

AHFS Category: 80:08

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# Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Tripedia<sup>®</sup>

DTaP

Rx only



## DESCRIPTION

Tripedia<sup>®</sup>, 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 sodium phosphate to control pH. After shaking, the vaccine is a homogeneous white suspension. Tripedia vaccine is distributed by Sanofi Pasteur Inc.

*Corynebacterium diphtheriae* cultures are grown in a modified Mueller and Miller medium.<sup>1</sup> *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.<sup>2</sup> 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.

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 and 23.4 µg of FHA. The inactivated acellular pertussis component contributes not more than 50 endotoxin units 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. The vaccine is formulated without preservatives, but contains a trace amount of thimerosal [(mercury derivative), (≤0.3 µg mercury/dose)] from the manufacturing process. Each 0.5 mL dose also 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.

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 Sanofi Pasteur Inc. Tripedia vaccine is filled, labeled, packaged, and released by Sanofi Pasteur Inc.

When Tripedia vaccine is used to reconstitute ActHIB<sup>®</sup> [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) manufactured by Sanofi Pasteur SA] the combination vaccine is TriHIBit<sup>®</sup>. Each single 0.5 mL dose of TriHIBit vaccine **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 vaccine package insert.)

## CLINICAL PHARMACOLOGY

Simultaneous immunization of infants and children against diphtheria, tetanus, and pertussis has been a routine practice in the US since the late 1940s, and has played a major role in markedly reducing disease and deaths from these infections.<sup>3</sup>

### 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*.

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.<sup>3</sup>

Prior to the widespread use of diphtheria toxoid in the late 1940s, diphtheria disease 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.<sup>3</sup> From 1980 through 2000, 51 cases of diphtheria were reported in the US. During the period 1980-1996, six fatal cases of diphtheria were reported. One case of diphtheria was reported each year in 1998-2000 with no fatalities.<sup>4</sup> Of 49 reported cases with known age since 1980, twenty-seven (55%) cases 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.<sup>5</sup>

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in the Newly Independent States (NIS) of the former Soviet Union beginning in 1990. In 1994-1995, the peak of the epidemic, >98,000 cases and 3,400 deaths were reported in the NIS.<sup>6</sup> This outbreak was believed to be due to several factors, including a lack of routine immunization of adults in these countries.<sup>7</sup>

Complete immunization significantly reduces the risk of developing diphtheria, and immunized persons who develop disease have milder illness. Following adequate immunization with diphtheria toxoid, protection is thought to last for at least 10 years. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective.<sup>8</sup> Immunization does not, however, eliminate carriage of *C diphtheriae* in the pharynx, nose, or on the skin.<sup>3</sup>

### Tetanus

Tetanus manifests systemic toxicity primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

Following routine use of tetanus toxoid in the US, the occurrence of tetanus disease decreased dramatically from 560 reported cases in 1947, to an average of 50-100 cases reported annually from the mid 1970s through the late 1990s, to 35 cases in 2000.<sup>4</sup> The case-fatality rate has declined from 30% to approximately 10% in recent years. During the years 1982-1998, 52% of reported cases were among persons 60 years of age or older. In the mid to late 1990s, 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. Persons <40 years increased from 28% of cases during 1991-1995 to 42% of cases during 1996-2000. In the US, tetanus occurs almost exclusively among unvaccinated or inadequately vaccinated persons.<sup>5</sup>

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. Following adequate immunization with tetanus toxoid, it is thought that protection persists for at least 10 years.<sup>3</sup> Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.<sup>9,10</sup> More recently, a level  $\geq 0.1$  to 0.2 IU/mL has been considered as protective.<sup>11</sup>

### 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 produced by *B pertussis* in either the pathogenesis of, or immunity to, pertussis is not well understood.<sup>12</sup>

Pertussis is highly communicable (with attack rates of up to 100% in susceptible individuals with intense exposure<sup>13</sup>) 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) was reported in 1934. Following introduction and widespread use of the whole-cell pertussis DTP vaccines (Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed – For Pediatric Use) among infants and children in the mid to late 1940s, pertussis incidence gradually declined, reaching a historical low of 1,010 cases in 1976.<sup>14</sup>

Concerns about the safety of whole-cell pertussis DTP vaccines prompted the development of less reactogenic DTaP vaccines that contain purified antigens of *B pertussis*. DTaP vaccines were first available for use in infants in the US in 1996 and have been routinely recommended for all doses of the vaccination series for infants and children 6 weeks to <7 years of age since 1997.<sup>15</sup>

The incidence of pertussis among children aged 6 months to 4 years has remained stable throughout the 1990s, suggesting that protection offered by vaccination has continued with the introduction of DTaP vaccines.<sup>14,16</sup> Conversely, an increase in pertussis among infants too young to receive 3 doses of pertussis-containing vaccine suggests a true increase in pertussis circulation.<sup>14</sup> Atypical infection, including nonspecific symptoms of bronchitis or upper respiratory tract infection, may occur at any age but more commonly in older children and adults, including some who were previously immunized. In these cases, pertussis may not be diagnosed because classic signs, particularly the inspiratory whoop, may be absent.<sup>17</sup> Surveillance data from the 1990s indicates an increase in the pertussis rate among adolescents and adults who may also play a role in transmission to infants.<sup>5,14</sup>

During 1997 to 2000, a total of 29,134 cases were reported, for an estimated average annual incidence rate of 2.7 per 100,000 population.<sup>14</sup> Among 29,048 cases for whom age was known, 29% were aged <1 year, 12% were aged 1 to 4 years, 10% were aged 5 to 9 years, 29% were aged 10 to 19 years and 20% were  $\geq 20$  years of age.<sup>14</sup> Average annual incidence rates during 1997 to 2000 were highest among infants aged <1 year (55.5 cases per 100,000 population) and lower in children aged 1 to 4 years (5.5), children aged 5 to 9 years (3.6), persons aged 10 to 19 years (5.5) and persons aged  $\geq 20$  years (0.8).<sup>14</sup>

The severity of pertussis remains highest in infants. Of 7,203 infants <6 months of age reported as having pertussis during the period 1997-2000, 63% were hospitalized, 12% had pneumonia, 1.4% had one or more seizures, 0.2% had encephalopathy and 0.8% died.<sup>14</sup>

### Efficacy of Tripedia Vaccine

#### Pertussis

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.<sup>18</sup> A second study was conducted in Germany using a three-dose schedule to evaluate the protective efficacy of Tripedia vaccine in younger infants.<sup>19</sup>

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.<sup>18</sup> 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.<sup>20</sup> 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%).<sup>20</sup>

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.<sup>21</sup>

A case-control study to evaluate the efficacy of Tripedia vaccine was conducted in Germany.<sup>19</sup> 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 Diphtheria and Tetanus Toxoids Adsorbed (DT) for Pediatric Use group). By parental choice, infants received Tripedia vaccine or whole-cell pertussis DTP vaccine (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 whole-cell pertussis DTP vaccine, DT vaccine, 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  $\geq 21$  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 Tripedia vaccine, 5 (3.6%) received two doses of Tripedia vaccine, 44 (31.4%) received two or three doses of DT vaccine, 44 (31.4%) received one dose of either Tripedia vaccine, whole-cell pertussis DTP vaccine or DT vaccine, and 18 (13%) received no vaccine. Of the 543 controls, 175 (32.2%) received three doses of Tripedia vaccine, 67 (12.3%) received two doses of Tripedia vaccine, 45 (8.3%) received two or three doses of whole-cell pertussis DTP vaccine, 73 (13.4%) received DT vaccine, 153 (28.2%) received one dose of either DT vaccine, whole-cell pertussis DTP vaccine, or Tripedia vaccine, 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 vaccine was 80% (95% CI; 59% to 90%).<sup>2</sup>

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 levels of antibodies 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.<sup>2</sup>

### Diphtheria

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.<sup>10</sup>

### Tetanus

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.<sup>10</sup>

### Tripedia Vaccine Combined With ActHIB Vaccine (TriHIBit vaccine) 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 vaccine (TriHIBit vaccine). All children received three doses of Haemophilus b Conjugate Vaccine [ActHIB vaccine or HibTITER® (Haemophilus b Conjugate Vaccine Diphtheria CRM197 Protein Conjugate manufactured by Lederle Laboratories)] and three doses of whole-cell pertussis DTP vaccine at approximately 2, 4, and 6 months of age. Table 1 shows the pertussis responses when Tripedia vaccine was used to reconstitute ActHIB vaccine (TriHIBit vaccine) 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  $\geq 1.0$   $\mu\text{g/mL}$ .<sup>2</sup> Responses to both diphtheria and tetanus toxoids were similar for children in the two groups.<sup>2</sup>

TABLE 1<sup>2</sup>

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

VACCINE GROUP N*	PRE-DOSE		POST-DOSE	
	TriHIBit Vaccine 92-93	Separate 102-103	TriHIBit Vaccine 93	Separate 98
Anti-PT				
GMT (ELISA units/mL)	26.30	24.56	471.00	363.90
% 4-Fold Rise	–	–	87.0	85.7
Anti-PT				
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

\* N = Number of Children

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

#### Concomitantly Administered Vaccines

In a clinical study, US infants received Tripedia vaccine, ActHIB vaccine, and hepatitis B vaccine (Recombinant), manufactured by Merck & Co., Inc., concomitantly at separate sites, and OPV vaccine (poliovirus vaccine live oral trivalent), manufactured by Lederle Laboratories. In one of the study groups, Tripedia vaccine, ActHIB vaccine and OPV vaccine were administered at 2, 4, and 6 months of age and hepatitis B vaccine was given at 2 and 4 months of age. One hundred percent of the 69 children who received Tripedia vaccine concomitantly with ActHIB vaccine demonstrated anti-PRP antibodies  $\geq 1.0$   $\mu\text{g/mL}$ . Sera from a subset of 12 infants who received hepatitis B vaccine concomitantly at 2 and 4 months of age showed that 93% had anti-HBs titers of  $\geq 10$  mIU/mL. Sera from a subset of 20 infants who received OPV vaccine concomitantly at 2, 4, and 6 months of age showed that 100% had protective neutralizing antibody responses to all three polio virus types.

In clinical studies evaluating concomitant administration of TriHIBit vaccine (ActHIB vaccine reconstituted with Tripedia vaccine) with measles, mumps and rubella (MMR) vaccine, manufactured by Merck & Co., 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 TriHIBit vaccine were 98% (46/47), 98% (42/43) and 96% (43/45) for measles, mumps and rubella, respectively.

Data on the concomitant administration of Tripedia vaccine or TriHIBit vaccine (ActHIB vaccine reconstituted with Tripedia vaccine) with varicella vaccine, inactivated poliovirus vaccine (IPV) or pneumococcal conjugate vaccine are not available.

#### INDICATIONS AND USAGE

Tripedia vaccine is indicated for active immunization against diphtheria, tetanus, and pertussis (whooping cough) as a five-dose series in infants and children 6 weeks to 7 years of age (prior to seventh birthday). Because of the substantial risks of complications from pertussis disease in infants, completion of a primary series of vaccine early in life is strongly recommended (see **DOSAGE AND ADMINISTRATION** section).<sup>3</sup>

When ActHIB vaccine is reconstituted with Tripedia vaccine (TriHIBit vaccine), 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 pertussis DTP vaccine or Tripedia vaccine and three or fewer doses of ActHIB vaccine within the first year of life for the prevention of diphtheria, tetanus, pertussis and invasive diseases caused by *H influenzae* type b.<sup>2</sup> (Refer to ActHIB vaccine package insert.)

Children who have had well-documented pertussis (ie, positive culture for *B pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination series with at least DT vaccine. Some experts recommend including the pertussis component as well (ie, administration of DTaP vaccine). Although well-documented pertussis disease is likely to confer immunity against pertussis, the duration of such immunity is unknown.<sup>15,22</sup>

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

If passive immunization is needed for tetanus prophylaxis or for treatment of diphtheria, either Tetanus Immune Globulin (Human) (TIG) or Diphtheria Antitoxin, respectively, should be administered as required.<sup>3,11</sup> (See **DOSAGE AND ADMINISTRATION** section.)

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

#### CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine is a contraindication to receipt of Tripedia vaccine (see **DESCRIPTION** section).<sup>15</sup>

It is a contraindication to use Tripedia vaccine after a serious allergic reaction (eg, anaphylaxis) temporally associated with a previous dose of this vaccine or with any components of this vaccine, including thimerosal and gelatin. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including Tripedia vaccine.<sup>11</sup>

- Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause;
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

In instances where the pertussis vaccine component is contraindicated, DT vaccine should be administered for the remaining doses in the vaccination schedule.

#### **WARNINGS**

The stopper of the vial contains dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

If any of the following events occurs in temporal relation with the receipt of either whole-cell pertussis DTP vaccine or a vaccine containing an acellular pertussis component, the decision to administer subsequent doses of Tripedia vaccine or any vaccine containing a pertussis component should be based on careful consideration of potential benefits and possible risks.<sup>15,23</sup>

1. Temperature of  $\geq 40.5^{\circ}\text{C}$  ( $105^{\circ}\text{F}$ ) within 48 hours, not attributable to another identifiable cause.
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
3. Persistent crying lasting  $\geq 3$  hours within 48 hours.
4. Convulsions with or without fever, occurring within 3 days.

When a decision is made to withhold the pertussis component, immunization with DT vaccine should be continued.<sup>3</sup>

If Guillain-Barré syndrome occurs within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give subsequent doses of Tripedia vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.<sup>11</sup>

Because of the risk of hemorrhage, Tripedia vaccine should not be given to infants or children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection, or to those on anticoagulant therapy, unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer Tripedia vaccine in such infants or children, it should be given with caution, with steps taken to avoid the risk of bleeding and hematoma formation following injection.

A family history of seizures or other central nervous system disorders is not a contraindication to pertussis vaccine.<sup>3,11,15,23</sup>

For infants or children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a vaccine containing an acellular pertussis component (including Tripedia vaccine) and for the ensuing 24 hours according to the respective prescribing information recommended dosage to reduce the possibility of post-vaccination fever.<sup>11,15</sup>

A committee of the Institute of Medicine (IOM) has concluded that evidence is consistent with a causal relationship between whole-cell pertussis DTP vaccine and acute neurologic illness, and under special circumstances, between whole-cell pertussis DTP vaccine and chronic neurologic disease in the context of the National Childhood Encephalopathy Study (NCES) report.<sup>24,25</sup> However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell pertussis DTP vaccine increased the overall risk of chronic neurologic disease.<sup>25</sup>

The decision to administer a pertussis-containing vaccine to children with stable central nervous system disorders must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) have issued guidelines for such children.<sup>15,22,23</sup> The parent or guardian should be advised of the potential increased risk involved (see **PRECAUTIONS, Information for Vaccine Recipients and Parents or Guardians** section).

The ACIP has published guidelines for vaccination of persons with recent or acute illness.<sup>11</sup>

**Except for reconstitution of Tripedia vaccine with ActHIB vaccine for administration of the fourth dose to children 15-18 months of age, Tripedia vaccine should not be combined through reconstitution with any vaccine (see PRECAUTIONS section, Drug Interactions subsection).**

#### **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), AND OTHER APPROPRIATE AGENTS AND EQUIPMENT 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 (see **WARNINGS** section), previous immunization history, and current health status (see **CONTRAINDICATIONS** section).

The expected immune response to Tripedia vaccine may not be obtained in immunosuppressed persons. Tripedia vaccine is not contraindicated for use in individuals with HIV infection.<sup>11,26</sup>

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 blood borne infectious agents from person to person. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

#### **Information For Vaccine Recipients and Parents/Guardians**

Before administration of this vaccine, health-care personnel should inform the parent, guardian or other responsible adult of the benefits and risks of the vaccine and the importance of completing the immunization series unless a contraindication to further immunization exists. (See **ADVERSE REACTIONS** and **WARNINGS** sections.)

The physician should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with Tripedia vaccine and other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VISs) that 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 RETURNS 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).

Adverse events following immunization should be reported by health-care providers to the Vaccine Adverse Events Reporting System (VAERS). (See **ADVERSE REACTIONS** section, **Reporting of Adverse Events** subsection.)

#### **Drug Interactions**

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

For information regarding concomitant administration of Tripedia vaccine with other vaccines, refer to **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines.<sup>11,26</sup>

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.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

#### **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 indicated for women of child-bearing age.

#### **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) vaccine is to be used in individuals 7 years of age or older.

#### **Geriatric Use**

Tripedia vaccine is NOT indicated for adults.

#### **ADVERSE REACTIONS**

Over 3,000 US and 12,000 German infants received one or more doses of Tripedia vaccine 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 vaccine. A subset of 580 German children were monitored for adverse events through a fifth successive dose of Tripedia vaccine.

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

In a double-blind, comparative US trial, 673 infants were randomized to receive either 3 doses of Tripedia vaccine or Sanofi Pasteur Inc.'s whole-cell pertussis DTP vaccine (**TABLE 2**).<sup>2</sup> Safety data are available for 672 infants, including 505 who received Tripedia vaccine and 167 who received whole-cell pertussis DTP vaccine. Following all three doses, rates for all reported local reactions, fever >101°F, irritability, drowsiness, and anorexia were significantly less in Tripedia vaccine recipients. Reaction rates generally peaked within the first 24 hours, and decreased substantially over the next two days.<sup>2,27,28</sup>

**TABLE 2<sup>2</sup> ADVERSE EVENTS OCCURRING WITHIN 72 HOURS FOLLOWING THE FIRST THREE DOSES OF TRIPEDIA VACCINE OR WHOLE-CELL PERTUSSIS DTP VACCINE GIVEN TO INFANTS 2 TO 6 MONTHS OF AGE**

EVENT	FREQUENCY					
	TRIPEDIA VACCINE REACTION %			WHOLE-CELL PERTUSSIS DTP VACCINE REACTION %		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of Infants <sup>†</sup>	505	499	490	167	159	152
<b>Local</b>						
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
<b>Systemic</b>						
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 vaccine for all doses.

\*\* p <0.05 when compared to whole-cell pertussis DTP vaccine.

† For certain adverse events information was not available for a small number of infants.

Adverse event data for Tables 2-9 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).<sup>29</sup> 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 have occurred following any of the three primary vaccinations.

**TABLE 3<sup>29</sup> 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 VACCINE OR WHOLE-CELL PERTUSSIS DTP VACCINE**

	N¶	ERYTHEMA	SWELLING	PAIN†	FEVER* >101°F	ANOREXIA	VOMITING	DROWSINESS	FUSSINESS‡
Tripedia Vaccine	135	32.6**	20.0**	9.6**	5.2**	22.2**	7.4	41.5**	19.3**
Whole-Cell Pertussis DTP Vaccine	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 vaccine.

† 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.<sup>2,29-31</sup> 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<sup>2,29-31</sup>

**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
<b>Local</b>					
Redness					
Any	12.6	12.7	19.1	17.1	33.3
>20 mm	2.2	0	3.8	NA <sup>‡</sup>	22.2 <sup>‡</sup>
Swelling					
Any	8.8	8.2	10.7	15.9	27.8
>20 mm	0.7	0.7	3.1	NA <sup>‡</sup>	16.7 <sup>‡</sup>
Pain*	8.1	3.7	2.3	7.3	11.1
<b>Systemic</b>					
Fever >101°F <sup>†</sup>	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  $\geq 100.1^\circ\text{F}$ .

‡ 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.<sup>30</sup> Post-dose 5, 5.6% of children had redness >50 mm, and none had swelling that exceeded 50 mm.<sup>31</sup>

A subset of children who participated in a German vaccine efficacy study were vaccinated with a fourth consecutive dose of Tripedia vaccine in the study I92-2923-01 (TABLE 5). 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 5<sup>2</sup> FREQUENCY OF ADVERSE EVENTS OCCURRING WITHIN THREE DAYS FOLLOWING VACCINATION WITH TRIPEDIA VACCINE IN CHILDREN 15 TO 18 MONTHS OF AGE WHO PREVIOUSLY RECEIVED THREE DOSES OF TRIPEDIA VACCINE**

Event	Trial I92-2923-01* 4th dose 1,010 subjects
<b>Local Reaction</b>	
Any	481/1008 (47.7%)
Redness	
Any Size	390/1007 (38.7%)
<2.5 cm	257/1007 (25.5%)
>2.5 cm	133/1002 (13.3%)
Swelling, any size	218/1004 (21.7%)
Pain	214/1002 (21.4%)
<b>Systemic Reactions</b>	
Temperature >100.4°F**	242/968 (25%)
Irritable	250/1005 (24.9%)
Loss of Appetite	146/1003 (14.6%)
Persistent Crying >3 hours	8/1005 (0.8%)

\* Subset of 12,514 subjects who received three doses of Tripedia vaccine 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 vaccine (n = 30).<sup>32</sup> Reaction rates are presented in Table 6.

TABLE 6<sup>2,32</sup>

**ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING VACCINATION  
WITH TRIPEDIA VACCINE IN CHILDREN 15 TO 20 MONTHS OF AGE WHO HAD RECEIVED THREE  
PREVIOUS DOSES OF TRIPEDIA VACCINE OR THREE DOSES OF WHOLE-CELL PERTUSSIS DTP VACCINE**

	N*	ERYTHEMA ≥1 INCH	SWELLING ≥1 INCH	PAIN	TEMPERATURE ≥101°F**	IRRITABILITY
Tripedia Vaccine Primed	109	30.3	29.4	19.3	5.5	19.3
Whole-Cell pertussis DTP Vaccine 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 consecutive dose of Tripedia vaccine administered to German children 4 to 6 years of age is shown in Table 7. 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 vaccine in which more than 12,000 infants received three doses of Tripedia vaccine. 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 vaccine are available (TABLE 5). 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 vaccine compared with the fourth dose.<sup>2</sup> Additional safety data in 96 US children who received a fifth dose of Tripedia vaccine following four previous doses of Tripedia vaccine or Tripedia vaccine combined with ActHIB vaccine (TriHIBit vaccine) also demonstrated an increase in the frequency and severity of local reactions following the fifth dose compared with the first three doses.<sup>2</sup>

TABLE 7<sup>2</sup>

**ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING A FIFTH DOSE  
OF TRIPEDIA VACCINE\* IN GERMAN CHILDREN 4 TO 6 YEARS OF AGE  
WHO PREVIOUSLY RECEIVED FOUR DOSES OF TRIPEDIA VACCINE\*\***

EVENT	PERCENT <sup>†</sup> (N = 490-580)
<b>Local</b>	
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 <sup>‡</sup>	20.5
<b>Systemic</b>	
Fever >100.4°F <sup>¶</sup>	3.8
Loss of Appetite	7.3
Vomiting	2.2
Drowsiness	15.5
Fussiness <sup>§</sup>	5.9

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

\*\* These subjects are a subset of 12,514 subjects who had received the first three doses of Tripedia vaccine 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 8 lists the frequency of adverse events 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.<sup>2</sup>

**TABLE 8<sup>2</sup> ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING TRIPEDIA VACCINE 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 PERTUSSIS DTP VACCINE**

EVENT	15 TO 20 MONTHS THREE PREVIOUS WHOLE-CELL PERTUSSIS DTP VACCINE DOSES REACTION % (N = 372 CHILDREN)	4 TO 6 YEARS FOUR PREVIOUS WHOLE-CELL PERTUSSIS DTP VACCINE DOSES REACTION % (N = 240 CHILDREN)
<b>Local</b>		
Erythema*	18.3	31.3
Swelling**	10.8	27.9
Tenderness	14.2	46.2
<b>Systemic</b>		
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.

When Tripedia vaccine was used to reconstitute ActHIB vaccine (TriHIBit vaccine) and administered to children 15 to 20 months of age who had received 3 prior doses of whole-cell pertussis DTP vaccine, 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 vaccine and ActHIB vaccine administered separately. However, local adverse event rates of the combined vaccines were comparable when taking into consideration reactions observed at the ActHIB vaccine site.<sup>2</sup> (*Refer to ActHIB vaccine package insert.*)

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 9. 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 9<sup>2</sup> MODERATELY SEVERE ADVERSE EVENTS OCCURRING WITHIN 48 HOURS FOLLOWING VACCINATION WITH TRIPEDIA VACCINE 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 frequencies of adverse experiences that are more serious and less common than those reported in Table 9 are not known at this time.

In the German case control 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 vaccine 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 following vaccination with Tripedia vaccine 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).<sup>2</sup>

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.<sup>33</sup> 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.

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. 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. All of these events occurred more than two weeks post immunization.<sup>2</sup> 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.<sup>34</sup> By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP<sup>35</sup> or DTaP vaccines.

#### Additional Adverse Reactions:

- As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for several weeks. Sterile abscess formation at the site of injection has been reported.<sup>3,36</sup>
- Rarely, an anaphylactic reaction (ie, hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.<sup>3</sup>
- 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 mononeuropathy and of cranial mononeuropathy have been reported following tetanus toxoid administration, although available evidence is inadequate to accept or reject a causal relation.<sup>37</sup>
- A review by the Institute of Medicine (IOM) found evidence for a causal relationship between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome.<sup>37</sup>
- A few cases of demyelinating diseases of the CNS have been reported following some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.<sup>37</sup>

Adverse events reported during post-approval use of Tripedia vaccine include idiopathic thrombocytopenic purpura, SIDS, anaphylactic reaction, cellulitis, autism, convulsion/grand mal convulsion, encephalopathy, hypotonia, neuropathy, somnolence and apnea. Events were included in this list because of the seriousness or frequency of reporting. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies or to establish a causal relationship to components of Tripedia vaccine.<sup>2</sup>

#### 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 of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act (or statute) further requires the health-care professional to report to the Secretary of the US Department of Health and Human Services, the occurrence following immunization of any events set forth in the statute or the Vaccine Injury Table, including anaphylaxis or anaphylactic shock within 7 days; encephalopathy or encephalitis within 7 days, brachial neuritis within 28 days; or an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Tripedia vaccine package insert.<sup>38,39</sup>

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccines should be reported by health-care providers to 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.<sup>38,39</sup>

Health-care providers also should report these events to the Pharmacovigilance Department, Sanofi 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.** After shaking, the vaccine is a homogeneous white suspension. 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.

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 intravenously or subcutaneously.*

#### Immunization Series

A 0.5 mL dose of Tripedia vaccine is approved for administration to infants and children 6 weeks to 7 years of age (prior to seventh birthday) as a five-dose series. The series consists of a primary immunization course of three doses administered at 2, 4, and 6 months of age, followed by two booster doses, recommended at 15 to 18 months of age, and at 4 to 6 years of age, respectively.<sup>15</sup> The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age. The recommended interval between the first three doses is 8 weeks, with a minimum interval of 4 weeks.<sup>14</sup> The recommended interval between the third and fourth dose is 6-12 months.<sup>15</sup> The fifth dose is recommended before entry into kindergarten or elementary school, and is not needed if the fourth dose was given after the fourth birthday.<sup>15</sup>

Interchanging Tripedia vaccine and DTaP vaccine from different manufacturers for successive doses of the vaccination series is not recommended because data are limited regarding the safety and efficacy of such regimens.

Tripedia vaccine may be used to complete the immunization series in infants and children who have received one or more doses of whole-cell pertussis DTP vaccine. However, the safety and efficacy of Tripedia vaccine to complete a primary series begun with whole-cell pertussis DTP vaccine have 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 vaccine (TriHIBit vaccine) for primary immunization.

Tripedia vaccine used to reconstitute ActHIB vaccine (TriHIBit vaccine) may be administered at 15 to 18 months of age for the fourth dose. (*Refer to ActHIB vaccine package insert.*)

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

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH TRIPEDIA VACCINE.<sup>3,22</sup>

Preterm infants should be vaccinated according to their chronological age from birth.<sup>3,22</sup>

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.

#### **Concomitant Administration with Other Vaccines and TIG**

For immunogenicity data on the concomitant administration of Tripedia vaccine with ActHIB vaccine, OPV vaccine, and hepatitis B vaccine, and on the concomitant administration of TriHIBit vaccine (ActHIB vaccine reconstituted with Tripedia vaccine) with MMR vaccine, see **CLINICAL PHARMACOLOGY** section.

There are no safety or immunogenicity data available on the concomitant administration of Tripedia vaccine or TriHIBit vaccine (ActHIB vaccine reconstituted with Tripedia vaccine) with varicella vaccine, or IPV vaccine, or pneumococcal conjugate vaccine.

When concomitant administration of other vaccines is required, they should be given with separate syringes and at different injection sites.

If Tripedia vaccine and TIG are administered concomitantly, separate syringes and separate injection sites should be used.

#### **HOW SUPPLIED**

Vial, 1 Dose (10 per package) – Product No. 49281-298-10

CPT® Code: 90700

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

CPT® Code: 90721

CPT is a registered trademark of the American Medical Association.

#### **STORAGE**

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

#### **REFERENCES**

1. Mueller JH, et al. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. *J Immunol* 1941;40:21-32.
2. Sanofi Pasteur Inc., Data on File – 072503.
3. Centers for Disease Control and Prevention (CDC). Recommendations of the Advisory Committee on Immunization Practices (ACIP). Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. *MMWR* 1991;40:(RR-10):1-28.
4. CDC. Notice to readers: final 2000 reports of notifiable diseases. *MMWR* 2001;50(33):712.
5. CDC. Epidemiology and prevention of vaccine-preventable diseases, Atkinson, W et al, eds. 7<sup>th</sup> ed. Atlanta, GA, 2003; Chapters 4,5,6.
6. Golaz A, et al. Epidemic diphtheria in the newly Independent States of the former Soviet Union: implications for diphtheria control in the United States. *J Infect Dis* 2000;181(Suppl 1):S237-S243.
7. Hardy IRB, et al. Current situation and control strategies for resurgence of diphtheria in newly independent states of the former Soviet Union. *Lancet* 1996;347:1739-1744.
8. Mortimer EA, et al. Diphtheria Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 3<sup>rd</sup> ed. Philadelphia, PA: WB Saunders Company 1999:140-157.
9. Wassilak SGF, et al. Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 3<sup>rd</sup> ed. Philadelphia, PA: WB Saunders Company 1999:441-474.
10. Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review: Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117.
11. CDC. General recommendations on immunization: Recommendations of the ACIP and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35.
12. Edwards KM, et al. Pertussis Vaccine. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 3<sup>rd</sup> ed. Philadelphia, PA: WB Saunders Company 1999;293-344.

13. Nelson Textbook of Pediatrics. – 16<sup>th</sup> ed. [edited by] Behrman RE, Kliegman RM, Jenson HB. WB Saunders Company 2000;838-842.
14. CDC. Pertussis – United States, 1997-2000. MMWR 2002;51(04):73-76.
15. CDC. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the ACIP. MMWR 1997;46(RR-7):1-25.
16. Güris D, et al. Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990-1996. Clin Infect Dis 1999;28:1230-1237.
17. Training and Education Branch, National Immunization Program, CDC. Pertussis. In: Atkinson W, et al, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 6<sup>th</sup> ed. Atlanta, GA: Public Health Foundation 2000:67-83.
18. Kallings LO, et al. Placebo-controlled trial of two acellular pertussis vaccines in Sweden – protective efficacy and adverse events. The Lancet 1988;955-960.
19. Liese JG, et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J 1997;16:1038-1044.
20. Blackwelder WC, et al. Acellular pertussis vaccines. Efficacy and evaluation of clinical case definitions. Am J Dis Child 1991;145(11):1285-1289.
21. Olin P, et al. Relative efficacy of two acellular pertussis vaccines during three years of passive surveillance. Vaccine 1992;10:142-144.
22. American Academy of Pediatrics. In: Pickering LK, ed. 2000 Red Book: Report of the Committee of Infectious Diseases. 26<sup>th</sup> Ed. Elk Grove Village, IL: American Academy of Pediatrics 2003.
23. CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the ACIP. MMWR 1996;45(RR-12):1-35.
24. Institute of Medicine (IOM). Adverse effects of pertussis and rubella vaccines. Howson CP, et al, Editors. Washington: National Academy Press 1991;154-157.
25. IOM. DTP Vaccine and chronic nervous system dysfunction: a new analysis. National Academy Press, Washington, DC 1994;Supplement:1-17.
26. CDC. Use of vaccines and immune globulins in persons with altered immunocompetence. Recommendations of the ACIP. MMWR 1993;42(RR-4).
27. Feldman S, et al. Comparison of two-component acellular and standard whole-cell pertussis vaccines, combined with diphtheria-tetanus toxoids, as the primary immunization series for infants. South Med J 1993;86:269-275,284.
28. Pichichero ME, et al. Acellular pertussis vaccination of 2-month-old infants in the United States. J Pediatr 1992;89:882-887.
29. Decker MD, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatr 1995;96:557-566.
30. Pichichero ME, et al. A Safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose in 15- to 20-month-old children. Pediatr 1997;100:772-788.
31. Pichichero ME, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. Pediatr 2000;105:e11.
32. Pichichero ME, et al. Safety and immunogenicity of an acellular pertussis vaccine booster in 15- to 20-month-old children previously immunized with acellular or whole-cell pertussis vaccine as infants. Pediatr 1993;91:756-760.
33. Storsaeter J, et al. Mortality and morbidity from invasive bacterial infections during a clinical trial of acellular pertussis vaccines in Sweden. Pediatr Infect Dis J 1988;7:637-645.
34. Willinger M, et al. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD. Pediatr 1994;93:814-819.
35. Walker AM, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. Am J Public Health 1987;77:945-951.
36. Fawcett HA. Injection-site granuloma due to aluminum. Arch Dermatol 1984;120:1318-1322.
37. Stratton KR, et al. Adverse events associated with childhood vaccines. Evidence bearing on causality. IOM. National Academy Press. Washington, DC 1994.
38. CDC. Vaccine Adverse Event Reporting System – United States. MMWR 1990;39:730-733.
39. CDC. National Childhood Vaccine Injury Act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37:197-200.

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