AHFS Category 80:08

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Tripedia®

℞ only

CAUTION: Federal (USA) law prohibits dispensing without prescription.

DESCRIPTION

Tripedia®, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), for intramuscular use, is a sterile preparation of diphtheria and tetanus toxoids adsorbed, with acellular pertussis vaccine in an isotonic sodium chloride solution containing thimerosal as a preservative and sodium phosphate to control pH. After shaking, the vaccine is a homogeneous white suspension. Tripedia® vaccine is distributed by Aventis Pasteur Inc. (AvP).

Corynebacterium diphtheriae cultures are grown in a modified Mueller and Miller medium.[2] *Clostridium tetani* cultures are grown in a peptone-based medium containing a bovine extract. The meat used in this medium is US sourced. Both toxins are detoxified with formaldehyde. The detoxified materials are then separately purified by serial ammonium sulfate fractionation and diafiltration.

The acellular pertussis vaccine components are isolated from culture fluids of Phase 1 *Bordetella pertussis* grown in a modified Stainer-Scholte medium.[1] After purification by salt precipitation, ultracentrifugation, and ultrafiltration, preparations containing varying amounts of both pertussis toxin (PT) and filamentous hemagglutinin (FHA) are combined to obtain a 1:1 ratio and treated with formaldehyde to inactivate PT.

The diphtheria and tetanus toxoids are adsorbed using aluminum potassium sulfate (alum). The adsorbed toxoids are combined with acellular pertussis concentrate, and diluted to a final volume using sterile phosphate-buffered physiological saline. The 1 dose vial of vaccine is formulated without preservatives but contains a trace amount of thimerosal [(mercury derivative), (≤ 0.3 µg mercury/dose)] from the manufacturing process. The multidose (7.5 mL) vial of vaccine contains the preservative thimerosal [(mercury derivative), 25 µg mercury/dose]. Each 0.5 mL dose contains, by assay, not more than 0.170 mg of aluminum and not more than 100 µg (0.02%) of residual formaldehyde. The vaccine contains gelatin and polysorbate 80 (Tween-80), which are used in the production of the pertussis concentrate.

Each 0.5 mL dose is formulated to contain 6.7 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test), and 46.8 µg of pertussis antigens. This is represented in the final vaccine as approximately 23.4 µg of inactivated PT (also referred to as lymphocytosis promoting factor or LPF) and 23.4 µg of FHA. The inactivated acellular pertussis component contributes not more than 50 endotoxin units (EU) to the endotoxin content of 1 mL of DTaP. The potency of the pertussis components is evaluated by measuring the antibody response to PT and FHA in immunized mice using an ELISA system.

Acellular Pertussis Vaccine Concentrates (For Further Manufacturing Use) are produced by The Research Foundation for Microbial Diseases of Osaka University (BIKEN), Osaka, Japan, under United States (US) license, and are combined with diphtheria and tetanus toxoids manufactured by AvP. The Tripedia® vaccine is filled, labeled, packaged, and released by AvP.

When Tripedia® vaccine is used to reconstitute ActHIB® the combination vaccine is TriHIBit®. Each single 0.5 mL dose of TriHIBit®, **for the fourth dose only**, is formulated to contain 6.7 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid (both toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test), 46.8 µg of pertussis antigens (approximately 23.4 µg of inactivated PT and 23.4 µg of FHA), 10 µg of purified *Haemophilus influenzae* type b capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, and 8.5% sucrose. ***(Refer to ActHIB® package insert.)***

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis, using a conventional "whole-cell" pertussis DTP vaccine (Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed – For Pediatric Use), has been a routine practice during infancy and childhood in the US since the late 1940s. This practice has played a major role in markedly reducing the incidence rates of cases and deaths from each of these diseases.[3]

Tripedia® vaccine combines diphtheria and tetanus toxoids with purified pertussis antigens (inactivated PT and FHA). These pertussis antigens have been used routinely for childhood vaccination in Japan since 1981[4-7] and have been used for investigational purposes in Sweden,[1,8-11] as well as in the US and Germany.[1,12-20] In the US, since 1992, Tripedia® vaccine has been indicated for immunization of children 15 months to 7 years of age (prior to the seventh birthday) who have previously been immunized with three or four doses of whole-cell pertussis DTP. In the US, since 1996, Tripedia® vaccine has been indicated for four consecutive doses of the DTaP immunization series in infants and children 6 weeks to 7 years of age (prior to the seventh birthday). In 2000, Tripedia® vaccine was indicated for five consecutive doses of the DTaP immunization series in this age group (see **DOSAGE AND ADMINISTRATION** section).

DIPHTHERIA

Corynebacterium diphtheriae may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibody to diphtheria toxin.

Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce diphtheria toxin cause severe manifestations, such as myocarditis and neuritis. Diphtheria remains a serious disease, with the highest case-fatality rates among infants and the elderly.[3]

Prior to the widespread use of diphtheria toxoid in the late 1940's, diphtheria was common in the US. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality rates were in the very young and the elderly. More recently, reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable.[3] From 1980 through 1999, only 49 cases of diphtheria were reported in the US. During the period 1980-1996, six fatal cases of diphtheria were reported. Only one case of diphtheria was reported each year in 1998 and 1999. Of 40 reported cases with known age in 1982-1998, 63% were in persons ≥ 20 years of age. Most cases have occurred in unimmunized or inadequately immunized persons. Although diphtheria disease is rare in the US, it appears that *C. diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria.[21]

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in the Newly Independent States of the former Soviet Union beginning in 1990. This epidemic has resulted in approximately 150,000 cases and 5,000 deaths during the years 1990-1997.[22] This outbreak is believed to be due to several factors, including a lack of routine immunization of adults in these countries.

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illness. Protection is thought to last at least 10 years. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx, nose, or on the skin.[3]

Efficacy of diphtheria toxoid used in Tripedia® vaccine was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[23]

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the US. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of serum antitoxin that persist for 10 or more years.[3]

Following routine use of tetanus toxoid in the US, the occurrence of tetanus decreased dramatically from 560 reported cases in 1947 to an average of 50-100 cases reported annually from the mid 1970's through the late 1990's. The case-fatality rate has been relatively constant at approximately 30%. During the years 1982-1998, 52% of reported cases were among persons 60 years of age or older. In the mid to late 1990's, the age distribution of reported cases shifted to a younger age group, in part due to an increased number of cases among injection drug users in California. From 1995-1997, persons 20 to 59 years of age accounted for 60% of all cases, with persons 60 years of age or older accounting for only 35%. In the US, tetanus occurs almost exclusively among unvaccinated or inadequately vaccinated persons.[21]

Efficacy of tetanus toxoid used in Tripedia® vaccine was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[23]

PERTUSSIS

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces a variety of biologically active components. The role of the different components in conferring protective immunity is not well understood. The use of Tripedia® vaccine as a primary series evokes an antibody response with respect to PT and FHA and has been shown to be effective in clinical studies.

Pertussis is highly communicable (with attack rates of up to 100% in susceptible individuals with intense exposure)[24] and can cause severe disease, particularly among young infants. Since pertussis became a nationally reportable disease in the US in 1922, the highest number of pertussis cases (approximately 260,000) were reported in 1934. Following introduction and widespread use of the whole cell pertussis DTP vaccine among infants and children in the mid to late 1940's, pertussis incidence gradually declined, reaching a historical low of 1,010 cases in 1976. However, during the 1980's and 1990's, pertussis incidence gradually increased. A total of 7,796 cases were reported in 1996, the largest number since 1967. A total of 7,405 cases were reported in 1998[25] and a provisional total of 6,031 cases were reported in 1999.[21] The reasons for the increase are not clear.

The incidence of reported pertussis and the severity of the disease remain highest in infants. Of 10,749 infants < 1 year of age reported as having pertussis during the period 1980 to 1989, 69% were hospitalized, 22% had pneumonia, 3% had one or more seizures, 0.9% had encephalopathy, and 0.6% died.[26]

Pertussis cases among adolescents and adults in the US were increasingly reported in the 1980's and 1990's. In older children and adults, including some who were previously immunized, infection may result in nonspecific symptoms of bronchitis or an upper respiratory tract infection, and pertussis may not be diagnosed because classic signs, particularly the inspiratory whoop, may be absent. Older preschool children and school age siblings who are not fully immunized and develop pertussis, as well as adolescents and adults with pertussis, may play a role in transmission to young infants.[21]

Acellular pertussis vaccines have been used in Japan since 1981, mostly in 2-year-old children. Evidence for the efficacy of these vaccines, as a group, is demonstrated by the decline in pertussis disease with their routine use in that country.[4,24] In addition, a review of epidemiological studies of the Japanese acellular pertussis vaccines estimated that these vaccines, as a group, were 88% efficacious in protecting against clinical pertussis on household exposure, with a 95% confidence interval (CI) of 79% to 93%.[27]

Two clinical studies were conducted to assess the protective efficacy of the acellular pertussis component of Tripedia® vaccine. A randomized, controlled clinical trial in Sweden assessed efficacy after two doses of the pertussis component in children 5-11 months of age.[10] A second study was conducted in Germany using a three-dose schedule to evaluate the protective efficacy of the Tripedia® vaccine in younger infants.[16]

In 1986-1987, a double-blind, randomized, placebo-controlled efficacy trial of two BIKEN acellular pertussis vaccines was conducted in Sweden. One of the vaccines was a two-component vaccine comparable to the acellular pertussis components contained in Tripedia® vaccine. This prospective trial used a standardized case definition and active case ascertainment. In this trial, 1,389 children, 5-11 months of age (median 8.5 months), received two doses of the acellular pertussis vaccine 7-13 weeks apart and 954 received a placebo control. During the 15 months of follow-up from 30 days after the second dose, culture-confirmed whooping cough (cough of any duration and a positive culture of *B. pertussis*) occurred in 40 placebo and 18 acellular pertussis vaccine recipients. The point estimate of protective efficacy for two doses of vaccine was 69% (95% CI; 47% to 82%) for all cases of culture-confirmed pertussis with any cough 1 day or longer and 79% (95% CI; 57% to 90%) using a secondary case definition of culture-confirmed cases with cough of over 30 days duration.[10] In a reanalysis of the Swedish data, efficacy estimates increased with duration of coughing spasms and when the case definition included whoops and whoops plus at least nine coughing spasms a day.[28] Using a case definition of 21 days or more of coughing spasms, confirmed by positive culture, resulted in an efficacy estimate of 81% (95% CI; 61% to 90%).[28]

Using a passive reporting system, three-year unblinded follow-up of vaccine and placebo recipients from the above Swedish study has shown a post-trial efficacy of 77% (95% CI; 65% to 85%) for all culture-proven cases of pertussis, and an efficacy of 92% (95% CI; 84% to 96%) for culture-proven cases with a cough of over 30 days duration.[29]

A case-control study to evaluate the efficacy of Tripedia® vaccine was conducted in Germany.[16] The study population consisted of patients in 63 pediatric practices who had no contraindications to pertussis immunization and were enrolled in the study between the ages of 6 and 17 weeks (actual range of age at first visit was up to 20 weeks for the DT group). By parental choice, infants received Tripedia® vaccine or whole-cell pertussis DTP (manufactured by Chiron Behring, Germany [formerly Behringwerke]) at approximately 3, 5, and 7 months of age, or DT, or no vaccine. Cases of pertussis were identified by obtaining cultures for *B. pertussis* from all patients between the ages of 2 and 24 months who presented to the physician's office with 7 or more days of cough. Identification of presumptive cases of pertussis was made by primary care physicians who were not blinded to the vaccine status of subjects. Cases were confirmed by positive culture in the subject or positive culture in a subject's household contact. Duration of cough in study subjects was determined at an office visit, by telephone, or by home visit 21-24 days after the onset of cough.

Four age-matched controls were selected for each case from the same pediatric practice. Selection of controls was done without knowledge of vaccination status. The vaccine (or no vaccine) and number of doses which each case and control subject received subsequently was determined from medical records.

In order to adjust for potentially confounding variables, information on sex, race, day-care attendance, well-baby visits, sick-child visits, pertussis vaccination status of siblings, age of siblings, number of siblings, day-care attendance of siblings, and parental employment status was obtained through interview of parents. Information on erythromycin use was not obtained for the study population.

A total of 16,780 infants were enrolled in the study, of whom 74.6% received Tripedia® vaccine and 10.9%, 12.5%, and 2.1% received DTP, DT, or no vaccine, respectively, by non-random parental choice. A total of 11,017 cultures for *B. pertussis* was obtained and 140 cases were identified using a primary case definition of cough ≥ 21 days, plus positive culture for *B. pertussis* or household contact with a person with culture-positive pertussis. Of the 140 cases, 130 cases were diagnosed on the basis of a positive culture and 10 on the basis of household contact with a culture-positive case. For the 140 cases, 543 controls were selected. Of the 140 cases, 29 (20.7%) received three doses of DTaP, 5 (3.6%) received two doses of DTaP, 44 (31.4%) received two or three doses of DT vaccine, 44 (31.4%) received one dose of either DTaP, whole-cell pertussis DTP or DT, and 18 (13%) received no vaccine. Of the 543 controls, 175 (32.2%) received three doses of DTaP, 67 (12.3%) received two doses of DTaP, 45 (8.3%) received two or three doses of whole-cell pertussis DTP, 73 (13.4%) received DT vaccine,153 (28.2%) received one dose of either DT, DTP, or DTaP, and 30 (5.5%) received no vaccine. Adjusting for sibling age, sibling pertussis immunization by age group, siblings in day care, number of siblings in day care, and father's employment status, the vaccine efficacy of three doses of Tripedia® vaccine compared to two or three doses of DT was 80% (95% CI; 59% to 90%).[1]

In a clinical study conducted in 65 US and 89 German infants, a single lot of Tripedia® vaccine was administered at 2, 4 and 6 months of age for the purpose of comparing immune responses to PT and FHA. This study showed that US and German infants, who received three doses of Tripedia® vaccine, expressed similar antibody responses to these antigens. The percentage of infants demonstrating a four-fold or greater antibody response, was also similar for PT and FHA in both groups.[1]

In a clinical study, US infants received Tripedia®, ActHIB®, OPV, and hepatitis B vaccines simultaneously at separate sites. In one of the study groups, Tripedia®, ActHIB®, and OPV were administered at 2, 4, and 6 months of age and hepatitis B was given at 2 and 4 months of age. One hundred percent of the 69 children who received ActHIB® simultaneously with Tripedia® vaccine demonstrated anti-PRP antibodies ≥ 1.0 µg/mL. Sera from a subset of 12 infants who received hepatitis B simultaneously at 2 and 4 months of age showed that 93% had anti-HBs titers of ≥ 10 mIU/mL. Sera from a subset of 20 infants who received OPV simultaneously at 2, 4, and 6 months of age showed that 100% had protective neutralizing antibody responses to all three polio virus types. Data on the simultaneous administration of Tripedia® with either inactivated poliovirus vaccine, or varicella vaccine or pneumococcal conjugate vaccine are not available.

TRIPEDIA® COMBINED WITH ActHIB® (TriHIBit®) BY RECONSTITUTION

Clinical studies examined the immune response in 15- to 20-month-old children when Tripedia® vaccine was used to reconstitute one lyophilized single dose vial of ActHIB® (TriHIBit®). All children received three doses of Haemophilus b Conjugate Vaccine (ActHIB® or HibTITER®) and three doses of whole-cell DTP at approximately 2, 4, and 6 months of age. Table 1 shows the diphtheria, tetanus, and pertussis responses when Tripedia® vaccine was used to reconstitute ActHIB® (TriHIBit®) compared to the two vaccines given concomitantly but at different sites. In children who received the vaccines separately or combined, 100% had an antibody response to the PRP component ≥ 1.0 µg/mL.[1]

TABLE 1[1] IMMUNE RESPONSES IN 15- TO 20-MONTH-OLD CHILDREN WHEN TRIPEDIA® VACCINE IS COMBINED WITH ActHIB® BY RECONSTITUTION (TriHIBit®) COMPARED TO THE VACCINES ADMINISTERED SEPARATELY

VACCINE GROUP N*	PRE-DOSE TriHIBit® 92-93	PRE-DOSE Separate 102-103	POST-DOSE TriHIBit® 93	POST-DOSE Separate 98
Anti-LPF				
GMT (ELISA units/mL)	26.30	24.56	471.00	363.90
% 4-Fold Rise	–	—	87.0	85.7
Anti-LPF				
GMT (CHO CELL)	33.48	31.78	806.70	701.60
% 4-Fold Rise	–	–	92.3	90.6
Anti-FHA				
GMT (ELISA units/mL)	3.83	3.61	44.68	38.81
% 4-Fold Rise	–	–	68.5**	80.6
Diphtheria Antitoxin				
GMT (units/mL)	0.15	0.16	6.31	6.65
% > 0.01 u/mL	–	–	100.00	100.00
Tetanus Antitoxin				
GMT (equivalents/mL)	0.05	0.06	1.10	1.15
% > 0.01 u/mL	–	–	100.00	100.00

* N = Number of Children

** The clinical significance of the difference in 4-fold rise of anti-FHA is unknown at present.

In clinical studies evaluating simultaneous administration of Tripedia® and ActHIB® with MMR vaccine to 15- to 20-month-old children, the data suggest that the combination vaccine does not interfere with the immunogenicity of the MMR vaccine. Overall seroconversion rates in children who received ActHIB® reconstituted with Tripedia® (TriHIBit®) vaccine were 98% (46/47), 98% (42/43) and 96% (43/45) for measles, mumps and rubella, respectively.

INDICATIONS AND USAGE

Tripedia® vaccine is indicated for active immunization against diphtheria, tetanus, and pertussis (whooping cough) simultaneously in infants and children 6 weeks to 7 years of age (prior to seventh birthday). Because of the substantial risks of complications of the disease, completion of a primary series of pertussis vaccine early in life is strongly recommended.[3] However, in instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) should be used for each of the remaining doses. (See **CONTRAINDICATIONS** section.)

When Tripedia® vaccine is used to reconstitute ActHIB® (TriHIBit®), the combined vaccines are indicated for the active immunization of children 15 to 18 months of age who have been immunized previously against diphtheria, tetanus and pertussis with three doses consisting of either whole-cell DTP or Tripedia® and three or fewer doses of ActHIB® within the first year of life for the prevention of diphtheria, tetanus, pertussis and invasive diseases caused by *H. influenzae* type b.[1] ***(Refer to ActHIB® package insert.)***

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin should be used.

Children who have had well-documented pertussis (i.e., positive culture for *B. pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination series with at least DT. Some experts recommend including the pertussis component as well (i.e., administration of DTaP). Although well-documented pertussis disease is likely to confer immunity against pertussis, the duration of such immunity is unknown.[30,31]

Tripedia® vaccine is not to be used for treatment of *B. pertussis, C. diphtheriae, or C. tetani* infections.

As with any vaccine, vaccination with Tripedia® vaccine may not protect 100% of susceptible individuals.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal and gelatin, is a contraindication.

It is a contraindication to use this vaccine after an immediate anaphylactic reaction temporally associated with a previous dose. Because of uncertainty as to which component of the vaccine might be responsible, no further vaccination with diphtheria, tetanus, or pertussis components should be carried out. Alternatively, because of the importance of tetanus vaccination, such individuals may be referred for evaluation by an allergist.[3,30]

The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. All vaccines can be administered to persons with mild illness such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low grade febrile illness. However, children with moderate or serious illnesses should not be immunized until recovered.[30,32]

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[33]

Encephalopathy not due to an identifiable cause, occurring within 7 days of a prior whole-cell pertussis DTP or DTaP immunization and consisting of major alterations of consciousness, unresponsiveness, generalized or focal seizures that persist for more than a few hours and failure to recover within 24 hours should be considered a contraindication to further use; this includes severe alterations in consciousness with generalized or focal neurologic signs. Even though causation cannot be established, no subsequent doses of pertussis vaccine should be given and immunization with DT should be continued to complete the series.[3,30]

WARNINGS

If any of the following events occurs in temporal relation with the receipt of either whole-cell pertussis DTP or DTaP, the decision to administer subsequent doses of vaccine containing the pertussis component should be carefully considered. Although these events were once considered contraindications to whole-cell pertussis DTP, there may be circumstances, such as high incidence of pertussis, in which the potential benefits outweigh the possible risks, particularly since the following events have not been proven to cause permanent sequelae:[3,30,31,34]

1. Temperature of ≥ 40.5°C (105°F) within 48 hours, not due to another identifiable cause.
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
3. Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours.
4. Convulsions with or without fever, occurring within 3 days.

Data from approximately 15,000 children participating in German and US studies, suggest that persistent, inconsolable crying lasting at least 3 hours following vaccination with Tripedia® vaccine may occur less frequently than has been observed historically for DTP vaccine.[1,35]

When a decision is made to withhold the pertussis component, immunization with DT should be continued.

Tripedia® vaccine should not be given to children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

A committee of the Institute of Medicine (IOM) has concluded that evidence is consistent with a causal relationship between DTP and acute neurologic illness, and under special circumstances, between DTP and chronic neurologic disease in the context of the NCES report.[37,38] However, the IOM committee concluded that the evidence was insufficient to indicate whether or not DTP increased the overall risk of chronic neurologic disease.[38] Acute encephalopathy or permanent neurological injury have not been reported in temporal association after administration of Tripedia® vaccine but the experience with this vaccine is insufficient to rule this out. (See **ADVERSE REACTIONS** section).

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following whole-cell pertussis vaccination.[3] Whether to administer Tripedia® vaccine to such children must be decided on an individual basis after consideration of the risks and benefits. An important consideration includes the current local incidence of pertussis. The Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) have issued guidelines for such children. [3,30,31]

In the opinion of the manufacturer, seizure disorder in children before or after any immunization with Tripedia® is considered a warning against further immunization with this vaccine. The ACIP and AAP recognize certain circumstances in which children with stable central nervous system disorders, including well-controlled seizures or satisfactorily explained single seizures, may receive acellular pertussis vaccine. [30,31]

Some studies suggest that infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 3.2-fold increased risk for neurologic events compared with those without such histories when given DTP.[27,36] However, a family history of convulsions in parents and siblings is not considered a contraindication to pertussis vaccination by either the AAP or the ACIP. The AAP and ACIP recommend that children with such family histories should receive pertussis vaccine according to the recommended schedule.[3,30,31]

In children with a personal or family history of convulsions, acetaminophen or other appropriate antipyretic should be given at the time of Tripedia® vaccination and for the ensuing 24 hours, according to the respective package insert recommended dosage, to reduce the possibility of post-vaccination fever.[3,30,31]

Tripedia® vaccine should not be combined through reconstitution with any vaccine for administration to infants younger than 15 months of age. Tripedia® vaccine should not be reconstituted with any vaccine other than ActHIB® for children 15 months of age or older.

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

EPINEPHRINE INJECTION (1:1,000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. The physician should have a current knowledge of the literature concerning the use of the vaccine under consideration, including the nature of the adverse reactions that may follow its use. The patient's medical history should be reviewed with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines, possible sensitivity to dry natural latex rubber, previous immunization history, and current health status (see **CONTRAINDICATIONS** section).

The expected immune response to Tripedia® may not be obtained in immunosuppressed patients. Tripedia® vaccine is not contraindicated in patients with HIV infection.[3]

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped but should be disposed of properly.

Caution: The stopper of the vial contains dry natural latex rubber which may cause allergic reactions.

INFORMATION FOR PATIENT

Parents should be fully informed of the benefits and risks of immunization with Tripedia® vaccine.

The physician should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with Tripedia® and other pertussis vaccine administration. The health-care provider should provide the Vaccine Information Statements (VISs) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. Parents or guardians should be instructed to report any adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN A CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES THAT THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF THE SAME VACCINE (SEE **CONTRAINDICATIONS** AND **ADVERSE REACTIONS** SECTIONS).

The health-care provider should inform the parent or guardian of the importance of completing the pertussis immunization series, unless a contraindication to further immunization exists.

DRUG INTERACTIONS

As with other IM injections use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.[3]

For information regarding simultaneous administration with other vaccines refer to **DOSAGE AND ADMINISTRATION** section.

If Tripedia® vaccine has been administered to persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

Tetanus Immune Globulin, or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.

Because recent clinical trials in infants younger than 15 months of age have indicated that the combination of Tripedia® vaccine with ActHIB® (TriHIBit®) may induce a lower immune response to the Hib vaccine component, this combination should NOT be used in infants for the first three doses. Tripedia® vaccine combined with ActHIB® (TriHIBit®) should only be used for the booster dose at 15-18 months of age.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Tripedia® vaccine has not been evaluated for its carcinogenic or mutagenic potentials or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Tripedia® vaccine. It is not known whether Tripedia® vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Tripedia® vaccine is NOT recommended for use in a pregnant woman.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF TRIPEDIA® VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (SEE **DOSAGE AND ADMINISTRATION** SECTION.)

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older.

Tripedia® vaccine should **not** be combined through reconstitution with any vaccine for administration to infants younger than 15 months of age. Tripedia® vaccine can only be combined with ActHIB® (TriHIBit®) by reconstitution for children 15 months of age or older.

ADVERSE REACTIONS

Over 3,000 US and 12,000 German infants received one or more doses of Tripedia® as part of the primary immunization series in clinical trials conducted by the sponsor and the National Institutes of Health (NIH). A subset of over 1,000 German and US children were monitored for adverse events through a fourth successive dose of Tripedia®. A subset of 580 German children were monitored for adverse events through a fifth successive dose of Tripedia®. Data on the safety of Tripedia® given as a fifth dose following four previous doses of Tripedia® or Tripedia® combined with ActHIB® (TriHIBit®) were available on 114 US children.[1]

Over 400 children who had received three doses of whole-cell DTP were assessed for adverse reactions following a booster dose of Tripedia® at 15 to 20 months of age.

When compared to whole-cell pertussis DTP vaccine manufactured by Aventis Pasteur Inc. (formerly Connaught Laboratories, Inc.), Tripedia® vaccine produced fewer local reactions such as erythema, swelling, and tenderness at the injection site and fewer systemic reactions such as fever, irritability, drowsiness, vomiting, anorexia and high-pitched unusual cry following the first three doses in the series.[1] In a double-blind,

comparative US trial, 673 infants were randomized to receive either 3 doses of Tripedia® vaccine or AvP's DTP vaccine (Table 2).[1] Safety data are available for 672 infants. Rates for all reported local reactions and other reactions such as fever > 101°F, irritability, drowsiness, and anorexia were significantly less in Tripedia® vaccine recipients. In contrast to whole-cell pertussis DTP, no hypotonic-hyporesponsive episodes occurred in Tripedia® vaccine recipients. Reaction rates generally peaked within the first 24 hours, and decreased substantially over the next two days.[1,14,15]

TABLE 2[1] ADVERSE EVENTS OCCURRING WITHIN 72 HOURS FOLLOWING THE FIRST THREE DOSES OF TRIPEDIA® OR WHOLE-CELL DTP VACCINE GIVEN TO INFANTS 2 to 6 MONTHS OF AGE

EVENT	FREQUENCY					
	TRIPEDIA® REACTION %			WHOLE-CELL PERTUSSIS DTP REACTION %		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of Infants†	505	499	490	167	159	152
Local						
Erythema*	9.0	9.8	16.9	28.3	32.9	32.9
Erythema > 1"*	1.2	1.8	2.2	7.8	8.4	7.4
Swelling*	6.4	4.5	6.5	28.3	23.9	27.5
Swelling > 1"*	1.4	0.6	1.0	12.7	11.0	11.4
Tenderness *	11.8	6.7	7.1	50.6	44.2	42.6
Systemic						
Fever > 101°F (rectal)*	0.4	1.6	3.5	3.6	7.5	11.2
Irritability*	35.3	30.1	27.1	72.9	71.8	57.7
Drowsiness*	39.4	17.6	15.9	59.6	45.2	25.5
Anorexia*	6.0	5.3	5.7	26.5	20.0	18.8
Vomiting	6.0**	5.5	3.7	10.8	7.1	2.7
High-pitched cry	2.4	1.0	1.4	10.8	5.8	3.4
Persistent cry	0.2	0.2	0.8	3.0	1.3	2.0

* $p < 0.01$ when compared to whole-cell pertussis DTP for all doses.
** $p < 0.05$ when compared to whole-cell pertussis DTP.
† For certain adverse events information was not available for a small number of infants.

Adverse event data for Tables 2-10 were actively collected using patient diaries, phone call follow-up, and/or by questioning the parent(s) at clinic visits. All data were recorded on standardized case report forms.

A similar reduction in adverse events was seen in a randomized, double-blind, comparative trial conducted in the US by the NIH when Tripedia® vaccine was compared to Lederle Laboratories whole-cell pertussis DTP vaccine (Table 3).[17] Each data point presented in Table 3 is a summary of the frequency of reactions following any of the three primary immunizing doses. Local adverse reactions, which include pain, erythema, swelling, and systemic reactions such as fever, anorexia, vomiting, drowsiness and fussiness may occur following any of the three primary vaccinations.

TABLE 3[17] PERCENT OF INFANTS WHO WERE REPORTED TO HAVE HAD THE INDICATED REACTION BY THE THIRD EVENING AFTER ANY OF THE FIRST THREE DOSES OF TRIPEDIA® OR WHOLE-CELL DTP VACCINE

	N¶	ERYTHEMA	SWELLING	PAIN†	FEVER* > 101°F	ANOREXIA	VOMITING	DROWSINESS	FUSSINESS‡
Tripedia®	135	32.6**	20.0**	9.6**	5.2**	22.2**	7.4	41.5**	19.3**
Whole-Cell Pertussis DTP	371	72.7	60.9	40.2	15.9	35.0	13.7	62.0	41.5

* Rectal Temperatures
** $p < 0.01$ when compared to whole-cell pertussis DTP.
† Moderate or severe = cried or protested to touch or when leg moved.
‡ Moderate or severe = prolonged or persistent crying that could not be comforted and refusal to play.
¶ N = Number of Infants

In a multicenter trial conducted by the NIH in the US, the frequency of adverse reactions following each dose in children who received only Tripedia® vaccine is shown in Table 4.[1,17,18,19] Of the 135 infants who received Tripedia® vaccine at 2, 4, and 6 months of age, a subset of 82 received a fourth dose of Tripedia® vaccine and a subset of 18 received a fifth dose of Tripedia® vaccine. A trend towards an increased frequency of redness and swelling was noted with successive doses.

TABLE 4 [1,17,18,19] ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING DOSES 1 TO 5 OF TRIPEDIA® VACCINE IN CHILDREN WHO RECEIVED TRIPEDIA® VACCINE FOR ALL DOSES

EVENT	PRIMARY (N = 135 INFANTS)			BOOSTER (N = 82 CHILDREN)	(N = 18 CHILDREN)
	DOSE 1 2 Months	DOSE 2 4 Months	DOSE 3 6 Months	DOSE 4 15 to 20 Months	DOSE 5 4 to 6 Years
Local					
Redness					
Any	12.6	12.7	19.1	17.1	33.3
> 20 mm	2.2	0	3.8	NA‡	22.2‡
Swelling					
Any	8.8	8.2	10.7	15.9	27.8
> 20 mm	0.7	0.7	3.1	NA‡	16.7‡
Pain*	8.1	3.7	2.3	7.3	11.1
Systemic					
Fever >101°F†	0.7	1.4	3.1	2.4	5.6
Anorexia	8.1	9.7	9.9	8.5	0
Vomiting	5.2	1.5	2.3	2.4	0
Drowsiness	28.9	17.9	4.6	6.1	5.6
Irritability**	8.1	7.4	7.6	3.7	0

* Moderate or severe = cried or protested to touch or when limb moved.

** Moderate or severe = prolonged or persistent crying that could not be comforted and refusal to play.

† Rectal temperatures for primary series, oral temperatures for Dose 4 and Dose 5. Dose 5 reported as ≥ 100.1°F.

‡ Post-dose 4, percent redness or swelling > 20 mm was not available; post-dose 4, 1.2% of subjects had redness > 50 mm, and 3.8% had swelling > 50 mm.[18] Post-dose 5, 5.6% of children had redness > 50 mm, and none had swelling that exceeded 50 mm.[19]

Table 5 provides the combined frequency of local reactions occurring within three days following vaccination with Tripedia® or Tripedia® combined with ActHIB® (TriHIBit®) at 2, 4 and 6 months of age from two studies. Study number 468-01 was a multi-centered, randomized, controlled, comparative, open-label trial. Vaccine was administered intramuscularly at 2, 4, and 6 months of age. This trial evaluated the safety and immunogenicity of Tripedia® combined with ActHIB® (TriHIBit®) compared to Tripedia® and ActHIB® administered at two separate sites. Parents were provided a standardized form at each visit on which they would record solicited reactions that occurred for three days following each immunization.[1]

Study number 468-02 was a multi-centered, open-label study. Vaccine was administered intramuscularly at 2, 4, and 6 months of age. This trial evaluated the safety of Tripedia® combined with ActHIB® (TriHIBit®). Parents were provided a standardized form at each visit on which they would record solicited reactions that occurred for three days following each immunization.

TABLE 5[1] FREQUENCY OF LOCAL ADVERSE EVENTS OCCURRING WITHIN THREE DAYS FOLLOWING VACCINATION WITH TRIPEDIA® OR TRIPEDIA® COMBINED WITH ACTHIB® (TRIHIBIT®) AT 2, 4, AND 6 MONTHS OF AGE

Trial Number	**Studies 468-01 and 468-02 combined***		
Dose	1	2	3
N**	2434	2320	2234
Local			
Any Reaction (%)	40.6	30.1	26.9
Redness	15.9	16.4	17.3
Swelling or Hardness	19.0	13.7	13.6
Tenderness	27.4	14.0	11.4
Pain	21.0	9.8	7.0

* In Clinical Trial 468-01, of 485 subjects, 389 subjects received TriHIBit® and 96 subjects received Tripedia®. In Clinical Trial 468-02, all 1956 subjects received TriHIBit®.

** N = Number of Children

A subset of children who participated in a German vaccine efficacy study were vaccinated with a fourth consecutive dose of Tripedia® in the study I92-2923-01 (Table 6). Data on the frequency of local and systemic reactions for 72 hours following vaccination was obtained from a diary provided to the parents at the time of vaccination and returned to the investigator by mail.

TABLE 6[1] FREQUENCY OF ADVERSE EVENTS OCCURRING WITHIN THREE DAYS FOLLOWING VACCINATION WITH TRIPEDIA® IN CHILDREN 15 to 18 MONTHS OF AGE WHO PREVIOUSLY RECEIVED THREE DOSES OF TRIPEDIA®

Event	Trial I92-2923-01* 4th dose 1010 subjects
Local Reaction	
Any Redness	481/1008 (47.7%)
Any Size	390/1007 (38.7%)
< 2.5 cm	257/1007 (25.5%)
> 2.5 cm	133/1002 (13.3%)
Swelling	218/1004 (21.7%)
Pain	214/1002 (21.4%)
Systemic Reactions	
Temperature > 100.4°F**	242/968 (25%)
Irritable	250/1005 (24.9%)
Loss of Appetite	146/1003(14.6%)
Inconsolable Crying > 3 hours	8/1005 (0.8%)

* Subset of 12, 514 subjects who received three doses of Tripedia® in a German case control study of vaccine efficacy.

**Temperatures measured orally.

In an open label US study additional safety data are available in 15- to 20-month-old children who had previously received three doses of either Tripedia® vaccine (n = 109) or whole-cell pertussis DTP (n = 30).[39] Reaction rates are presented in Table 7.

TABLE 7[1,40] ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING VACCINATION WITH TRIPEDIA® IN CHILDREN 15 TO 20 MONTHS OF AGE WHO HAD RECEIVED THREE PREVIOUS DOSES OF TRIPEDIA® OR THREE DOSES OF WHOLE-CELL DTP

	N*	ERYTHEMA ≥ 1 INCH	SWELLING ≥ 1 INCH	PAIN	TEMPERATURE ≥ 101°F**	IRRITABILITY
Tripedia® Primed	109	30.3	29.4	19.3	5.5	19.3
Whole-Cell pertussis DTP Primed	30	23.3	20.0	10.3	3.3	13.3

* N= Number of Children

** Temperatures measured rectally.

The frequency of adverse events following a fifth dose of Tripedia® in US children 4 to 6 years of age who previously received four doses of Tripedia® or Tripedia® combined with ActHIB® (TriHIBit®) is shown in Table 8. The fifth dose study was an open label study performed at 8 sites. A total of 242 subjects were enrolled during the period May 1998 through October 1999. At the time of writing this package insert, adverse event data were available on the first 96 participants (enrolled from five study sites). Information on systemic and local reactions, including actual sizes of local reactions > 2 inches, as measured by the parents, was collected on diary forms for 14 days following vaccination. The subjects in this study are a subset of subjects included in Table 5. Of six subjects who had injection site swelling ≥ 4 inches following the fifth dose of Tripedia®, all also reported pain, six had injection site redness and one had fever > 100.4°F, within three days following vaccination. Although not specifically solicited, there were no reports of redness or swelling involving the complete upper arm. The onset of local reactions was typically within the first three days after vaccination, and reactions generally resolved within one week. Two subjects had a local reaction that lasted more than 14 days- one subject had redness for 27 days and one subject had swelling for 18 days. A comparison of the safety data from this study with data in Table 5 suggests an increased frequency and severity of local reactions following the fifth dose of Tripedia® compared with the first three doses of Tripedia® or Tripedia® combined with ActHIB® (TriHIBit®).[1]

TABLE 8 [1] ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING A FIFTH DOSE OF TRIPEDIA® IN US CHILDREN 4 to 6 YEARS OF AGE WHO PREVIOUSLY RECEIVED FOUR DOSES OF TRIPEDIA® OR TRIPEDIA® COMBINED WITH ACTHIB® (TRIHIBIT®) *

EVENT	PERCENT (N = 96)
Local	
Redness (any)	61.5
> 2 inches	20.8
≥ 4 inches	9.3
Swelling/Hardness (any)	63.5
> 2 inches	13.5
≥ 4 inches	6.2
Pain/Soreness**	8.3
Systemic	
Temperature > 100.4°F†	2.1
Loss of Appetite	13.5
Vomiting	3.1
Drowsiness	16.7
Irritability**	5.2

* These subjects are a subset of the > 2,200 subjects included in Table 5.

** Moderate = discomforting enough to interfere with or limit usual daily activity. There were no reports of pain/soreness or irritability graded as severe, which was defined as disabling, unable to perform daily activities required, bedrest or results in absenteeism.

† Temperatures measured orally.

The frequency of adverse events following a fifth consecutive dose of Tripedia® administered to German children 4 to 6 years of age is shown in Table 9. This fifth dose study was an open label study that enrolled 580 subjects from 24 sites. These subjects were recruited from subjects who had participated in the case-control study of the efficacy of Tripedia® in which more than 12,000 infants received three doses of Tripedia®. In the fifth dose study, information on systemic and local reactions was collected on diary forms for 3 days following vaccination for all subjects, and for 14 days following vaccination for a subset of 241 subjects. For 490 subjects, the actual sizes of local reactions > 5 cm, as measured by the parents, was also documented on the diary forms. Local reactions, including those measured as ≥ 11 cm, typically had an onset within the first three days after vaccination and generally resolved within five days. Three subjects had a local reaction that lasted more than 21 days - one subject had swelling for 25 days, one subject had redness for 26 days, and one subject had redness for 28 days. Twenty-eight (4.8%) of 580 subjects had redness and/or swelling that led to a medical visit. There were no reported permanent sequelae associated with any local reactions. Thirty-two of 490 subjects (6.5%) had swelling reported as ≥ 11 cm, including 14 subjects (2.9%) who reported swelling of the entire upper arm. Swelling of the entire upper arm was not specifically solicited. Of 32 subjects with swelling reported as ≥ 11 cm, 19 also reported pain, 30 had redness and 2 had fever > 38°C. All cases of swelling ≥ 11 cm resolved spontaneously without treatment, except for a few subjects who were treated with cool packs. The subjects in the fifth dose study are not necessarily a subset of the 1,010 German children for whom safety data following the fourth dose of Tripedia® are available (Table 6). However, children in both the fourth and fifth dose studies were recruited from subjects who had participated in the German case-control study. Available data from these studies suggest an increased frequency and severity of local reactions following the fifth successive dose of Tripedia® compared with the fourth dose.[1]

TABLE 9 [1] ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING A FIFTH DOSE OF TRIPEDIA®* IN GERMAN CHILDREN 4 to 6 YEARS OF AGE WHO PREVIOUSLY RECEIVED FOUR DOSES OF TRIPEDIA® **

EVENT	PERCENT† (N = 490-580)
Local	
Redness (any)	59.8
> 5.0 cm	31.0
≥ 11.0 cm	6.1
Swelling (any)	61.4
> 5.0 cm	25.0
≥ 11.0 cm	6.5
Pain/Tenderness‡	20.5
Systemic	
Fever > 100.4°F¶	3.8
Loss of Appetite	7.3
Vomiting	2.2
Drowsiness	15.5
Fussiness§	5.9

* Note: one child was a protocol violation as he had received four doses of whole cell DTP previously.

** These subjects are a subset of 12,514 subjects who had received the first three doses of Tripedia® in the German case-control study of vaccine efficacy.

† Redness ≥ 11 cm and swelling ≥ 11 cm available for 490 subjects and information on other reactions was available for 580 subjects.

‡ Moderate or severe = crying or protesting to touch or crying when arm moved.

¶ Temperatures measured orally.

§ Moderate or severe = prolonged irritability, occasional crying and refusal to play or prolonged irritability, frequent crying, bed rest.

Table 10 lists the frequency of adverse reactions in 372 US children who received Tripedia® vaccine at 15 to 20 months of age and 240 US children who received Tripedia® vaccine at 4 to 6 years of age in a study conducted from 1989-1990. These children had previously received three or four doses of whole-cell pertussis DTP vaccine at approximately 2, 4, 6, and 18 months of age.[1]

TABLE 10[1] ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING TRIPEDIA® IMMUNIZATIONS GIVEN AT 15 to 20 MONTHS AND 4 to 6 YEARS OF AGE IN CHILDREN WHO HAD RECEIVED THREE OR FOUR DOSES OF WHOLE-CELL DTP

EVENT	15 to 20 MONTHS THREE PREVIOUS DTP DOSES REACTION % (N = 372 CHILDREN)	4 to 6 YEARS FOUR PREVIOUS DTP DOSES REACTION % (N = 240 CHILDREN)
Local		
Erythema*	18.3	31.3
Swelling**	10.8	27.9
Tenderness	14.2	46.2
Systemic		
Fever >101°F†	4.7	4.8
Diarrhea	6.3	0.8
Vomiting	2.2	1.7
Anorexia	7.8	5.4
Drowsiness	12.4	15.0
Irritability	21.2	15.8
High-pitched unusual cry	1.1	NA

* Includes all occurrences of erythema.
** Includes all occurrences of swelling.
NA Data not collected in this age group.
† Temperatures measured rectally for 15- to 20-month old children and measured orally for 4 to 6 year old children.

The results of an open label, non-controlled clinical study, of 2,457 US children targeted to evaluate less common and more severe adverse events following three doses of Tripedia® vaccine in the primary series are shown in Table 11. Data were collected by parental interview at subsequent immunization visits, chart review and telephone calls to the parents 60 days after the third dose.

TABLE 11[1] MODERATELY SEVERE ADVERSE EVENTS OCCURRING WITHIN 48 HOURS FOLLOWING VACCINATION WITH TRIPEDIA® AT 2, 4, OR 6 MONTHS OF AGE (N = 7,102 DOSES)

EVENT	NUMBER	RATE/1,000 DOSES
Fever ≥ 105°F	2	0.28
Hypotonic/Hyporesponsive Episode	1	0.14
Persistent cry ≥ 3 hours	4	0.56
Convulsions*	0	0

* One seizure episode was noted between 48 and 72 hours.

The frequency of adverse experiences that are more serious and less common than those reported in Table 11 are not known at this time.

In the large German efficacy study that enrolled 16,780 infants, 12,514 of whom received 41,615 doses of Tripedia® vaccine, hospitalization rates and death rates were similar between Tripedia® vaccine and DT recipients. Adverse events were monitored by spontaneous reporting by parents and a medical history obtained at each subsequent vaccination. Adverse events (rates per 1,000 doses) occurring within 7 days including those events interpreted by the investigator as related as well as those interpreted as unrelated to vaccination included: unusual cry (0.96), persistent cry > 3 hours (0.12), febrile seizure (0.05), afebrile seizure (0.02) and hypotonic/hyporesponsive episodes (0.05).[1] In contrast to the first Swedish pertussis efficacy trial conducted in 1986-87,[10] no deaths due to invasive bacterial infections were reported.[1]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[3]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.[41]

Whole-cell pertussis DTP has been associated with acute encephalopathy.[37] A 10-year follow-up to the National Childhood Encephalopathy Study (NCES) of children who experienced acute neurologic disorders in infancy concluded that serious acute neurologic illness increased the risk of chronic neurologic disease or death.[42] A committee of the Institute of Medicine (IOM) has concluded that, because DTP may cause acute neurologic illness, DTP may also cause chronic neurologic disease in the context of the NCES report.[38] However, the IOM committee concluded that the evidence was insufficient to indicate whether or not DTP increased the overall risk of chronic neurologic disease.[38]

Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of whole-cell pertussis DTP and DTaP. Large case-control studies of SIDS in the US have shown that receipt of whole-cell pertussis DTP was not causally related to SIDS.[43,44,45] It should be recognized that the first three primary immunizing doses of whole-cell pertussis DTP and DTaP are usually administered to infants 2-6 months old and that approximately 85% of SIDS cases occur at ages 1-6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP[45] or DTaP. A review by a committee of the IOM concluded that available evidence did not indicate a causal relation between DTP vaccine and SIDS.[37]

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.[46] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.[3]

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported, although a causal relationship has not been established.[37,47-49]

The above findings regarding possible association of unusual neurologic events and SIDS relate only to DTP vaccine containing whole-cell pertussis. At this time there are insufficient data to determine their relevance to Tripedia® vaccine.

A review by the IOM found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.[41] The following illnesses have been reported as temporally associated with vaccine containing tetanus toxoid: neurological complications[50,51] including cochlear lesion,[52] brachial plexus neuropathies,[52,53] paralysis of the radial nerve,[54] paralysis of the recurrent nerve,[52] accommodation paresis, and EEG disturbances with encephalopathy.[55] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[56,57]

In the German case-control study and US open-label safety study in which 14,971 infants received Tripedia® vaccine, 13 deaths in Tripedia® vaccine recipients were reported to study investigators. Causes of deaths included seven SIDS, and one of each of the following: enteritis, Leigh Syndrome, adrenogenital syndrome, cardiac arrest, motor vehicle accident, and accidental drowning. None of these events were determined to be vaccine-related and all occurred more than two weeks past immunization.[1] The rate of SIDS observed in the German case-control study was 0.4/1,000 vaccinated infants. The rate of SIDS observed in the US open-label safety study was 0.8/1,000 vaccinated infants and the reported rate of SIDS in the US from 1985-1991 was 1.5/1,000 live births.[58] By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP[45] or DTaP.

In the Swedish efficacy trial where 1,419 recipients received the pertussis components in Tripedia® vaccine, three deaths due to invasive bacterial infections occurred. Further investigation revealed no evidence for a causal relation between vaccination and altered resistance to invasive disease caused by encapsulated bacteria.[11] While the hypothesis that the two variables are related cannot be ruled out in the Swedish trial, deaths due to invasive bacterial infections have been monitored in other trials. In contrast to the Swedish trial, in the German case-control study and US open-label safety study, 14,971 infants received Tripedia® vaccine and no deaths due to invasive bacterial infections were reported.

When Tripedia® vaccine was used to reconstitute ActHIB® (TriHIBit®) and administered to children 15 to 20 months of age, the systemic adverse experience profile was comparable to that observed when the two vaccines were given separately. An increase in rates of minor local reactions was observed within the 24-hour period after immunization when compared to the Tripedia® and ActHIB® vaccines administered separately. However, local adverse event rates of the combined vaccines were comparable when taking into consideration reactions observed at the ActHIB® site.[1] ***(Refer to ActHIB® package insert.***

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act (i.e. those listed in the vaccine injury table) for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[59]

Reporting by parents and patients of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967. [39,59]

The health-care provider also should report these events to the Director of Scientific and Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose.* Inject 0.5 mL of Tripedia® vaccine intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

The primary series for children less than 7 years of age is three intramuscular doses of 0.5 mL. The customary age for the first dose is 2 months of age but may be given as early as 6 weeks of age and up to the seventh birthday.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Fractional doses (doses < 0.5 mL) should not be given. The effect of fractional doses on the frequency of serious adverse events and on efficacy has not been determined.

Do NOT administer this product subcutaneously.

PRIMARY IMMUNIZATION

The primary series consists of three doses administered at intervals of 4-8 weeks. It is recommended that Tripedia® vaccine be given for all three doses since no interchangeability data on DTaP vaccines exist for the primary series.

Tripedia® vaccine may be used to complete the primary series in infants who have received one or two doses of whole-cell pertussis DTP. However, the safety and efficacy of Tripedia® vaccine in such infants has not been evaluated.

Tripedia® vaccine should not be combined through reconstitution with any other vaccine for administration to infants younger than 15 months of age. Available serologic data do not support the use of Tripedia® vaccine to reconstitute ActHIB® (TriHIBit®) for primary immunization.

BOOSTER IMMUNIZATION

When Tripedia® vaccine is given for the primary series, a fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. When Tripedia® is given for the first four doses, a fifth dose of Tripedia® is recommended at 4 to 6 years of age, preferably prior to school entry.[30,31] If the fourth dose was administered after the fourth birthday, a fifth dose prior to school entry is not necessary.[30,31]

If a child receives whole-cell pertussis DTP for one or more doses, Tripedia® vaccine may be given to complete the five-dose series. A fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. Children 4 to 6 years of age (up to the seventh birthday) who received all four doses by the fourth birthday, including one or more doses of whole-cell pertussis DTP, should receive a single dose of Tripedia® vaccine before entering kindergarten or elementary school. This dose is not needed if the fourth dose was given on or after the fourth birthday.[30,31]

Tripedia® vaccine combined with ActHIB® (TriHIBit®) by reconstitution may be administered at 15 to 18 months of age for the fourth dose. ***(Refer to ActHIB® package insert.)***

If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series.

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH TRIPEDIA® VACCINE.[3,30]
Preterm infants should be vaccinated according to their chronological age from birth.[3,30]

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with Tripedia® vaccine. There is no need to start the series over again, regardless of the time between doses.

Routine simultaneous administration of DTaP, IPV, Haemophilus b conjugate vaccine, MMR, pneumococcal conjugate vaccine, varicella vaccine, and hepatitis B vaccine is encouraged 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 (see **CLINICAL PHARMACOLOGY** section).[32]

There are no data available on the simultaneous administration of Tripedia® with varicella vaccine, or IPV, or pneumococcal conjugate vaccine.

Data are unavailable to the manufacturer concerning the effects on immune responses to IPV when IPV is given concurrently at separate sites with ActHIB® reconstituted with Tripedia® (TriHIBit®) as a booster.

If passive immunization is needed for tetanus prophylaxis, Tetanus Immune Globulin (Human) (TIG) is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG are administered concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.

HOW SUPPLIED

Vial, 1 Dose (contains NO preservative) (10 per package) - Product No. 49281-298-10
Vial, 15 Dose (contains preservative) (7.5 mL) – Product No. 49281-288-15

TriHIBit®, Five 0.6 mL vials of Tripedia® vaccine as Diluent (contains NO preservative) packaged with Five 1 Dose vials of lyophilized ActHIB® (contains NO preservative) Administer vaccine immediately (within 30 minutes) after reconstitution – Product No. 49281-597-05

STORAGE

Store between 2° – 8°C (35° – 46°F). DO NOT FREEZE. Temperature extremes may adversely affect resuspendability of this vaccine.

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