

**Diphtheria and Tetanus Toxoids and  
Acellular Pertussis Vaccine Adsorbed  
DAPTACEL™**



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**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.

1 *Corynebacterium diphtheriae* is grown in modified Mueller's growth medium.<sup>2</sup> After ammonium  
2 sulfate fractionation, the diphtheria toxin is detoxified with formalin and diafiltered. *Clostridium*  
3 *tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion.<sup>3</sup>  
4 Tetanus toxin is detoxified with formalin and purified by ammonium sulfate fractionation and  
5 diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.  
6  
7 The adsorbed diphtheria, tetanus and acellular pertussis components are combined in a sterile  
8 isotonic sodium chloride solution containing 2-phenoxyethanol as preservative.

9  
10 Both diphtheria and tetanus toxoids induce at least 2 units of antitoxin per mL in the guinea pig  
11 potency test. The potency of the acellular pertussis vaccine components is evaluated by the  
12 antibody response of immunized mice to pertussis toxin, FHA, PRN and fimbriae types 2 and 3  
13 measured by enzyme-linked immunosorbent assay (ELISA).

#### 14 15 **CLINICAL PHARMACOLOGY**

16 Simultaneous immunization of infants and children against diphtheria, tetanus and pertussis with  
17 conventional whole-cell pertussis DTP vaccine (Diphtheria and Tetanus Toxoids and Pertussis  
18 Vaccine Adsorbed - For Pediatric Use) has been a routine practice in the US since the late 1940s.  
19 This has played a major role in markedly reducing disease and deaths from these infections.<sup>4</sup>  
20 DTaP (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) vaccines were  
21 first available for use in infants in the US in 1996 and have been routinely recommended for all  
22 doses of the vaccination series for infants and children <7 years of age since 1997.<sup>5</sup>

#### 23 24 **Diphtheria**

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

29  
30 Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease but only strains that  
31 produce diphtheria toxin cause severe manifestations such as myocarditis and neuritis. Diphtheria  
32 is a serious disease, with the highest case-fatality rates among infants and the elderly.<sup>4,6</sup>

33  
34 Prior to the widespread use of diphtheria toxoid in the late 1940s, diphtheria disease was common  
35 in the US. More than 200,000 cases, primarily among children, were reported in 1921.  
36 Approximately 5% - 10% of cases were fatal; the highest case-fatality rates were in the very young

1 and the elderly. More recently, reported cases of diphtheria of all types declined from 306 in 1975  
2 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous  
3 diphtheria was no longer reportable.<sup>4</sup> From 1980 through 2000, only 50 cases of diphtheria were  
4 reported in the US. During the period 1980-1996, six fatal cases of diphtheria were reported. Only  
5 1 case of diphtheria was reported each year in 1998-2000 with no fatalities.<sup>7</sup> Of 40 reported cases  
6 with known age in 1982-1998, 63% were in persons  $\geq 20$  years of age. Most cases have occurred  
7 in unimmunized or inadequately immunized persons. Although diphtheria disease is rare in the US,  
8 it appears that *C. diphtheriae* continues to circulate in areas of the country with previously  
9 endemic diphtheria.<sup>8</sup>

10  
11 Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred  
12 in the newly Independent States of the former Soviet Union beginning in 1990. This epidemic  
13 resulted in approximately 150,000 cases and 5,000 deaths during the years 1990-1997.<sup>9</sup> This  
14 outbreak is believed to be due to several factors, including a lack of routine immunization of adults  
15 in these countries.<sup>10</sup>

16  
17 Complete immunization significantly reduces the risk of developing diphtheria and immunized  
18 persons who develop disease have milder illness. Following adequate immunization with diphtheria  
19 toxoid, protection is thought to last for at least 10 years. Immunization does not, however,  
20 eliminate carriage of *C. diphtheriae* in the pharynx, nose or on the skin.<sup>4</sup>

## 21 22 **Tetanus**

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

25  
26 Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to  
27 tetanus toxin does not occur in the US. Thus, universal primary immunization, with subsequent  
28 maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary  
29 to protect all age groups. Tetanus toxoid is a highly effective antigen and a completed primary  
30 series generally induces protective levels of serum antitoxin that persist for 10 years or more.<sup>4</sup>

1 Following routine use of tetanus toxoid in the US, the occurrence of tetanus disease decreased  
2 dramatically from 560 reported cases in 1947 to an average of 50-100 cases reported annually  
3 from the mid 1970s through the late 1990s to 35 cases in 2000.<sup>7</sup> The case-fatality rate has been  
4 relatively constant at approximately 30%. During the years 1982-1998, 52% of reported cases  
5 were among persons 60 years of age or older. In the mid to late 1990s, the age distribution of  
6 reported cases shifted to a younger age group, in part due to an increased number of cases  
7 among injection drug users in California. From 1995-1997, persons 20-59 years of age accounted  
8 for 60% of all cases, with persons 60 years of age or older accounting for only 35%. In the US,  
9 tetanus occurs almost exclusively among unvaccinated or inadequately vaccinated persons.<sup>8</sup>

### 11 **Pertussis**

12 Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*.  
13 This gram-negative coccobacillus produces a variety of biologically active components. The role of  
14 the different components produced by *B. pertussis* in either the pathogenesis of, or immunity to,  
15 pertussis is not well understood.<sup>6</sup>

17 Pertussis is highly communicable (attack rates of 90% have been reported for susceptible individuals exposed  
18 to a case in the home<sup>11</sup>) and can cause severe disease, particularly among young infants. Since pertussis  
19 became a nationally reportable disease in the US in 1922, the highest number of pertussis cases  
20 (approximately 260,000) was reported in 1934. Following the introduction and widespread use of whole-cell  
21 pertussis DTP vaccine among infants and children in the mid to late 1940s, pertussis incidence gradually  
22 declined, reaching a historical low of 1,010 cases reported in 1976.<sup>12</sup>

24 During the 1980s and 1990s, the number of reported pertussis cases in the US has gradually increased,  
25 particularly among adolescents and adults.<sup>12,13</sup> Improvements in the diagnosis and reporting of pertussis in  
26 older age groups is thought to have contributed, at least in part, to the increase in reported cases. The  
27 number of cases of pertussis reported among children aged 6 months to 4 years has remained stable  
28 throughout the 1990s, suggesting that protection offered by vaccination has continued with the introduction of  
29 DTaP vaccines.<sup>12</sup>

31 During 1997-2000, a total of 29,134 cases were reported, for an estimated average annual incidence rate of  
32 2.7 per 100,000 population.<sup>12</sup> Among 29,048 cases for whom age was known, 29% were aged < 1 year, 12%  
33 were aged 1-4 years, 10% were aged 5-9 years, 29% were aged 10-19 years and 20% were ≥20 years of  
34 age.<sup>12</sup> Average annual incidence rates during 1997-2000 were highest among infants aged <1 year (55.5  
35 cases per 100,000 population) and lower in children aged 1-4 years (5.5), children aged 5-9 years (3.6),  
36 persons aged 10-19 years (5.5) and persons aged =20 years (0.8).<sup>12</sup>

1  
2 The severity of pertussis remains highest in infants. Of 7,203 infants <6 months of age reported as having  
3 pertussis during the period 1997-2000, 63% were hospitalized, 12% had pneumonia, 1.4% had one or more  
4 seizures, 0.2% had encephalopathy and 0.8% died.<sup>12</sup>  
5  
6 Atypical infection, including nonspecific symptoms of bronchitis or upper respiratory tract infection, may occur  
7 at any age but more commonly in older children and adults, including some who were previously immunized.  
8 In these cases, pertussis may not be diagnosed because classic signs, particularly the inspiratory whoop,  
9 may be absent. Older preschool-aged and school-aged children, as well as adolescents and adults who  
10 develop pertussis, may play a role in transmission to young infants.<sup>8</sup>  
11  
12 Concerns about the safety of whole-cell pertussis DTP vaccines prompted the development of less  
13 reactogenic DTaP vaccines that contain purified antigens of *B. pertussis*. The pertussis component of DTaP  
14 vaccines contains inactivated pertussis toxin and may contain one or more of FHA, PRN and fimbriae types 2  
15 and 3. DTaP vaccines were first available for use in infants in the US in 1996 and have been routinely  
16 recommended by the Advisory Committee on Immunization Practices (ACIP) for all doses of the vaccination  
17 series for infants and children <7 years of age since 1997.<sup>5</sup>  
18  
19 Since 1991, 7 studies conducted in Europe and Africa have evaluated the efficacy of 8 DTaP  
20 vaccines administered to infants. The vaccines, produced by different manufacturers, contained a  
21 varying number and quantity of antigens. The derivation and formulation of the individual antigens  
22 also varied among different vaccines. The studies differed in study design and 3, including the  
23 Sweden I Efficacy Trial (1992-1995), were randomized placebo-controlled clinical trials. Because  
24 of these and other differences, comparisons among studies should be made with caution. Within  
25 individual studies however, the efficacy of acellular pertussis vaccines can be compared directly  
26 with that of a placebo control or whole-cell pertussis DTP. The efficacy of 3 doses of acellular  
27 pertussis vaccines in preventing moderate to severe pertussis disease was within the range  
28 expected for most whole-cell pertussis DTP vaccines. Point estimates of the efficacy of DTaP  
29 vaccines ranged from 59% - 89%.<sup>5</sup>  
30  
31 The effectiveness of pertussis vaccine among US children aged 7-18 months in 1998 and 1999  
32 was calculated using the screening method. During this time, the National Immunization Survey  
33 reported 66% of children aged  $\leq 18$  months received DTaP rather than whole-cell pertussis DTP.<sup>12</sup>  
34 The screening estimate of 88% reflects the effectiveness of the overall vaccination program that  
35 used approximately two thirds DTaP and one third whole-cell pertussis DTP in children aged 7-18  
36 months. This estimate is similar to that observed in clinical trials for acellular pertussis vaccines.

1 During 1997-2000, the incidence rates were highest among infants aged <1 year, lower in children  
2 aged 1-4 years and remained stable among children aged 5-9 years.<sup>12</sup>

#### 4 **Efficacy of DAPTACEL™**

##### 5 **Pertussis**

6 A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in  
7 Sweden from 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National Institute  
8 of Allergy and Infectious Diseases (NIAID). A total of 9,829 infants received 1 of 4 vaccines:  
9 DAPTACEL™ (n = 2,587); another investigational acellular pertussis vaccine (n = 2,566); whole-  
10 cell pertussis DTP vaccine (n = 2,102); or DT vaccine as placebo (Swedish National  
11 Bacteriological Laboratory, n = 2,574). Infants were immunized at 2, 4 and 6 months of age. The  
12 mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of  
13 DAPTACEL™ against pertussis after 3 doses of vaccine using the World Health Organization  
14 (WHO) case definition ( $\geq 21$  consecutive days of paroxysmal cough with culture or serologic  
15 confirmation or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI]  
16 80.1 to 88.6).<sup>14</sup> The protective efficacy of DAPTACEL™ against mild pertussis ( $\geq 1$  day of cough  
17 with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2).<sup>15</sup> Protection against pertussis by  
18 DAPTACEL™ was sustained for the 2-year follow-up period.<sup>14,15</sup>

19  
20 In order to assess the antibody response to the pertussis antigens of DAPTACEL™ in the US  
21 population, 2 lots of DAPTACEL™, including the lot used in the Sweden I Efficacy Trial, were  
22 administered to US infants in the US Bridging Study.<sup>15</sup> In this study, antibody responses following  
23 3 doses of DAPTACEL™ given to US children at 2, 4 and 6 months of age were compared to those  
24 from a subset of the infants enrolled in the Sweden I Efficacy Trial. Assays were performed in  
25 parallel on the available sera from the US and Swedish infants. Antibody responses to all the  
26 antigens were similar except for those to the PRN component. For both lots of DAPTACEL™, the  
27 geometric mean concentration (GMC) and percent response to PRN in US infants (Lot 006,  
28 n = 107; Lot 009, n = 108) were significantly lower after 3 doses of vaccine than in Swedish infants  
29 (n = 83). In a separate study performed in Canada (Phase II), in which children received 4 doses  
30 of DAPTACEL™ at 2, 4, 6 and 17-18 months of age, antibody responses following the fourth dose  
31 (n = 275) were equivalent or higher than those seen in the Swedish infants after 3 doses. While a  
32 serologic correlate of protection for pertussis has not been established, the antibody response to  
33 all antigens in North American infants after 4 doses of DAPTACEL™ at 2, 4, 6 and 17-20 months  
34 of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated  
35 after 3 doses of DTaP at 2, 4 and 6 months of age.<sup>15</sup>

**1 Diphtheria and Tetanus**

2 In a Canadian clinical study, 324 children were enrolled to receive DAPTACEL™ at 2, 4, 6 and  
3 17-18 months of age. The proportion of children with post-dose 3 diphtheria (n = 313) and tetanus  
4 (n = 313) antitoxin levels  $\geq 0.01$  IU/mL was 100% and  $\geq 0.10$  IU/mL was 85% and 100%,  
5 respectively.<sup>15</sup> The proportion with post-dose 4 diphtheria (n = 296) and tetanus (n = 296) antitoxin  
6 levels  $\geq 0.10$  IU/mL was 100%.<sup>15</sup> The efficacy of the diphtheria and tetanus toxoids used in  
7 DAPTACEL™ was determined on the basis of immunogenicity studies with a comparison to a  
8 serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of  
9 Bacterial Vaccines and Toxoids.<sup>16</sup>

10  
11 In the US Bridging Study, for which data are only available following 3 doses, 99.2% (n = 261)  
12 achieved diphtheria antitoxin levels of  $\geq 0.01$  IU/mL, 80.6% (n = 261) achieved levels of  
13  $\geq 0.10$  IU/mL and 100% (n = 260) achieved tetanus antitoxin levels of 0.01 U/mL and 0.10 U/mL.<sup>15</sup>

14

**15 Concurrently Administered Vaccines**

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

24  
25 In the same study, hepatitis B vaccine (supplied by different manufacturers) was also given to  
26 children by different schedules. Hepatitis B vaccine was given concurrently with DAPTACEL™ at 2  
27 and 6 months of age to a subset of infants who received a birth dose of hepatitis B vaccine. Of  
28 infants with adequate serum available for serology testing (n = 82), 97% achieved anti-HBs  
29 antibody levels  $\geq 10$  mIU/mL post dose 3.<sup>15</sup>

30

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

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## 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.

- 1 • *Encephalopathy not attributable to another identifiable cause* (e.g., an acute, severe central  
2 nervous system disorder occurring within 7 days after vaccination and consisting of major  
3 alterations in consciousness, unresponsiveness or generalized or focal seizures that persist  
4 more than a few hours, without recovery within 24 hours). In such cases, DT vaccine should be  
5 administered for the remaining doses in the vaccination schedule.

6  
7 The decision to administer or delay vaccination because of a current or recent febrile illness  
8 depends on the severity of symptoms and on the etiology of the disease. According to the ACIP,  
9 all vaccines can be administered to persons with mild illness such as diarrhea, mild upper-  
10 respiratory infection with or without low-grade fever, or other low grade febrile illness.<sup>17,18</sup>  
11 However, children with moderate or serious illness should not be immunized until recovered.<sup>4</sup>  
12

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

#### 15 16 **WARNINGS**

17 The stopper to the vial of this product contains dry natural latex rubber that may cause allergic  
18 reactions.  
19

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

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

27  
28 When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be  
29 continued.<sup>4</sup>  
30

31 Because of the risk of hemorrhage, DAPTACEL™ should not be given to children with any  
32 coagulation disorder, including thrombocytopenia, which would contraindicate intramuscular  
33 injection unless the potential benefit clearly outweighs the risk of administration.  
34

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

7  
8 **If an infant or young child with a personal or family history of febrile or non-febrile**  
9 **convulsions is to be immunized, acetaminophen or other appropriate antipyretic should be**  
10 **given at the time of DTaP vaccination and for the ensuing 24 hours according to the**  
11 **respective package insert recommended dosage to reduce the possibility of post-**  
12 **vaccination fever.**<sup>4,17,18</sup>

13  
14 A committee of the Institute of Medicine (IOM) has concluded that the evidence is consistent with a  
15 causal relationship between whole-cell pertussis DTP vaccine and acute neurologic illness and,  
16 under special circumstances, between whole-cell pertussis DTP vaccine and chronic neurologic  
17 disease in the context of the National Childhood Encephalopathy Study (NCES) report.<sup>23,24</sup>  
18 However, the IOM committee concluded that the evidence was insufficient to determine whether  
19 whole-cell pertussis DTP vaccine increased the overall risk of chronic neurologic disease.<sup>24</sup> Acute  
20 encephalopathy (with or without permanent neurological injury) or permanent neurological injury  
21 has not been reported following administration of DAPTACEL™ but the experience with this  
22 vaccine is insufficient to rule this out. (See ADVERSE REACTIONS.)

23  
24 Infants and children with recognized possible or potential underlying neurologic conditions seem to  
25 be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder  
26 within 2 or 3 days following whole-cell pertussis DTP vaccine immunization.<sup>4</sup> Whether to  
27 administer DAPTACEL™ to children with proven or suspected underlying neurologic disorders  
28 must be decided on an individual basis after consideration of the risks and benefits. An important  
29 consideration includes the current local incidence of pertussis. The ACIP has issued guidelines for  
30 such children.<sup>25</sup>

**1 PRECAUTIONS****2 General**

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

4  
5 Epinephrine Hydrochloride Solution (1:1,000), other appropriate agents and equipment must be  
6 available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.  
7 Health-care providers must be familiar with current recommendations for the initial management of  
8 anaphylaxis in non-hospital settings, including proper airway management.<sup>17,26</sup>

9  
10 Before an injection of any vaccine, all known precautions should be taken to prevent adverse  
11 reactions. This includes a review of the patient's history with respect to possible sensitivity to the  
12 vaccine, similar vaccines or to dry natural latex rubber (see WARNINGS), previous immunization  
13 history, current health status (see CONTRAINDICATIONS) and a current knowledge of the  
14 literature concerning the use of the vaccine under consideration including the nature of adverse  
15 events that may follow its use.

16  
17 The expected immune response to DAPTACEL™ may not be obtained in immunosuppressed  
18 persons.<sup>4</sup> Pertussis-containing vaccines are not contraindicated in persons with HIV infection.<sup>17</sup>

19  
20 Special care should be taken to ensure that the injection does not enter a blood vessel.

21  
22 A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient  
23 to prevent transmission of hepatitis or other infectious agents from person to person. Needles  
24 should not be recapped but should be disposed of according to biohazard waste guidelines.

**25  
26 Information for Vaccine Recipients and Parents/Guardians**

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

31  
32 The physician should inform the parent or guardian about the potential for adverse reactions that  
33 have been temporally associated with DAPTACEL™ and other pertussis-containing vaccines. The  
34 health-care provider should provide the Vaccine Information Statements (VIS) which are required  
35 by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The

1 parent or guardian should be instructed to report any serious adverse reactions to their health-care  
2 provider.

3  
4 IT IS EXTREMELY IMPORTANT WHEN A CHILD RETURNS FOR THE NEXT DOSE IN THE  
5 SERIES THAT THE PARENT OR GUARDIAN SHOULD BE QUESTIONED CONCERNING ANY  
6 SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF  
7 VACCINE. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

8  
9 Adverse events following immunization should be reported by health-care providers to the Vaccine  
10 Adverse Events Reporting System (VAERS). (See ADVERSE REACTIONS, Reporting of Adverse  
11 Events.)

### 12 13 **Drug Interactions**

14 As with other intramuscular (I.M.) injections, use with caution in patients on anticoagulant therapy.

15  
16 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic  
17 drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune  
18 response to vaccines. Although no specific studies with pertussis vaccine are available, if  
19 immunosuppressive therapy is to be soon discontinued, it seems reasonable to defer immunization  
20 until the patient has been off therapy for one month; otherwise, the patient should be vaccinated  
21 while still on therapy.<sup>4</sup>

22  
23 If DAPTACEL™ is administered to persons with an immunodeficiency disorder, on  
24 immunosuppressive therapy or after a recent injection of immune globulin, an adequate  
25 immunologic response may not occur.

26  
27 For information regarding simultaneous administration with other vaccines refer to DOSAGE AND  
28 ADMINISTRATION.

29  
30 If passive immunization is needed for tetanus or diphtheria prophylaxis, Tetanus Immune Globulin  
31 (Human) (TIG), or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate  
32 needle and syringe.<sup>18</sup>

### 33 34 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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**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>14,15,27,28,29,30,31</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>14</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.

1  
2 **TABLE 1<sup>14,15</sup> PERCENTAGE OF INFANTS FROM SWEDEN I EFFICACY TRIAL WITH LOCAL OR**  
3 **SYSTEMIC REACTIONS WITHIN 24 HOURS POST-DOSE 1, 2 AND 3 OF DAPTACEL™**  
4 **COMPARED WITH DT AND WHOLE-CELL PERTUSSIS DTP VACCINES**  
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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* <sup>§</sup>	3.9	10.5
<b>Systemic</b>									
Fever <sup>†</sup> ≥38°C (100.4°F)	7.8*	7.6	72.3	19.1*	18.4	74.3	23.6*	22.1	65.1
Fretfulness <sup>††</sup>	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

7 N = Number of evaluable subjects

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

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

10 <sup>§</sup> p<0.0001: DAPTACEL™ versus DT

11 <sup>†</sup> Rectal temperature

12 <sup>††</sup> Statistical comparisons were not made for this variable

13 DT: Swedish National Biologics Laboratories

14 DTP: Aventis Pasteur Inc.

15  
16 The incidence of serious and less common selected systemic events in this trial are summarized in  
17 Table 2.<sup>14,15</sup>  
18

1

**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

2

N = Number of evaluable subjects

3

4

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>

11

12

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

14

15

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>

21

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

7  
 8 **TABLE 3**<sup>15,29</sup> **PERCENTAGE OF CHILDREN FROM PHASE II STUDY IN CANADA WITH LOCAL OR**  
 9 **SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL™**  
 10 **AND WHOLE-CELL PERTUSSIS DTP VACCINE AT 2, 4, 6 AND 17-18 MONTHS OF**  
 11 **AGE**  
 12

EVENT	Dose 1 (2 MONTHS)		Dose 2 (4 MONTHS)		Dose 3 (6 MONTHS)		Dose 4 (18 MONTHS)	
	DAPTACEL <sup>Δ</sup> N = 324	DTP <sup>†</sup> N = 108	DAPTACEL <sup>Δ</sup> N = 321	DTP <sup>†</sup> N = 106	DAPTACEL <sup>Δ</sup> N = 320	DTP <sup>†</sup> N = 104	DAPTACEL <sup>Δ</sup> N = 301	DTP <sup>†</sup> 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 <sup>‡</sup>								
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 <sup>§</sup>								
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 <sup>¶</sup>								
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>‡</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

<sup>†</sup> DTP: whole-cell pertussis DTP vaccine (Aventis Pasteur Limited)

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

<sup>‡</sup> Moderate = sustained cry with gentle pressure at injection site; Severe = cries when leg is moved

<sup>§</sup> Temperature measurements were axillary

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

<sup>‡</sup> Moderate = more difficulty with settling, even with cuddling; Severe = persistent crying/screaming and inability to console

<sup>¶</sup> Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds

<sup>¶</sup> Moderate = sleeping much more than normal; Severe = sleeping most of the time with difficulty arousing

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 22  
 23 The US Bridging Study was designed, in part, to assess the safety of DAPTACEL™ in infants at 2, 4 and 6  
 24 months of age, with routinely recommended, concurrently given childhood vaccines (*Haemophilus influenzae*  
 25 type b vaccine, OPV and hepatitis B). For adverse events, parents recorded information for 72 hours post-

1 immunization in a diary card. Local reactions were assessed and measured by the parents. Study staff  
2 collected the information from the parents during a structured telephone interview on days 4 and 14 post-  
3 immunization and recorded the information in the case report form.<sup>15</sup> The incidence of redness, swelling, pain  
4 or tenderness at the injection site and systemic symptoms after each dose is shown as pooled data from 2  
5 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  
6 subjects. The incidence of severe systemic symptoms including irritability, tiredness, anorexia, rash and  
7 vomiting ranged from 0.3% - 0.6%. One afebrile seizure occurred within 24 hours post dose 2 immunization  
8 (n = 321).<sup>15</sup>

9  
10 In an ongoing study (P3T06) initiated in May 2001 and anticipated to be completed in 2004, which was  
11 designed to assess the safety of DAPTACEL™ given with routinely recommended vaccines (*Haemophilus*  
12 *influenzae* type b vaccine, IPV, hepatitis B and pneumococcal conjugate vaccine) in the US (in which 777  
13 children have received their first dose, 350 have received their second dose and 86 their third dose with  
14 safety data still being collected from children in this study), one afebrile seizure was reported within 24 hours  
15 of receipt of dose 1.

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**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)**

<b>EVENT</b>	<b>Dose 1 (2 MONTHS) N = 321</b>	<b>Dose 2 (4 MONTHS) N = 317</b>	<b>Dose 3 (6 Months) N = 315</b>
<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

6 N = Number of evaluable subjects

7 \* Rectal temperature

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

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

10 Severe = disabling, unable to perform daily activities

11

1  
2 NIAID sponsored a multicenter Phase I/II clinical trial to compare the safety and immunogenicity of  
3 13 acellular pertussis vaccines with a conventional whole-cell pertussis DTP vaccine in infants in  
4 the US. The common local and systemic adverse experiences, after all 3 doses, for DAPTACEL™  
5 and the participating acellular vaccines that have subsequently been licensed in the US were  
6 generally similar in type and frequency and were reduced in comparison to the whole-cell pertussis  
7 DTP vaccine.<sup>28</sup>

8  
9 Additional adverse reactions evaluated in conjunction with pertussis, diphtheria and tetanus  
10 vaccination are as follows:

- 11 • As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for  
12 several weeks. Sterile abscess formation at the site of injection has been reported.<sup>4,32</sup>
- 13 • Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing,  
14 hypotension or shock) have been reported after receiving preparations containing diphtheria,  
15 tetanus and/or pertussis antigens.<sup>4</sup>

16  
17 Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting  
18 2-8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral  
19 neuropathy have been reported following tetanus toxoid administration, although the evidence is  
20 inadequate to accept or reject a causal relation.<sup>33</sup>

21  
22 A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and  
23 brachial neuritis and Guillian-Barré syndrome.<sup>34</sup> The following illnesses have been reported as  
24 temporally associated with some vaccines containing tetanus toxoid: neurological  
25 complications<sup>35,36</sup> including cochlear lesion, brachial plexus neuropathies,<sup>37</sup> paralysis of the radial  
26 nerve,<sup>33</sup> paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with  
27 encephalopathy (with or without permanent intellectual or motor function impairment).<sup>38,39</sup> In the  
28 differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing  
29 tetanus toxoid, tetanus toxoid should be considered as a possible etiology.<sup>39</sup>

30

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

8  
9 Persistent, inconsolable crying lasting  $\geq 3$  hours and high-pitched, unusual screaming, 1% and  
10 0.1% respectively, after 15,752 doses of whole-cell pertussis DTP vaccine have been reported.<sup>38</sup>  
11 Convulsions and hypotonic-hyporesponsive episodes (HHE) have each been reported to occur at a  
12 frequency of about 1:1,750 injections of whole-cell pertussis DTP.<sup>17,26,38</sup> Most convulsions are  
13 brief, generalized and self-limited and are usually associated with fever. Neither febrile nor afebrile  
14 convulsions associated with whole-cell pertussis DTP vaccine have been shown to be associated  
15 with subsequent seizure disorder.<sup>17</sup> Persistent, inconsolable crying  $\geq 3$  hours, convulsions and HHE  
16 have also been reported following DTaP vaccines, including DAPTACEL™.<sup>5</sup>

17  
18 In another large study (Sweden II Efficacy Trial), 3 DTaP vaccines and a whole-cell pertussis DTP  
19 vaccine, none of which are licensed in the US, were evaluated to assess relative safety and  
20 efficacy.<sup>41</sup> This study included HCPDT, a vaccine made of the same components as DAPTACEL™  
21 but containing twice the amount of PT and four times the amount of FHA (20  $\mu$ g pertussis toxoid  
22 and 20  $\mu$ g FHA). Hypotonic-hyporesponsive episodes (HHE) were observed following 29 (0.047%)  
23 of 61,220 doses of HCPDT; 16 (0.026%) of 61,219 doses of an acellular pertussis vaccine made  
24 by another manufacturer; and 34 (0.056%) of 60,792 doses of a whole-cell pertussis DTP vaccine.  
25 There were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of  
26 33 (0.047%) in 69,525 doses.<sup>15,41</sup> (See CONTRAINDICATIONS and PRECAUTIONS.)

27  
28 Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of whole-  
29 cell pertussis DTP and DTaP. Large case-control studies of SIDS in the US have shown that  
30 receipt of whole-cell pertussis DTP was not causally related to SIDS.<sup>42,43</sup> It should be recognized  
31 that the first 3 immunizing doses of whole-cell pertussis DTP and DTaP (including DAPTACEL™)  
32 are usually administered to infants 2-6 months of age and that approximately 85% of SIDS cases  
33 occur at ages 1-6 months with the peak incidence occurring at 6 weeks to 4 months of age. By  
34 chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP<sup>17</sup>  
35 and acellular pertussis vaccines. A review by a committee of the IOM concluded that available  
36 evidence did not indicate a causal relation between whole-cell pertussis DTP vaccine and SIDS.<sup>23</sup>

1  
2 Whole-cell pertussis DTP vaccine has been associated with acute encephalopathy.<sup>23</sup> A 10-year  
3 follow-up to the National Childhood Encephalopathy Study (NCES) of children who experienced  
4 acute neurologic disorders in infancy concluded that serious acute neurologic illness increased the  
5 risk of chronic neurologic disease or death.<sup>44</sup> A committee of the Institute of Medicine (IOM) has  
6 concluded that, because whole-cell pertussis DTP may cause acute neurologic illness, whole-cell  
7 pertussis DTP may also cause chronic neurologic disease in the context of the NCES report.<sup>24</sup>  
8 However, the IOM committee concluded that the evidence was insufficient to indicate whether or  
9 not whole-cell pertussis DTP increased the overall risk of chronic neurologic disease.<sup>24</sup>

10  
11 A bulging fontanel associated with increased intracranial pressure which occurred within 24 hours  
12 following whole-cell pertussis DTP immunization has been reported, although a causal relationship  
13 has not been established.<sup>45,46,47</sup>

#### 14 15 **Reporting of Adverse Events**

16 The National Vaccine Injury Compensation Program, established by the National Childhood  
17 Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer  
18 vaccines to maintain permanent vaccination records of the manufacturer and lot number of the  
19 vaccine administered in the vaccine recipient's permanent medical record along with the date of  
20 administration of the vaccine and the name, address and title of the person administering the  
21 vaccine. The Act (or statute) further requires the health-care professional to report to the  
22 Secretary of the US Department of Health and Human Services the occurrence following  
23 immunization of any events set forth in the statute or the Vaccine Injury Table, including  
24 anaphylaxis or anaphylactic shock within 7 days; encephalopathy or encephalitis within 7 days,  
25 brachial neuritis within 28 days; or an acute complication or sequelae (including death) of an  
26 illness, disability, injury, or condition referred to above, or any events that would contraindicate  
27 further doses of vaccine, according to this DAPTACEL™ package insert.<sup>17,48</sup>

28  
29 Reporting by parents or guardians of all adverse events after vaccine administration should be  
30 encouraged. Adverse events following immunization with vaccine should be reported by health-  
31 care providers to VAERS. Reporting forms and information about reporting requirements or  
32 completion of the form can be obtained from VAERS through a toll-free number  
33 1-800-822-7967.<sup>48,49</sup>

1 **Health-care providers should also report these events to the Pharmacovigilance**  
2 **Department, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call**  
3 **1-800-822-2463.**

#### 4 5 **DOSAGE AND ADMINISTRATION**

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

11  
12 JUST BEFORE USE, SHAKE THE VIAL WELL, until a uniform, cloudy suspension results.  
13 WITHDRAW AND INJECT A 0.5 mL DOSE. When administering a dose from a rubber-stoppered  
14 vial, do not remove either the rubber stopper or the metal seal holding it in place. Aseptic  
15 technique must be used for withdrawal of each dose.

16  
17 Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.  
18 After insertion of the needle into the muscle, aspirate to ensure that the needle has not entered a  
19 blood vessel.

20  
21 Administer the vaccine **intramuscularly** (I.M.). In children younger than 1 year (i.e., infants), the  
22 anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection.  
23 In older children, the deltoid muscle is usually large enough for I.M. injection. The vaccine should  
24 not be injected into the gluteal area or areas where there may be a major nerve trunk.<sup>17</sup>

25  
26 Fractional doses (doses <0.5 mL) should not be given. The effect of fractional doses on the  
27 frequency of serious adverse events and on efficacy has not been determined.

28  
29 *Do NOT administer this product intravenously or subcutaneously.*  
30

**1 Immunization Series**

2 A 0.5 mL dose of DAPTACEL™ is approved for administration as a 4 dose series at 2, 4 and 6  
3 months of age, at intervals of 6-8 weeks and at 17-20 months of age. (See CLINICAL  
4 PHARMACOLOGY.) The customary age for the first dose is 2 months of age, but it may be given  
5 as early as 6 weeks of age and up to the seventh birthday. The interval between the third and  
6 fourth dose should be at least 6 months. It is recommended that DAPTACEL™ be given for all  
7 doses in the series because no data on the interchangeability of DAPTACEL™ with other DTaP  
8 vaccines exist. At this time, data are insufficient to establish the frequency of adverse events  
9 following a fifth dose of DAPTACEL™ in children who have previously received 4 doses of  
10 DAPTACEL™.<sup>50</sup>

11  
12 DAPTACEL™ may be used to complete the immunization series in infants who have received 1 or  
13 more doses of whole-cell pertussis DTP. However, the safety and efficacy of DAPTACEL™ in such  
14 infants has not been fully demonstrated.<sup>5</sup>

15  
16 PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL™  
17 OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.<sup>18</sup>

18  
19 DAPTACEL™ should not be combined through reconstitution or mixed with any other vaccine.

20  
21 If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be  
22 given as needed to complete the series.

23  
24 Pre-term infants should be vaccinated according to their chronological age from birth.<sup>17</sup>

25  
26 Interruption of the recommended schedule with a delay between doses should not interfere with  
27 the final immunity achieved with DAPTACEL™. There is no need to start the series over again,  
28 regardless of the time between doses.

**29 Simultaneous Vaccine Administration**

30  
31 In clinical trials, DAPTACEL™ was routinely administered, at separate sites, concomitantly with  
32 one or more of the following vaccines: OPV, hepatitis B vaccine and *Haemophilus influenzae*  
33 type b vaccine.<sup>15</sup> No safety and immunogenicity data are currently available on the simultaneous  
34 administration of pneumococcal conjugate vaccine, MMR vaccine and varicella vaccine and no  
35 immunogenicity data are currently available on the simultaneous administration of IPV. Two  
36 afebrile seizures, occurring within 24 hours of immunization, have been reported from 2 US trials

1 where DAPTACEL™ was given with other concomitant vaccines. (See ADVERSE REACTIONS.)  
2 When concomitant administration of other vaccines is required, they should be given with different  
3 syringes and at different injection sites.  
4

5 ACIP encourages routine simultaneous administration of DTaP, IPV, *Haemophilus influenzae*  
6 type b vaccine, pneumococcal conjugate vaccine, MMR, varicella vaccine and hepatitis B vaccine  
7 for children who are the recommended age to receive these vaccines and for whom no specific  
8 contraindications exist at the time of the visit, unless, in the judgment of the provider, complete  
9 vaccination of the child will not be compromised by administering different vaccines at different  
10 visits. Simultaneous administration is particularly important if the child might not return for  
11 subsequent vaccinations.<sup>18</sup> (See CLINICAL PHARMACOLOGY.)  
12

13 If passive immunization is needed for tetanus prophylaxis, Tetanus Immune Globulin (Human)  
14 (TIG) is the product of choice. It provides longer protection than antitoxin of animal origin and is  
15 associated with few adverse reactions. The currently recommended prophylactic dose of TIG for  
16 wounds of average severity is 250 units intramuscularly. When tetanus toxoid-containing vaccines  
17 and TIG and/or Diphtheria Antitoxin are administered concurrently, separate syringes and separate  
18 sites should be used.  
19

#### 20 **HOW SUPPLIED**

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

22 Vial, 5 x 1 Dose - Product No. 49281-286-05  
23

#### 24 **STORAGE**

25 DAPTACEL™ should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has  
26 been exposed to freezing should not be used. Do not use after expiration date.  
27

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