

AHFS Category 80:08

# Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

## DAPTACEL™


 Rx only
 

### DESCRIPTION

DAPTACEL™, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, for intramuscular use, manufactured by Aventis Pasteur Limited, is a sterile suspension of pertussis antigens and diphtheria and tetanus toxoids adsorbed on aluminum phosphate in a sterile isotonic sodium chloride solution. After shaking, the vaccine is a white homogeneous cloudy suspension. Each dose of DAPTACEL™ contains the following active ingredients:

pertussis toxoid	10 µg
filamentous hemagglutinin (FHA)	5 µg
pertactin (PRN)	3 µg
fimbriae types 2 and 3	5 µg
diphtheria toxoid	15 Lf
tetanus toxoid	5 Lf

Other ingredients per dose include 3.3 mg (0.6% v/v) 2-phenoxyethanol as the preservative, 0.33 mg of aluminum as the adjuvant, <0.1 mg residual formaldehyde and <50 ng residual glutaraldehyde.

The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium<sup>1</sup> modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. The fimbriae types 2 and 3 are extracted from the bacterial cells and the pertussis toxin, FHA and PRN are prepared from the supernatant. These proteins are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. Pertussis toxin is inactivated with glutaraldehyde and FHA is treated with formaldehyde. The individual antigens are adsorbed separately onto aluminum phosphate.

*Corynebacterium diphtheriae* is grown in modified Mueller's growth medium.<sup>2</sup> After ammonium sulfate fractionation, the diphtheria toxin is detoxified with formalin and diafiltered. *Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion.<sup>3</sup> Tetanus toxin is detoxified with formalin and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined in a sterile isotonic sodium chloride solution containing 2-phenoxyethanol as preservative.

Both diphtheria and tetanus toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized mice to pertussis toxin, FHA, PRN and fimbriae types 2 and 3 measured by enzyme-linked immunosorbent assay (ELISA).

### CLINICAL PHARMACOLOGY

Simultaneous immunization of infants and children against diphtheria, tetanus and pertussis with conventional whole-cell pertussis DTP vaccine (Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed - For Pediatric Use) has been a routine practice in the US since the late 1940s. This has played a major role in markedly reducing disease and deaths from these infections.<sup>4</sup> DTaP (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) 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 <7 years of age since 1997.<sup>5</sup>

#### Diphtheria

*Corynebacterium diphtheriae* may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein 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 is a serious disease, with the highest case-fatality rates among infants and the elderly.<sup>4,6</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% – 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>4</sup> From 1980 through 2000, only 50 cases of diphtheria were reported in the US. During the period 1980–1996, six fatal cases of diphtheria were reported. Only 1 case of diphtheria was reported each year in 1998–2000 with no fatalities.<sup>7</sup> 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.<sup>8</sup>

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 resulted in approximately 150,000 cases and 5,000 deaths during the years 1990-1997.<sup>9</sup> This outbreak is believed to be due to several factors, including a lack of routine immunization of adults in these countries.<sup>10</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. Immunization does not, however, eliminate carriage of *C. diphtheriae* in the pharynx, nose or on the skin.<sup>4</sup>

### Tetanus

Tetanus manifests systemic toxicity 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 years or more.<sup>4</sup>

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>7</sup> 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 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. From 1995-1997, persons 20-59 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.<sup>8</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>6</sup>

Pertussis is highly communicable (attack rates of 90% have been reported for susceptible individuals exposed to a case in the home<sup>11</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 the introduction and widespread use of whole-cell pertussis DTP vaccine among infants and children in the mid to late 1940s, pertussis incidence gradually declined, reaching a historical low of 1,010 cases reported in 1976.<sup>12</sup>

During the 1980s and 1990s, the number of reported pertussis cases in the US has gradually increased, particularly among adolescents and adults.<sup>12,13</sup> Improvements in the diagnosis and reporting of pertussis in older age groups is thought to have contributed, at least in part, to the increase in reported cases. The number of cases of pertussis reported 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>12</sup>

During 1997-2000, a total of 29,134 cases were reported, for an estimated average annual incidence rate of 2.7 per 100,000 population.<sup>12</sup> Among 29,048 cases for whom age was known, 29% were aged < 1 year, 12% were aged 1-4 years, 10% were aged 5-9 years, 29% were aged 10-19 years and 20% were ≥20 years of age.<sup>12</sup> Average annual incidence rates during 1997-2000 were highest among infants aged <1 year (55.5 cases per 100,000 population) and lower in children aged 1-4 years (5.5), children aged 5-9 years (3.6), persons aged 10-19 years (5.5) and persons aged ≥20 years (0.8).<sup>12</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>12</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. Older preschool-aged and school-aged children, as well as adolescents and adults who develop pertussis, may play a role in transmission to young infants.<sup>8</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*. The pertussis component of DTaP vaccines contains inactivated pertussis toxin and may contain one or more of FHA, PRN and fimbriae types 2 and 3. DTaP vaccines were first available for use in infants in the US in 1996 and have been routinely recommended by the Advisory Committee on Immunization Practices (ACIP) for all doses of the vaccination series for infants and children <7 years of age since 1997.<sup>5</sup>

Since 1991, 7 studies conducted in Europe and Africa have evaluated the efficacy of 8 DTaP vaccines administered to infants. The vaccines, produced by different manufacturers, contained a varying number and quantity of antigens. The derivation and formulation of the individual antigens also varied among different vaccines. The studies differed in study design and 3, including the Sweden I Efficacy Trial (1992-1995), were randomized placebo-controlled clinical trials. Because of these and other differences, comparisons among studies should be made with caution. Within individual studies, however, the efficacy of acellular pertussis vaccines can be compared directly with that of a placebo control or whole-cell pertussis DTP. The efficacy of 3 doses of acellular pertussis vaccines in preventing moderate to severe pertussis disease was within the range expected for most whole-cell pertussis DTP vaccines. Point estimates of the efficacy of DTaP vaccines ranged from 59% - 89%.<sup>5</sup>

The effectiveness of pertussis vaccine among US children aged 7-18 months in 1998 and 1999 was calculated using the screening method. During this time, the National Immunization Survey reported 66% of children aged ≤18 months received DTaP rather than whole-cell pertussis DTP.<sup>12</sup> The screening estimate of 88% reflects the effectiveness of the overall vaccination program that used approximately two thirds DTaP and one third whole-cell pertussis DTP in children aged 7-18 months. This estimate is similar to that observed in clinical trials for acellular pertussis vaccines. During 1997-2000, the incidence rates were highest among infants aged <1 year, lower in children aged 1-4 years and remained stable among children aged 5-9 years.<sup>12</sup>

## Efficacy of DAPTACEL™

### Pertussis

A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in Sweden from 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National Institute of Allergy and Infectious Diseases (NIAID). A total of 9,829 infants received 1 of 4 vaccines: DAPTACEL™ (n = 2,587); another investigational acellular pertussis vaccine (n = 2,566); whole-cell pertussis DTP vaccine (n = 2,102); or DT vaccine as placebo (Swedish National Bacteriological Laboratory, n = 2,574). Infants were immunized at 2, 4 and 6 months of age. The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL™ against pertussis after 3 doses of vaccine using the World Health Organization (WHO) case definition ( $\geq 21$  consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1 to 88.6).<sup>14</sup> The protective efficacy of DAPTACEL™ against mild pertussis ( $\geq 1$  day of cough with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2).<sup>15</sup> Protection against pertussis by DAPTACEL™ was sustained for the 2-year follow-up period.<sup>14,15</sup>

In order to assess the antibody response to the pertussis antigens of DAPTACEL™ in the US population, 2 lots of DAPTACEL™, including the lot used in the Sweden I Efficacy Trial, were administered to US infants in the US Bridging Study.<sup>15</sup> In this study, antibody responses following 3 doses of DAPTACEL™ given to US children at 2, 4 and 6 months of age were compared to those from a subset of the infants enrolled in the Sweden I Efficacy Trial. Assays were performed in parallel on the available sera from the US and Swedish infants. Antibody responses to all the antigens were similar except for those to the PRN component. For both lots of DAPTACEL™, the geometric mean concentration (GMC) and percent response to PRN in US infants (Lot 006, n = 107; Lot 009, n = 108) were significantly lower after 3 doses of vaccine than in Swedish infants (n = 83). In a separate study performed in Canada (Phase II), in which children received 4 doses of DAPTACEL™ at 2, 4, 6 and 17–18 months of age, antibody responses following the fourth dose (n = 275) were equivalent or higher than those seen in the Swedish infants after 3 doses. While a serologic correlate of protection for pertussis has not been established, the antibody response to all antigens in North American infants after 4 doses of DAPTACEL™ at 2, 4, 6 and 17-20 months of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated after 3 doses of DTaP at 2, 4 and 6 months of age.<sup>15</sup>

### Diphtheria and Tetanus

In a Canadian clinical study, 324 children were enrolled to receive DAPTACEL™ at 2, 4, 6 and 17–18 months of age. The proportion of children with post-dose 3 diphtheria (n = 313) and tetanus (n = 313) antitoxin levels  $\geq 0.01$  IU/mL was 100% and  $\geq 0.10$  IU/mL was 85% and 100%, respectively.<sup>15</sup> The proportion with post-dose 4 diphtheria (n = 296) and tetanus (n = 296) antitoxin levels  $\geq 0.10$  IU/mL was 100%.<sup>15</sup> The efficacy of the diphtheria and tetanus toxoids used in DAPTACEL™ 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 and Toxoids.<sup>16</sup>

In the US Bridging Study, for which data are only available following 3 doses, 99.2% (n = 261) achieved diphtheria antitoxin levels of  $\geq 0.01$  IU/mL, 80.6% (n = 261) achieved levels of  $\geq 0.10$  IU/mL and 100% (n = 260) achieved tetanus antitoxin levels of 0.01 U/mL and 0.10 U/mL.<sup>15</sup>

### Concurrently Administered Vaccines

In a clinical trial conducted in the US, DAPTACEL™ was given simultaneously with *Haemophilus influenzae* type b vaccine and with live oral poliovirus vaccine (OPV) at 2, 4 and 6 months of age according to local practices. Two hundred eighty-one infants received 3 doses of *Haemophilus influenzae* type b vaccine and 305 received 3 doses of OPV. Immune responses to these vaccines were evaluated in a subset of 258 children. One month after the third dose, 96.9% (n = 253) achieved anti-PRP antibody levels of at least 0.15  $\mu$ g/mL, 82.7% (n = 216) achieved antibody levels of at least 1.0  $\mu$ g/mL; and 100% (n = 178), had protective neutralizing antibody of  $\geq 1:8$  for poliovirus types 1 and 2 and 98.3% (n = 175) for poliovirus type 3.<sup>15</sup>

In the same study, hepatitis B vaccine (supplied by different manufacturers) was also given to children by different schedules. Hepatitis B vaccine was given concurrently with DAPTACEL™ at 2 and 6 months of age to a subset of infants who received a birth dose of hepatitis B vaccine. Of infants with adequate serum available for serology testing (n = 82), 97% achieved anti-HBs antibody levels  $\geq 10$  mIU/mL post dose 3.<sup>15</sup>

No immunogenicity data are available for concurrent administration of DAPTACEL™ with IPV; pneumococcal conjugate vaccine; measles, mumps and rubella vaccine (MMR) or varicella vaccine.

### INDICATIONS AND USAGE

DAPTACEL™ is indicated for active immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday).

Children who have had well-documented pertussis (culture positive for *B. pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination series with DT; some experts recommend including acellular pertussis vaccine as well. Although well-documented pertussis disease is likely to confer immunity, the duration of protection is unknown.<sup>17</sup>

DAPTACEL™ is not to be used for the treatment of *B. pertussis*, *C. diphtheriae* or *C. tetani* infections.

When passive protection is required, Tetanus Immune Globulin and/or Diphtheria Antitoxin may also be administered at separate sites with separate needles and syringes.<sup>4</sup> (See DOSAGE AND ADMINISTRATION.)

As with any vaccine, vaccination with DAPTACEL™ may not protect 100% of susceptible individuals.

### CONTRAINDICATIONS

This vaccine is contraindicated in children and adults seven years of age and older.

Hypersensitivity to any component of the vaccine is a contraindication to further administration.<sup>5</sup>

The following events after receipt of DAPTACEL™ are contraindications to further administration of any pertussis-containing vaccine:<sup>5</sup>

- *An immediate anaphylactic reaction.* Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with diphtheria, tetanus or pertussis components should be carried out. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.
- *Encephalopathy not attributable to another identifiable cause* (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and consisting of major alterations in consciousness, unresponsiveness or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours). In such cases, DT vaccine should be administered for the remaining doses in the vaccination schedule.

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. According to the ACIP, 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.<sup>17,18</sup> However, children with moderate or serious illness should not be immunized until recovered.<sup>4</sup>

Elective immunization procedures should be deferred during an outbreak of poliomyelitis because of the risk of provoking paralysis.<sup>19,20,21</sup>

## WARNINGS

The stopper to the vial of this product contains dry natural latex rubber that may cause allergic reactions.

If any of the following events occur within the specified period after administration of a whole-cell pertussis DTP or DTaP vaccine, providers and parents should evaluate the risks and benefits of subsequent doses of whole-cell pertussis DTP or DTaP vaccines:<sup>5</sup>

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

When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be continued.<sup>4</sup>

Because of the risk of hemorrhage, DAPTACEL™ should not be given to children with any coagulation disorder, including thrombocytopenia, which would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Studies suggest that, when given whole-cell pertussis DTP vaccine, infants and children with a history of convulsions in first-degree family members have a 2.4-fold increased risk for neurologic events.<sup>22</sup> However, ACIP has concluded that a history of convulsions or other central nervous system disorders in parents or siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive DTaP vaccines according to the recommended schedule.<sup>4,17,18</sup>

**If an infant or young child with a personal or family history of febrile or non-febrile convulsions is to be immunized, acetaminophen or other appropriate antipyretic should be given at the time of DTaP vaccination and for the ensuing 24 hours according to the respective package insert recommended dosage to reduce the possibility of post-vaccination fever.**<sup>4,17,18</sup>

A committee of the Institute of Medicine (IOM) has concluded that the 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>23,24</sup> However, the IOM committee concluded that the evidence was insufficient to determine whether whole-cell pertussis DTP vaccine increased the overall risk of chronic neurologic disease.<sup>24</sup> Acute encephalopathy (with or without permanent neurological injury) or permanent neurological injury has not been reported following administration of DAPTACEL™ but the experience with this vaccine is insufficient to rule this out. (See ADVERSE REACTIONS.)

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 2 or 3 days following whole-cell pertussis DTP vaccine immunization.<sup>4</sup> Whether to administer DAPTACEL™ to children with proven or suspected underlying neurologic disorders 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 ACIP has issued guidelines for such children.<sup>25</sup>

## PRECAUTIONS

### General

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

Epinephrine Hydrochloride Solution (1:1,000), other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers must be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.<sup>17,26</sup>

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

The expected immune response to DAPTACEL™ may not be obtained in immunosuppressed persons.<sup>4</sup> Pertussis-containing vaccines are not contraindicated in persons with HIV infection.<sup>17</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 hepatitis or other 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.)

The physician should inform the parent or guardian about the potential for adverse reactions that have been temporally associated with DAPTACEL™ and other pertussis-containing vaccines. The health-care provider should provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The parent or guardian should be instructed to report any serious 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 OR GUARDIAN SHOULD BE QUESTIONED CONCERNING ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF VACCINE. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

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

**Drug Interactions**

As with other intramuscular (I.M.) 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 is to be soon discontinued, it seems reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.<sup>4</sup>

If DAPTACEL™ is administered to persons with an immunodeficiency disorder, on immunosuppressive therapy or after a recent injection of immune globulin, an adequate immunologic response may not occur.

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

If passive immunization is needed for tetanus or diphtheria prophylaxis, Tetanus Immune Globulin (Human) (TIG), or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.<sup>1,8</sup>

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

DAPTACEL™ has not been evaluated for its carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy Category C**

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

**Geriatric Use**

This product is NOT recommended for use in adult populations.

**Pediatric Use**

*SAFETY AND EFFECTIVENESS OF DAPTACEL™ IN INFANTS BELOW 6 WEEKS OF AGE HAVE NOT BEEN ESTABLISHED.* (See DOSAGE AND ADMINISTRATION.)

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

**ADVERSE REACTIONS**

Over 11,400 doses of DAPTACEL™ have been administered to infants and toddlers in 6 clinical studies. In all, 3,694 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL™.<sup>1,4,15,27,28,29,30,31</sup>

In the Sweden I Efficacy Trial, DAPTACEL™ was compared with DT and a whole-cell pertussis DTP vaccine. A standard diary card was kept for 14 days after each dose and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months after the last injection. There were fewer of the common local and systemic reactions following DAPTACEL™ than following the whole-cell pertussis DTP vaccine. As shown in Table 1, the 2,587 infants who enrolled to receive DAPTACEL™ at 2, 4 and 6 months of age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving whole-cell pertussis DTP.<sup>1,4</sup>

The rates of local reactions reported 1 day after any dose were lower in the DAPTACEL™ and DT groups than in the whole-cell pertussis DTP vaccine group.

**TABLE 1<sup>14,15</sup> PERCENTAGE OF INFANTS FROM SWEDEN I EFFICACY TRIAL WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 24 HOURS POST-DOSE 1, 2 AND 3 OF DAPTACEL™ COMPARED WITH DT AND WHOLE-CELL PERTUSSIS DTP VACCINES**

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL™ N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL™ N = 2,563	DT N = 2,555	DTP N = 2,040	DAPTACEL™ N = 2,549	DT N = 2,538	DTP N = 2,001
<b>Local</b>									
Tenderness (Any)	8.0*	8.4	59.5	10.1*	10.3	60.2	10.8*	10.0	50.0
Redness ≥2 cm	0.3*	0.3	6.0	1.0*	0.8	5.1	3.7*	2.4	6.4
Swelling ≥2 cm	0.9*	0.7	10.6	1.6*	2.0	10.0	6.3*§	3.9	10.5
<b>Systemic</b>									
Fever† ≥38°C (100.4°F)	7.8*	7.6	72.3	19.1*	18.4	74.3	23.6*	22.1	65.1
Fretfulness††	32.3	33.0	82.1	39.6	39.8	85.4	35.9	37.7	73.0
Anorexia	11.2*	10.3	39.2	9.1*	8.1	25.6	8.4*	7.7	17.5
Drowsiness	32.7*	32.0	56.9	25.9*	25.6	50.6	18.9*	20.6	37.6
Crying ≥1 hour	1.7*	1.6	11.8	2.5*	2.7	9.3	1.2*	1.0	3.3
Vomiting	6.9*	6.3	9.5	5.2**	5.8	7.4	4.3	5.2	5.5

N = Number of evaluable subjects

\* p<0.001: DAPTACEL™ versus whole-cell pertussis DTP

\*\* p<0.003: DAPTACEL™ versus whole-cell pertussis DTP

§ p<0.0001: DAPTACEL™ versus DT

† Rectal temperature

†† Statistical comparisons were not made for this variable

DT: Swedish National Biologics Laboratories

DTP: Aventis Pasteur Inc.

The incidence of serious and less common selected systemic events in this trial are summarized in Table 2.<sup>14,15</sup>

**TABLE 2<sup>14,15</sup> SELECTED SYSTEMIC EVENTS: RATES PER 1,000 DOSES AFTER VACCINATION AT 2, 4, AND 6 MONTHS OF AGE IN SWEDEN I EFFICACY TRIAL**

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL™ N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL™ N = 2,565	DT N = 2,556	DTP N = 2,040	DAPTACEL™ N = 2,551	DT N = 2,539	DTP N = 2,002
Rectal temperature ≥40°C (104°F) within 48 hours of vaccination	0.39	0.78	3.33	0	0.78	3.43	0.39	1.18	6.99
Hypotonic-hyporesponsive episode within 24 hours of vaccination	0	0	1.9	0	0	0.49	0.39	0	0
Persistent crying ≥3 hours within 24 hours of vaccination	1.16	0	8.09	0.39	0.39	1.96	0	0	1.0
Seizures within 72 hours of vaccination	0	0.39	0	0	0.39	0.49	0	0.39	0

N = Number of evaluable subjects

One case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL™. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL™. Over the entire study period, 6 seizures were reported in the DAPTACEL™ group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccinees, respectively. One case of infantile spasms was reported in the DAPTACEL™ group. There were no instances of invasive bacterial infection or death.<sup>14,15</sup>

Rates of serious adverse events that are less common than those reported in the Sweden I Efficacy Trial are not known at this time.

Table 3 summarizes the safety results from the Phase II Study in Canada in children who were immunized at 2, 4, 6 and 17–18 months of age with DAPTACEL™. For adverse events, parents recorded information for 72 hours post-immunization in a diary card. Local reactions of redness and swelling were assessed and measured by the parents using a template with graded size markings. Study staff collected the information from the parents during a structured telephone interview at 2–6, 8–12, 24, 48 and 72 hours and 7 days post-immunization and recorded the information in the case report form.<sup>15,29</sup>

Local and systemic adverse events were consistently less common in DAPTACEL™ recipients at 2, 4 and 6 months of age than in those who received whole-cell pertussis DTP vaccine. Following the fourth dose, the same trends were observed, except for rates of severe redness and swelling which did not differ between the 2 vaccine groups. Rates of local reactions of redness and swelling were increased following the fourth dose compared with the first 3 doses as was mild tenderness but there was no increase in severe tenderness.

**TABLE 3<sup>15,29</sup> PERCENTAGE OF CHILDREN FROM PHASE II STUDY IN CANADA WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL™ AND WHOLE-CELL PERTUSSIS DTP VACCINE AT 2, 4, 6 AND 17–18 MONTHS OF AGE**

EVENT	Dose 1 (2 MONTHS)		Dose 2 (4 MONTHS)		Dose 3 (6 MONTHS)		Dose 4 (18 MONTHS)	
	DAPTACEL™ N = 324	DTP# N = 108	DAPTACEL™ N = 321	DTP# N = 106	DAPTACEL™ N = 320	DTP# N = 104	DAPTACEL™ N = 301	DTP# N = 97
<b>Local</b>								
Redness								
Any	12.7*	44.4	20.6*	57.5	22.2*	51.9	36.5*	55.7
≥10 mm	1.2*	13.9	7.8*	22.6	10.0*	17.3	27.9	36.1
≥35 mm	0.3*	3.7	0.3*	5.7	1.6	1.9	21.9	20.6
Swelling								
Any	4.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
≥10 mm	1.9*	15.7	2.2*	21.7	3.8*	14.4	15.9*	25.8
≥35 mm	0.3*	6.5	0*	5.7	0.9*	4.8	11.3	15.5
Tenderness†								
Any	10.2*	37.0	7.5*	51.9	8.8*	48.1	23.9*	86.6
Moderate + Severe	0.9*	13.0	1.2*	20.8	1.3*	17.3	3.0*	53.6
Severe	0*	4.6	0.3*	7.5	0*	4.8	0.3*	12.4
<b>Systemic</b>								
Fever‡§								
Any ≥37.5°C (99.5°F)	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
≥38°C (100.4°F)	0.7	1.9	0*	7.8	1.2*	11.7	1.9*	17.9
≥40°C (104°F)	0.3	0	0	1.0	0	1.1	0	0
Irritability¶								
Any	41.0*	65.7	41.4*	68.9	40.9*	67.3	36.9*	79.4
Moderate + Severe	9.0*	18.5	6.9*	22.6	5.0*	22.1	5.0*	24.7
Severe	0	1.9	0.3	0	0	1.0	0	2.1
Anorexia <sup>Ω</sup>								
Any	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
Moderate + Severe	1.5	3.7	0.9	2.8	1.3	1.9	2.0*	13.4
Severe	0	0	0.3	0	0	0	0	2.1
Drowsiness <sup>∇</sup>								
Any	43.2	52.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Moderate + Severe	7.7	8.3	2.8*	7.5	1.3	0	1.0*	6.2
Severe	0.3	0	0	0	0	0	0	0
Crying ≥3 Hours	0.6	0.9	0.3	0.9	0	1.0	0	1.0

N = Number of evaluable subjects

# DTP: whole-cell pertussis DTP vaccine (Aventis Pasteur Limited)

\* Significantly less reactogenic than whole-cell DTP vaccine,  $p < 0.05$

† Moderate = sustained cry with gentle pressure at injection site; Severe = cries when leg is moved

‡ Temperature measurements were axillary

§ Number of evaluable subjects for DAPTACEL™/DTP = 301/103, 298/102, 257/94 and 207/78 at 2, 4, 6 and 18 months, respectively

¶ Moderate = more difficulty with settling, even with cuddling; Severe = persistent crying/screaming and inability to console

Ω Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds

∇ Moderate = sleeping much more than normal; Severe = sleeping most of the time with difficulty arousing

The US Bridging Study was designed, in part, to assess the safety of DAPTACEL™ in infants at 2, 4 and 6 months of age, with routinely recommended, concurrently given childhood vaccines (*Haemophilus influenzae* type b vaccine, OPV and hepatitis B). For adverse events, parents recorded information for 72 hours post-immunization in a diary card. Local reactions were assessed and measured by the parents. Study staff collected the information from the parents during a structured telephone interview on days 4 and 14 post-immunization and recorded the information in the case report form.<sup>15</sup> The incidence of redness, swelling, pain or tenderness at the injection site and systemic symptoms after each dose is shown as pooled data from 2 lots of DAPTACEL™ (Lots 006 and 009) in Table 4. Fever  $\geq 38^\circ\text{C}$  ( $100.4^\circ\text{F}$ ) was observed in 9.9% – 11.9% of subjects. The incidence of severe systemic symptoms including irritability, tiredness, anorexia, rash and vomiting ranged from 0.3% – 0.6%. One afebrile seizure occurred within 24 hours post dose 2 immunization ( $n = 321$ ).<sup>15</sup>

In an ongoing study (P3T06) initiated in May 2001 and anticipated to be completed in 2004, which was designed to assess the safety of DAPTACEL™ given with routinely recommended vaccines (*Haemophilus influenzae* type b vaccine, IPV, hepatitis B and pneumococcal conjugate vaccine) in the US (in which 777 children have received their first dose, 350 have received their second dose and 86 their third dose with safety data still being collected from children in this study), one afebrile seizure was reported within 24 hours of receipt of dose 1.

**TABLE 4<sup>15</sup> PERCENTAGE OF CHILDREN FROM US BRIDGING STUDY WITH ANY LOCAL AND SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL™ AT 2, 4 AND 6 MONTHS OF AGE (LOTS 006 AND 009 POOLED)**

EVENT	Dose 1 (2 MONTHS) N = 321	Dose 2 (4 MONTHS) N = 317	Dose 3 (6 MONTHS) N = 315
<b>Local</b>			
Redness			
Any	12.5	15.8	19.7
<1 inch	11.8	15.1	18.7
≥1 inch	0.6	0.6	1.0
Swelling			
Any	14.3	15.4	17.8
<1 inch	13.7	15.1	16.2
≥1 inch	0.6	0.3	1.6
Tenderness			
Any	30.5	19.6	15.9
Moderate + Severe	8.1	4.4	1.0
Severe	0	0	0
<b>Systemic</b>			
Fever**			
Any ≥38°C (100.4°F)	11.9	9.9	9.9
≥39°C (102.2°F)	0.3	0.3	0.6
≥40°C (104°F)	0	0	0
Irritability			
Any	72.0	61.2	56.2
Moderate + Severe	33.6	25.2	18.7
Severe	0.3	0.3	0
Anorexia			
Any	26.2	14.8	17.8
Moderate + Severe	5.6	3.8	4.8
Severe	0	0.3	0
Drowsiness			
Any	62.0	44.8	35.6
Moderate + Severe	24.0	8.5	7.3
Severe	0.6	0.3	0
Crying ≥3 Hours	0.3	0	0

N = Number of evaluable subjects

\* Rectal temperature

† N = 319, 314 and 313 at 2, 4 and 6 months respectively

Moderate = discomforting enough to interfere with or limit usual daily activity

Severe = disabling, unable to perform daily activities

NIAID sponsored a multicenter Phase I/II clinical trial to compare the safety and immunogenicity of 13 acellular pertussis vaccines with a conventional whole-cell pertussis DTP vaccine in infants in the US. The common local and systemic adverse experiences, after all 3 doses, for DAPTACEL™ and the participating acellular vaccines that have subsequently been licensed in the US were generally similar in type and frequency and were reduced in comparison to the whole-cell pertussis DTP vaccine.<sup>28</sup>

Additional adverse reactions evaluated in conjunction with pertussis, diphtheria and tetanus vaccination are as follows:

- 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>4,32</sup>
- Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing, hypotension or shock) have been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.<sup>4</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 neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.<sup>33</sup>



A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.<sup>34</sup> The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications<sup>35,36</sup> including cochlear lesion, brachial plexus neuropathies,<sup>37</sup> paralysis of the radial nerve,<sup>33</sup> paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).<sup>38,39</sup> In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.<sup>39</sup>

Onset of infantile spasms has occurred in infants who have recently received whole-cell pertussis DTP or DT. Analysis of data from the National Childhood Encephalopathy Study (NCES) on children with infantile spasms failed to demonstrate that receipt of DT or whole-cell pertussis DTP vaccines was causally related to infantile spasms.<sup>23,40</sup> The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of whole-cell pertussis DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of whole-cell pertussis DTP.<sup>4</sup>

Persistent, inconsolable crying lasting  $\geq 3$  hours and high-pitched, unusual screaming, 1% and 0.1% respectively, after 15,752 doses of whole-cell pertussis DTP vaccine have been reported.<sup>38</sup> Convulsions and hypotonic-hyporesponsive episodes (HHE) have each been reported to occur at a frequency of about 1:1,750 injections of whole-cell pertussis DTP.<sup>17,26,38</sup> Most convulsions are brief, generalized and self-limited and are usually associated with fever. Neither febrile nor afebrile convulsions associated with whole-cell pertussis DTP vaccine have been shown to be associated with subsequent seizure disorder.<sup>17</sup> Persistent, inconsolable crying  $\geq 3$  hours, convulsions and HHE have also been reported following DTaP vaccines, including DAPTACEL™.<sup>5</sup>

In another large study (Sweden II Efficacy Trial), 3 DTaP vaccines and a whole-cell pertussis DTP vaccine, none of which are licensed in the US, were evaluated to assess relative safety and efficacy.<sup>41</sup> This study included HCPDT, a vaccine made of the same components as DAPTACEL™ but containing twice the amount of PT and four times the amount of FHA (20  $\mu$ g pertussis toxoid and 20  $\mu$ g FHA). Hypotonic-hyporesponsive episodes (HHE) were observed following 29 (0.047%) of 61,220 doses of HCPDT; 16 (0.026%) of 61,219 doses of an acellular pertussis vaccine made by another manufacturer; and 34 (0.056%) of 60,792 doses of a whole-cell pertussis DTP vaccine. There were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of 33 (0.047%) in 69,525 doses.<sup>15,41</sup> (See CONTRAINDICATIONS and PRECAUTIONS.)

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.<sup>42,43</sup> It should be recognized that the first 3 immunizing doses of whole-cell pertussis DTP and DTaP (including DAPTACEL™) are usually administered to infants 2-6 months of age 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<sup>17</sup> and acellular pertussis vaccines. A review by a committee of the IOM concluded that available evidence did not indicate a causal relation between whole-cell pertussis DTP vaccine and SIDS.<sup>23</sup>

Whole-cell pertussis DTP vaccine has been associated with acute encephalopathy.<sup>23</sup> 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.<sup>44</sup> A committee of the Institute of Medicine (IOM) has concluded that, because whole-cell pertussis DTP may cause acute neurologic illness, whole-cell pertussis DTP may also cause chronic neurologic disease in the context of the NCES report.<sup>24</sup> However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell pertussis DTP increased the overall risk of chronic neurologic disease.<sup>24</sup>

A bulging fontanel associated with increased intracranial pressure which occurred within 24 hours following whole-cell pertussis DTP immunization has been reported, although a causal relationship has not been established.<sup>45,46,47</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 DAPTACEL™ package insert.<sup>17,48</sup>

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to 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>48,49</sup>

**Health-care providers should also report these events to the Pharmacovigilance Department, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.**

### DOSAGE AND ADMINISTRATION

DAPTACEL™ is a sterile white homogenous cloudy suspension of acellular pertussis vaccine components and diphtheria and tetanus toxoids adsorbed on aluminum in a sterile isotonic sodium chloride solution and containing 2-phenoxyethanol as preservative. Inspect the vial visually for extraneous particulate matter and/or discoloration before administration. If these conditions exist, the product should not be administered.

JUST BEFORE USE, SHAKE THE VIAL WELL, until a uniform, cloudy suspension results. WITHDRAW AND INJECT A 0.5 mL DOSE. When administering a dose from a rubber-stoppered vial, do not remove either the rubber stopper or the metal seal holding it in place. Aseptic technique must be used for withdrawal of each dose.

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

Administer the vaccine **intramuscularly** (I.M.). In children younger than 1 year (i.e., infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for I.M. injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.<sup>17</sup>

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 DAPTACEL™ is approved for administration as a 4 dose series at 2, 4 and 6 months of age, at intervals of 6–8 weeks and at 17–20 months of age. (See CLINICAL PHARMACOLOGY.) The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The interval between the third and fourth dose should be at least 6 months. It is recommended that DAPTACEL™ be given for all doses in the series because no data on the interchangeability of DAPTACEL™ with other DTaP vaccines exist. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL™ in children who have previously received 4 doses of DAPTACEL™.<sup>50</sup>

DAPTACEL™ may be used to complete the immunization series in infants who have received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of DAPTACEL™ in such infants have not been fully demonstrated.<sup>5</sup>

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL™ OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.<sup>18</sup>

DAPTACEL™ should not be combined through reconstitution or mixed with any other vaccine.

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

Pre-term infants should be vaccinated according to their chronological age from birth.<sup>17</sup>

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

### Simultaneous Vaccine Administration

In clinical trials, DAPTACEL™ was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: OPV, hepatitis B vaccine and *Haemophilus influenzae* type b vaccine.<sup>15</sup> No safety and immunogenicity data are currently available on the simultaneous administration of pneumococcal conjugate vaccine, MMR vaccine and varicella vaccine and no immunogenicity data are currently available on the simultaneous administration of IPV. Two afebrile seizures, occurring within 24 hours of immunization, have been reported from 2 US trials where DAPTACEL™ was given with other concomitant vaccines. (See ADVERSE REACTIONS.) When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

ACIP encourages routine simultaneous administration of DTaP, IPV, *Haemophilus influenzae* type b vaccine, pneumococcal conjugate vaccine, MMR, varicella vaccine and hepatitis B vaccine for children who are the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit, unless, in the judgment of the provider, complete vaccination of the child will not be compromised by administering different vaccines at different visits. Simultaneous administration is particularly important if the child might not return for subsequent vaccinations.<sup>18</sup> (See CLINICAL PHARMACOLOGY.)

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 is associated with few adverse reactions. The currently recommended prophylactic dose of TIG for wounds of average severity is 250 units intramuscularly. When tetanus toxoid-containing vaccines and TIG and/or Diphtheria Antitoxin are administered concurrently, separate syringes and separate sites should be used.

### HOW SUPPLIED

Vial, 1 x 1 Dose - Product No. 49281-286-01

Vial, 5 x 1 Dose - Product No. 49281-286-05

### STORAGE

DAPTACEL™ should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.

### REFERENCES

1. Stainer DW, Scholte MJ. A simple chemically defined medium for the production of phase I *Bordetella pertussis*. J Gen Microbiol 1970;63:211-220.
2. Stainer DW. Production of diphtheria toxin. In: Manclark CR, ed. Proceeding of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, MD. DHHS Publication No. (FDA) 91-1174. 1991:7-11.
3. Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J Bacteriol 1953;67:271-277.
4. 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.
5. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. MMWR 1997;46(RR-7):1-25.
6. Plotkin SA, et al. *Vaccines. 3rd ed.* Philadelphia, W. B. Saunders Company. 1999:140-157,293-344,441-474.
7. Centers for Disease Control and Prevention (CDC). Notice to readers: Final 2000 reports of notifiable diseases. MMWR 2001;50(33):1-10.

8. Atkinson W, et al, editors. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 6<sup>th</sup> ed. Centers for Disease Control and Prevention (CDC); Public Health Foundation. 2000:51-72.
9. American Public Health Association (APHA). *Control of Communicable Diseases Manual*. 2000;(17):166-167.
10. 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.
11. Bedson SP, et al. The prevention of whooping-cough by vaccination. A Medical Research Council Investigation. *Br Med J* 1951;1:1463-1471.
12. Centers for Disease Control and Prevention (CDC). Pertussis-United States, 1997-2000. *MMWR* 2002;51(4):1-92.
13. 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.
14. Gustafsson L, et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996;6:349-355.
15. Aventis Pasteur Limited: Data on File.
16. Department of Health and Human Services, Food and Drug Administration. Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule. *Federal Register* 1985; 50(240):51002-51117.
17. American Academy of Pediatrics. In: Pickering LK, ed. *2000 Red Book: Report on the Committee of Infectious Diseases*. 25<sup>th</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics 2000:17,31-35,51-53,54,65,68,442-443,759-765.
18. Recommendations of the Advisory Committee on Immunization Practices (ACIP). General recommendations on immunization. *MMWR* 1994;43(RR-1):1-38.
19. Expanded programme on immunization, injection and paralytic poliomyelitis. *Wkly Epidem Rec* 1980;5:38-40.
20. Sutter RW, et al. Attributable risk of DTP (diphtheria and tetanus toxoids and pertussis vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman. *J Infect Dis* 1992;165:444-449.
21. Christie AB. *Infectious diseases: Epidemiology and Clinical Practice*. 4<sup>th</sup> ed. Edinburgh, Churchill Livingstone. 1987;2:817-825.
22. Livengood JR, et al. Family history of convulsion and use of pertussis vaccine. *J Pediatr* 1989;115(4):527-531.
23. Howson CP, et al. *Adverse Effects of Pertussis and Rubella Vaccines, Pertussis Vaccines and CNS Disorders*. Institute of Medicine (IOM). National Academy Press, Washington, DC, 1991:7-169.
24. Institute of Medicine (IOM). DTP vaccine and chronic nervous system dysfunction: A new analysis. National Academy Press, Washington, DC, 1994;Supplement:1-17.
25. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Update: Vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996;45(RR-12):1-35.
26. National Advisory Committee on Immunization (NACI): *Canadian Immunization Guide, 5<sup>th</sup> ed*. Minister of Public Works and Government Services Canada. 1998:9-13,133-139.
27. Edwards KM, et al. Comparison of 13 acellular pertussis vaccines: Overview and serologic response. *American Academy of Pediatrics* 1995;Supplement:548-557.
28. Decker MD, et al. Comparison of 13 acellular pertussis vaccines: Adverse reactions. *Pediatr* 1995;96:557-566.
29. Halperin SA et al. Adverse reactions and antibody response to four doses of acellular or whole-cell pertussis combined with diphtheria and tetanus toxoids in the first 19 months of life. *Vaccine* 1996;14(18):767-772.
30. Halperin SA, et al. Safety and immunogenicity of two acellular pertussis vaccines with different pertussis toxoid and filamentous hemagglutinin content in infants 2-6 months old. *Scand J Infect Dis* 1995;27:279-287.
31. Halperin SA, et al. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell acellular pertussis vaccine at two, four and six months of age. *Pediatr Infect Dis J* 1995;14:792-797.
32. Fawcett HA, Smith NP. Injection-site granuloma due to aluminum. *Arch Dermatol* 1984;120:1318-1322.
33. Blumstein GI, et al. Peripheral neuropathy following tetanus toxoid administration. *JAMA* 1966;198:1030-1031.
34. Institute of Medicine (U.S.). *Adverse Effects of Pertussis and Rubella Vaccines*. Howson CP, et al, editors. Washington: National Academy Press. 1991:154-157.
35. Rutledge SL, et al. Neurological complications of immunizations. *J Pediatr* 1986;109:917-924.
36. Walker AM, et al. Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatr* 1988;81:345-349.
37. Tsairis P, et al. Natural history of brachial plexus neuropathy. *Arch Neurol* 1972;27:109-117.
38. Cody CL, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatr* 1981;68(5):650-660.
39. Schlenska GK. Unusual neurological complications following tetanus toxoid administration. *J Neurol* 1977;215:299-302.
40. Alderslade R, et al. The National Childhood Encephalopathy Study: a report on 1000 cases of serious neurological disorders in infants and young children from the NCES Research Team. In: Department of Health and Social Security. Whooping cough: reports from the Committee on the Safety of Medicines and the Joint Committee on Vaccination and Immunization. London: Her Majesty's Stationery Office 1981:79-169.
41. Olin P, et al. Randomized controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet* 1997;1569-1577.
42. Griffin MR, et al. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med* 1988:618-623.
43. Hoffman HJ, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: Results of the National Institute of Child Health and Human Development cooperative epidemiological study of sudden infant death syndrome risk factors. *Pediatr* 1987;79(4):598-611.
44. Miller D, et al. *Pertussis Immunisation and Serious Acute Neurological Illnesses in Children*. Academic Department of Public Health, St. Mary's Hospital Medical School, University of London, 1993.
45. Jacob J, et al. Increased intracranial pressure after diphtheria, tetanus and pertussis immunization. *Am J Dis Child* 1979;133:217-218.

46. Mathur R, et al. Bulging fontanel following triple vaccine. *Indian Pediatr* 1981;18(6):417-418.
47. Shendurnikar N, et al. Bulging fontanel following DTP vaccine. *Indian Pediatr* 1986;23(11):960.
48. Centers for Disease Control and Prevention (CDC). National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37(13):197-200.
49. Center for Disease Control and Prevention (CDC). Vaccine Adverse Event Reporting System – United States. *MMWR* 1990;39:730-733.
50. Pichichero MD, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four six-year-old children. *Pediatr* 2000;105(1),e11:1-8.

Manufactured by:  
**Aventis Pasteur Limited**  
Toronto Ontario Canada

Product information  
as of May 2002.

Distributed by:  
**Aventis Pasteur Inc.**  
Swiftwater PA 18370 USA

Printed in Canada.

US Patents: 4500639, 4687738, 4784589, 4997915, 5444159, 5667787, 5877298.

R0-0502 USA

***Aventis Pasteur***

 ***Aventis***