< 1%	< 1%	< 1%	1.8%	1.5%
Redness ≥ 2 cm	1	0	0	1	6	0	5	4	0
	< 1%	-	-	< 1%	1.6%	-	1.5%	1.2%	-

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	Dose 1 n = 401			Dose 2 n = 383			Dose 3 n = 334		
Symptoms	Same Day As Vacc.	+1 Day	+2 Days	Same Day As Vacc.	+1 Day	+2 Days	Same Day As Vacc.	+1 Day	+2 Days
Warmth ≥ 2 cm	1	1	0	2	1	0	1	6	0
	< 1%	< 1%	-	< 1%	< 1%	-	< 1%	1.8%	-
Swelling ≥ 2 cm	5	1	0	2	2	0	1	0	0
	1.2%	< 1%	-	< 1%	< 1%	-	< 1%	-	-

*DTP and HibTITER given 2 weeks apart with DTP having been given first.

The following complaints were also observed after 1,118 vaccinations with HibTITER: irritability (133), sleepiness (91), prolonged crying [≥4 hours] (38), appetite loss (23), vomiting (9), diarrhea (2), and rash (1).

Additional safety data with HibTITER are available from the efficacy studies conducted in young infants.[30] There were 79,483 doses 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 OPV; 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 rate and type of reactions associated with the vaccinations were no 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. The incidence and type of side effects reported within 24 hours of vaccination were similar to those cited in Table 1. In addition, analysis of emergency room (ER) visits within 30 days and hospitalization within 60 days after receipt of 23,800 doses of HibTITER showed no increase in the rates of any type of ER visit or hospitalization.

Table 2 details the side effects associated with a single vaccination of HibTITER given (without DTP) to infants of 15 to 23 months of age.

TABLE 2 Selected Adverse Reactions* in Children of 15-23 Months of Age Following Vaccination with HibTITER

Adverse Reaction	No. of Subjects	Reaction Within 24 h	% Postvaccination At 48 h
Fever			
>38.3°C	354	1.4	0.6
Erythema	354	2.0	–
Swelling	354	1.7	–
Tenderness	354	3.7	0.3

* The following complaints were reported after vaccination of these 354 children in the indicated number of children: diarrhea (9), vomiting (5), prolonged crying [>4 hours] (4), and rashes (2).

Similar results have been observed in the analysis of 2,285 subjects of 18 to 60 months of age, vaccinated as part of a postmarketing safety study of HibTITER.[20] These data were collected by telephone survey 24 to 48 hours postvaccination. Additional observations included irritability, restless sleep, and Gl symptoms (diarrhea, vomiting, and loss of appetite) in the group that received HibTITER alone. A cause and effect relationship between these observations and the vaccinations has not been established.

Post Approval Experience

The following adverse reactions have been identified during post approval use of HibTITER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to the vaccine for post marketing surveillance information.

Injection Site Reactions

Injection site reactions including hypersensitivity (including urticaria), induration, inflammation, mass, and skin discoloration.

Systemic Events

Anaphylactoid/anaphylactic reactions (including shock), angioneurotic edema, convulsions,[53] erythema multiforme, facial edema, febrile seizures, Guillain-Barré syndrome,[54] headache, hives (urticaria), hypersensitivity reaction, lethargy, and malaise. Also reported, hypotonia or hyporesponsive-hypotonic-episodes (in many instances pertussis-containing vaccine was coadministered).

There have been spontaneous reports of apnea in temporal association with the administration of HibTITER. In most cases HibTITER was administered concomitantly with other vaccines including DTP, DTaP, hepatitis B vaccine, IPV, OPV, pneumococcal 7-valent conjugate vaccine, MMR, and/or meningococcal group C conjugate vaccine (not licensed in the US). In addition, in

some of the reports existing medical conditions such as prematurity and/or history of apnea were present.

Reporting of Adverse Reactions
Any suspected adverse events following immunization should be reported by the healthcare professional to the US Department of Health and Human Services (DHHS). The National Vaccine Injury Compensation Program requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare professional in the vaccine recipient's permanent medical record (or in a permanent office log or file), along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine. The DHHS has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[42] The VAERS FDA web site is:

http://www.fda.gov/cber/vaers/vaers.htm

The VAERS toll-free number for VAERS forms and information is 800-822-7967.

OVERDOSAGE
There have been reports of overdose with HibTITER. Many cases were due to inadvertent coadministration with another Haemophilus b conjugate-containing vaccine. Most individuals were asymptomatic. In general, adverse events reported with overdosage have also been reported with recommended single doses of HibTITER.

DOSAGE AND ADMINISTRATION
HibTITER is for intramuscular use only.
Any parenteral drug product should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, or if cloudy, HibTITER should not be administered.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel.

The vaccine should be injected intramuscularly, preferably into the midlateral muscles of the thigh or deltoid, with care to avoid major peripheral nerve trunks. Do not inject in the gluteal area.

The vaccine is to be administered immediately after being drawn up into a syringe. Single dose 0.5 mL vial contains no preservative. Use one dose per vial; do not re-enter vial. Discard unused portions.

The vaccine is not to be mixed with other vaccines/products in the same syringe.

HibTITER is indicated for children 2 months to 71 months 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. Previously unvaccinated infants

from 7 through 11 months of age should receive two separate injections approximately 2 months apart. Children from 12 through 14 months of age who have not been vaccinated previously receive one injection. All vaccinated children receive a single booster dose at 15 months of age or older, but not less than 2 months after the previous dose. Previously unvaccinated children 15 to 71 months of age receive a single injection of HibTITER.[32,33] Preterm infants should be vaccinated with HibTITER according to their chronological age, from birth.[32]

Recommended Immunization Schedule

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

Interruption of the recommended schedules with a delay between doses does not interfere with the final immunity achieved nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.[32,33]

Data support that HibTITER may be interchanged with other *Haemophilus influenzae* type b conjugate vaccines for the primary immunization series and booster dose.[55,56,57]

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.

STORAGE
DO NOT FREEZE. Store refrigerated away from freezer compartments at 2°C-8°C (36°F-46°F). Discard if the vaccine has been frozen.

HOW SUPPLIED
Vial, 1 Dose (5 per package) – Product No. 0005-0104-32

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