

253 2023531

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed DAPTACEL[®]

DTaP

Rx only



DESCRIPTION

DAPTACEL[®], Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, for intramuscular use, is a sterile isotonic suspension of pertussis antigens and diphtheria and tetanus toxoids adsorbed on aluminum phosphate. After shaking, the vaccine is a white homogeneous cloudy suspension. Each 0.5 mL dose of DAPTACEL vaccine contains the following active ingredients:

acellular pertussis	
detoxified pertussis toxin (PT)	10 µg
filamentous haemagglutinin (FHA)	5 µg
fimbriae types 2 and 3 (FIM)	5 µg
pertactin (PRN)	3 µg
diphtheria toxoid	15 Lf
tetanus toxoid	5 Lf

Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg of aluminum) as the adjuvant, ≤5 µg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative).

The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (1) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. The FIM components are extracted and co-purified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde, and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (2) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. *Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (3) Tetanus toxin is detoxified with formaldehyde 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 with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection.

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 detoxified PT, FHA, FIM and PRN as measured by enzyme-linked immunosorbent assay (ELISA).

CLINICAL PHARMACOLOGY

The efficacy of DAPTACEL vaccine against pertussis was evaluated in a clinical efficacy study conducted in Sweden (Sweden I Efficacy Trial). Antibody responses to the pertussis antigens were evaluated in a US Bridging study in which infants received three doses of DAPTACEL vaccine, a Canadian study in which children received four doses of DAPTACEL vaccine, and a US study in which children received four doses of DAPTACEL vaccine administered concomitantly with other routinely recommended vaccines. In each of these studies, the efficacy of DAPTACEL vaccine against diphtheria and tetanus was evaluated on the basis of antibody responses using established serologic correlates of protection.

Diphtheria

Strains of *C diphtheriae* that produce diphtheria toxin can cause severe or fatal illness characterized by membranous inflammation of the upper respiratory tract and toxin-induced damage to the myocardium and nervous system. Protection against disease attributable to toxin-producing strains of *C diphtheriae* is due to the development of neutralizing antibodies to the toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (4) Levels of 1.0 IU/mL have been associated with long term protection. (5)

In the US study in which children received 4 doses of DAPTACEL vaccine at 2, 4, 6 and 15-17 months of age, after the third dose, 100% (N = 1,099) achieved diphtheria antitoxin levels of ≥0.01 IU/mL and 98.5% achieved diphtheria antitoxin levels of ≥0.10 IU/mL. Among a random subset of children who received the fourth dose of DAPTACEL vaccine at 15-16 months of age, 96.5% (N = 659) achieved diphtheria antitoxin levels of ≥1.0 IU/mL after the fourth dose.

Tetanus

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C tetani*. The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. Protection against disease attributable to *C tetani* is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (4) (6) A tetanus antitoxin level ≥ 0.1 IU/mL as measured by the ELISA used in clinical studies of DAPTACEL vaccine is considered protective.

In the US study in which children received 4 doses of DAPTACEL vaccine at 2, 4, 6 and 15-17 months of age, after the third dose, 100% (N = 1,037) achieved tetanus antitoxin levels of ≥ 0.10 IU/mL. Among a random subset of children who received the fourth dose of DAPTACEL vaccine at 15-16 months of age, 98.8% (N = 681) achieved tetanus antitoxin levels of ≥ 1.0 IU/mL after the fourth dose.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B pertussis*. This gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

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. A total of 9,829 infants received 1 of 4 vaccines: DAPTACEL vaccine (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 vaccine against pertussis after 3 doses using the World Health Organization (WHO) case definition (≥ 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). The protective efficacy of DAPTACEL vaccine against mild pertussis (≥ 1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by DAPTACEL vaccine was sustained for the 2-year follow-up period.

In order to assess the antibody response to the pertussis antigens of DAPTACEL vaccine in the US population, 2 lots of DAPTACEL vaccine, including the lot used in the Sweden I Efficacy Trial, were administered to US infants in the US Bridging Study. In this study, antibody responses following 3 doses of DAPTACEL vaccine 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 vaccine, 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 separate US and Canadian studies in which children received DAPTACEL vaccine at 2, 4 and 6 months of age, with a fourth dose at either 17-20 months (Canadian study) or 15-16 months (random subset from US study) of age, antibody responses to each pertussis antigen following the fourth dose (Canadian study N = 275; US study N = 237-347) were at least as high as 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 vaccine at 2, 4, 6 and 15-20 months of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated after 3 doses of DAPTACEL vaccine at 2, 4 and 6 months of age.

Concurrently Administered Vaccines

In the US Bridging study, DAPTACEL vaccine was given simultaneously with *Haemophilus influenzae* type b (Hib) conjugate vaccine according to local practices. Anti-PRP immune response was evaluated in 261 infants who received 3 doses of Hib conjugate vaccine. One month after the third dose, 96.9% achieved anti-PRP antibody levels of at least 0.15 $\mu\text{g/mL}$ and 82.7% achieved antibody levels of at least 1.0 $\mu\text{g/mL}$.

In the US study in which children received 4 doses of DAPTACEL vaccine, Hib conjugate (tetanus toxoid conjugate) vaccine and inactivated poliovirus vaccine (IPV), both manufactured by sanofi pasteur, and 7-valent pneumococcal conjugate vaccine manufactured by Wyeth Pharmaceuticals Inc. were concomitantly administered with DAPTACEL vaccine at 2, 4 and 6 months of age. Infants received the first dose of Hepatitis B vaccine (recombinant) (manufacturer unspecified) at 0 months of age. At 2 and 6 months of age, Hepatitis B vaccine (recombinant) manufactured by Merck and Co. was concomitantly administered with DAPTACEL vaccine. At 7 months of age, 100.0% of subjects (N = 1,050-1,097) had protective neutralizing antibody levels ($\geq 1:8$ 1/dil) for poliovirus types 1, 2 and 3; and 92.4% (N = 998) achieved anti-hepatitis B surface antigen levels ≥ 10.0 mIU/mL. Although there is no established serologic correlate of protection for any of the pneumococcal serotypes, at 7 months of age 91.3%-98.9% (N = 1,027-1,029) achieved anti-pneumococcal polysaccharide levels ≥ 0.5 $\mu\text{g/mL}$ for serotypes 4, 9V, 14, 18C, 19F and 23F and 80.7% (N = 1,027) achieved an anti-pneumococcal polysaccharide level ≥ 0.5 $\mu\text{g/mL}$ for serotype 6B. Measles, mumps and rubella vaccine (MMR) and varicella vaccine manufactured by Merck and Co. and the same Hib and 7-valent pneumococcal conjugate vaccines used for the first three doses, were given at 15-16 months of age concomitantly (N = 307) or non-concomitantly (N = 312) with the fourth dose of DAPTACEL vaccine. The mumps seroresponse rate was lower when DAPTACEL vaccine was administered concomitantly (86.6%) vs. non-concomitantly (90.1%) with MMR [upper limit of 90% confidence interval for difference in rates (non-concomitant minus concomitant) $>5\%$]. There was no evidence for interference in the immune response to the measles, rubella, and varicella antigens or to the fourth dose of the 7-valent pneumococcal conjugate vaccine with concomitant administration of the fourth dose of DAPTACEL vaccine.

INDICATIONS AND USAGE

DAPTACEL vaccine 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). Vaccination with DAPTACEL vaccine may not protect 100% of individuals.

CONTRAINDICATIONS

Known systemic hypersensitivity to any component of DAPTACEL vaccine is a contraindication to administration of DAPTACEL vaccine. (See **DESCRIPTION**.) A serious allergic reaction (eg, anaphylaxis) after a previous dose of DAPTACEL vaccine or any other tetanus toxoid, diphtheria toxoid, or pertussis-containing vaccine, or any component of this vaccine is a contraindication to administration of DAPTACEL vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are considered.

The following events are contraindications to administration of any pertussis-containing vaccine, (7) including DAPTACEL vaccine:

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

WARNINGS

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

DAPTACEL vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risks of administration. If the decision is made to administer DAPTACEL vaccine in such persons, it should be given with caution, with steps taken to avoid hematoma formation following injection.

If any of the following events occur within the specified period after administration of a whole-cell pertussis vaccine or a vaccine containing an acellular pertussis component, the decision to administer DAPTACEL vaccine should be based on careful consideration of potential benefits and possible risks. (7) When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be continued.

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

If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give DAPTACEL vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (7)

The ACIP has published guidelines for vaccination of persons with recent or acute illness. (7)

PRECAUTIONS**General**

Before administration of DAPTACEL vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS**.)

Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

For infants or children at higher risk for seizures than the general population, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL vaccine) and for the following 24 hours, to reduce the possibility of post-vaccination fever. (7)

If DAPTACEL vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and Parents/Guardians

Before administration of DAPTACEL 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.

The health-care provider should inform the parent or guardian about the potential for adverse reactions that have been temporally associated with DAPTACEL vaccine and other vaccines containing similar components. 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.

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting adverse events after vaccination to VAERS by parents or guardians should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to DAPTACEL vaccine.

For information regarding simultaneous administration with other vaccines refer to **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy Category C

Animal reproduction studies have not been conducted with DAPTACEL vaccine. It is also not known whether DAPTACEL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. DAPTACEL vaccine is not indicated for women of child-bearing age.

Geriatric Use

DAPTACEL vaccine is not indicated for use in adult populations.

Pediatric Use

Safety and effectiveness of DAPTACEL vaccine in infants below 6 weeks of age have not been established.

DAPTACEL vaccine is not indicated for persons 7 years of age or older.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

A total of 16,928 doses of DAPTACEL vaccine have been administered to infants and toddlers in 7 clinical studies. In all, 4,998 children received 3 doses and 1,725 of these children received 4 doses of DAPTACEL vaccine.

In the Sweden I Efficacy Trial, DAPTACEL vaccine 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 vaccine than following the whole-cell pertussis DTP vaccine. As shown in Table 1, the 2,587 infants who enrolled to receive DAPTACEL vaccine 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.

Table 1 Percentage of Infants from Sweden I Efficacy Trial with Local or Systemic Reactions within 24 Hours Post-Dose 1, 2 and 3 of DAPTACEL vaccine compared with DT and Whole-Cell Pertussis DTP Vaccines

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL vaccine N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL vaccine N = 2,563	DT N = 2,555	DTP N = 2,040	DAPTACEL vaccine N = 2,549	DT N = 2,538	DTP N = 2,001
Local									
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
Systemic									
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 vaccine versus whole-cell pertussis DTP
 ** p<0.003: DAPTACEL vaccine versus whole-cell pertussis DTP
 § p<0.0001: DAPTACEL vaccine versus DT
 † Rectal temperature
 †† Statistical comparisons were not made for this variable
 DT: Swedish National Biologics Laboratories
 DTP: Sanofi Pasteur Inc.

The incidence of serious and less common selected systemic events in the Sweden I Efficacy Trial is summarized in Table 2.

Table 2 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 vaccine N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL vaccine N = 2,565	DT N = 2,556	DTP N = 2,040	DAPTACEL vaccine 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

In the Sweden I Efficacy Trial, one case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL vaccine. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL vaccine. Over the entire study period, 6 seizures were reported in the DAPTACEL vaccine 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 vaccine group. There were no instances of invasive bacterial infection or death.

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

In the US study in which children received 4 doses of DAPTACEL vaccine, safety was assessed by monitoring solicited local and systemic adverse events and unsolicited adverse events within 7 days of vaccination, events that required a telephone call or visit to the physician's office or an emergency room visit within 60 days of vaccination and serious adverse events through 6 months following the fourth dose. Solicited adverse events were recorded daily in a diary card. For Days 0 and 1 following the first three doses of DAPTACEL vaccine, events solicited in the diary card included signs and symptoms of hypotonic-hyporesponsive episodes (HHE). Telephone calls to inquire about adverse events were made at Day 2 or 3, Day 8, Day 30, and Day 60 after each dose and 6 months after the fourth dose.

In this US study in which children received 4 doses of DAPTACEL vaccine, DAPTACEL vaccine was given concomitantly with Hib and 7-valent pneumococcal conjugate vaccine and IPV at 2, 4 and 6 months of age and also concomitantly with hepatitis B vaccine at 2 and 6 months of age. Children who received the first three doses of DAPTACEL vaccine were randomized to one of three groups for the fourth dose. Children in Group 1 were given MMR, varicella vaccine and 7-valent pneumococcal conjugate vaccine at 12 months of age and DAPTACEL vaccine concomitantly with HIB conjugate vaccine at 15-16 months of age. Children in Group 2 were given DAPTACEL vaccine concomitantly with Hib and 7-valent pneumococcal conjugate vaccines, MMR, and varicella vaccine at 15-16 months of age. Children in Group 3 were given Hib and 7-valent pneumococcal conjugate vaccines, MMR, and varicella vaccine at 15-16 months of age and DAPTACEL vaccine alone at 16-17 months of age.

In the US study in which children received 4 doses of DAPTACEL vaccine, a total of 1,454 infants received DAPTACEL vaccine and were included in the safety analyses. Of these 51.7% were female, 77.2% Caucasian, 6.3% Black, 6.5% Hispanic, 0.9% Asian and 9.1% other races. The incidence and severity of selected solicited local and systemic adverse events that occurred within 3 days of DAPTACEL vaccination are shown in Table 3. In the table, Groups 1, 2 and 3 were pooled for the fourth dose.

Table 3 Number (Percentage) of Children from US Study with Selected Solicited Local and Systemic Adverse Events by Severity Occurring Between 0 to 3 Days after Each Dose of DAPTACEL Vaccine

		Dose 1 N = 1390-1406 %	Dose 2 N = 1346-1360 %	Dose 3 N = 1301-1312 %	Dose 4 N = 1118-1144 %^
Local Events (DAPTACEL vaccine injection site)					
Redness	>5 mm	6.2	7.1	9.6	17.3
	>5 - <25 mm	5.2	6.6	7.7	7.9
	25 - 50 mm	0.6	0.5	1.9	6.3
	>50 mm	0.4	0.1	0.0	3.1
Swelling	>5 mm	4.0	4.0	6.5	11.7
	>5 - <25 mm	2.4	3.3	5.4	7.0
	25 - 50 mm	1.2	0.6	1.0	3.2
	>50 mm	0.4	0.1	0.1	1.6
Tenderness*	Any	48.8	38.2	40.9	49.5
	Mild	28.1	26.0	28.7	35.0
	Moderate	16.5	9.9	10.6	12.3
	Severe	4.1	2.3	1.7	2.2
Increase in Arm Circumference†	>5 mm				30.1
	>5 - <20 mm	-	-	-	22.7
	20 - 40 mm				7.0
	>40 mm				0.4
Systemic Events					
Fever‡	>38.0°C	9.3	16.1	15.8	10.5
	38.0-38.5°C	7.7	11.8	10.7	7.0
	>38.5-39.5°C	1.5	3.9	4.8	2.7
	>39.5°C	0.1	0.4	0.3	0.7
Decreased Activity§	Any	51.1	37.4	33.2	25.3
	Mild	26.8	21.5	20.5	16.0
	Moderate	23.0	14.4	12.1	8.2
	Severe	1.2	1.4	0.6	1.0
Inconsolable Crying	Any	58.5	51.4	47.9	37.1
	<1 Hour	42.1	35.4	35.7	27.9
	1-3 Hours	14.2	12.6	10.8	7.7
	>3 Hours	2.2	3.4	1.4	1.5
Fussiness	Any	75.8	70.7	67.1	54.4
	<1 Hour	42.5	40.2	40.9	34.1
	1-3 Hours	27.7	25.0	22.0	16.3
	>3 Hours	5.6	5.5	4.3	3.9

* Mild: subject whimpers when site is touched, no crying; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.

† The circumference of the DAPTACEL vaccine-injected arm at the level of the axilla was monitored following the fourth dose only. Increase in arm circumference was calculated by subtracting the baseline circumference pre-vaccination (Day 0) from the circumference post-vaccination.

‡ The protocol specified that temperatures should be measured rectally. For Doses 1-3, 53.7% of temperatures were measured rectally, 45.1% were measured axillary, 1.0% were measured orally, and 0.1% were measured by an unspecified route. For Dose 4, 35.7% of temperatures were measured rectally, 62.3% were measured axillary, 1.5% were measured orally, and 0.5% were measured by an unspecified route. Fever is based upon actual temperatures recorded with no adjustments to the measurement for route.

§ Mild: usual daily activity is not affected; Moderate: interferes with and limits usual daily activity; Severe: disabling, not interested in usual daily activity.

^ For the fourth dose of DAPTACEL vaccine, data are pooled for Groups 1, 2 and 3 (see text for details regarding concomitantly administered vaccines for each Group). In general, the incidence of solicited systemic events following DAPTACEL vaccine was highest in Group 2. Rates of adverse events following vaccines not co-administered with DAPTACEL vaccine are not presented.

In the US study in which children received four doses of DAPTACEL vaccine, of 1,455 subjects who received DAPTACEL vaccine, 5 (0.3%) subjects experienced a seizure within 60 days following any dose of DAPTACEL vaccine. One seizure occurred within 7 days post-vaccination: an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days post-vaccination, 3 were associated with fever. In this study, there were no reported cases of HHE following DAPTACEL vaccine.

In the US study in which children received 4 doses of DAPTACEL vaccine, there was one death due to aspiration 222 days post-vaccination in a subject with ependymoma. Within 30 days following any dose of DAPTACEL vaccine, 57 (3.9%) subjects reported at least one serious adverse event. During this period, the most frequently reported serious adverse event was bronchiolitis, reported in 28 (1.9%) subjects. Other serious adverse events that occurred within 30 days following DAPTACEL vaccine included three cases of pneumonia, two cases of meningitis and one case each of sepsis, pertussis (post-dose 1), irritability and unresponsiveness.

In another 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. This study included HCPDT, a vaccine made of the same components as DAPTACEL vaccine but containing twice the amount of detoxified PT and four times the amount of FHA (20 µg detoxified PT and 20 µg FHA). HHE was 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.

Data From Post-Marketing Experience

The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on severity, frequency of reporting or the strength of causal association to DAPTACEL vaccine.

- **Cardiac disorders**
Cyanosis
- **Gastro-intestinal disorders**
Nausea, diarrhea
- **General disorders and administration site conditions:**
Local reactions: injection site pain, injection site rash, injection site nodule, injection site mass
- **Infections and infestations**
Injection site cellulitis, cellulitis, injection site abscess
- **Immune system disorders**
Hypersensitivity, allergic reaction, anaphylactic reaction (edema, face edema, swelling face, pruritus, rash generalized and other types of rash (erythematous, macular, maculo-papular))
- **Nervous system disorders**
Convulsions: febrile convulsion, grand mal convulsion, partial seizures
Hypotonic-hyporesponsive episode, hypotonia, somnolence
- **Psychiatric disorders**
Screaming

Additional Adverse Reactions

Additional adverse reactions, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria toxoid, tetanus toxoid and/or pertussis antigens.

Anaphylaxis has been reported after receipt of some preparations containing diphtheria toxoid, tetanus toxoid, and/or pertussis antigens.

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid.

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (8)

A few cases of demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies have been reported following vaccines containing tetanus and/or diphtheria toxoids, although the IOM concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccination. (8)

Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of DTaP vaccines. By chance alone, some cases of SIDS can be expected to follow receipt of DTaP vaccines.

Reporting of Adverse Events

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 further requires the health-care provider to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in 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 vaccine package insert. (9) These events should be reported 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 or through www.vaers.hhs.gov.

Reporting adverse events after vaccination to VAERS by parents or guardians should also be encouraged.

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

DOSAGE AND ADMINISTRATION

Just before use, shake the vial well, until a uniform, cloudy suspension results. Inspect the vial visually for extraneous particulate matter and/or discoloration before administration. If these conditions exist, the product should not be administered.

When withdrawing 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. A separate, sterile syringe and needle, or a sterile disposable unit, must be used for each person to prevent transmission of blood-borne infectious agents. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

Each 0.5 mL dose of DAPTACEL vaccine is to be administered intramuscularly. In infants younger than 1 year, 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 injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously or subcutaneously.

Immunization Series

DAPTACEL vaccine 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 15-20 months of age. Four doses of DAPTACEL vaccine constitute a primary immunization course for pertussis. Three doses of DAPTACEL vaccine constitute a primary immunization course for diphtheria and tetanus; the fourth dose constitutes a booster for diphtheria and tetanus. (See **CLINICAL PHARMACOLOGY**.) The customary age for the first dose is 2 months, but it may be given as early as 6 weeks of age. The recommended interval between the third and fourth dose is 6-12 months. (7) At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL vaccine in children who have previously received 4 doses of DAPTACEL vaccine.

Data are not available on the safety and immunogenicity of using mixed sequences of DAPTACEL vaccine and DTaP vaccines from different manufacturers for successive doses of the DTaP vaccination series. DAPTACEL vaccine 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 vaccine in such infants have not been fully demonstrated.

Persons 7 years of age or older should not be administered DAPTACEL vaccine.

DAPTACEL vaccine 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. (7)

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with DAPTACEL vaccine. There is no need to start the series over again, regardless of the time between doses. (7)

Concomitant Administration with Other Vaccines

In clinical trials, DAPTACEL vaccine has been administered, at separate sites, concomitantly with one or more of the following: Hib conjugate, IPV, hepatitis B, 7-valent pneumococcal conjugate, MMR and varicella vaccines. (See **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS**.) When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

HOW SUPPLIED

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

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

Vial, 10 x 1 Dose - Product No. 49281-286-10

CPT® Code: **90700**

CPT is a registered trademark of the American Medical Association.

STORAGE

DAPTACEL vaccine 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;63:211-20.
- 2 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings 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 91-1174. 1991. p. 7-11.
- 3 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J Bacteriol 1954;67(3):271-7.
- 4 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):51002-117.
- 5 Wharton M, et al. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia, PA: W. B. Saunders 2004 p. 211-28.
- 6 Wassilak SGF, et al. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia, PA: W. B. Saunders 2004 p. 745-81.
- 7 CDC. General recommendations on immunization: Recommendations of the ACIP and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR-2):1-35. <http://www.cdc.gov/mmwr/PDF/rr/rr5102.pdf>
- 8 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington D.C.: National Academy Press. 1994. p. 67-117.
- 9 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.

Product information as of November 2006.

Printed in Canada.

Manufactured by:

Sanofi Pasteur Limited
Toronto Ontario Canada

Distributed by:

Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

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

R4-1106 USA
D72-372MQ
2023531-253

sanofi pasteur