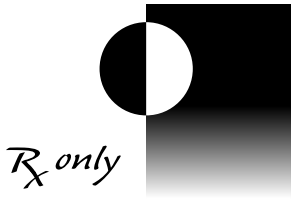
AHFS Category 80:08

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed



DAPTACEL®

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 2-phenoxyethanol (not as a 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[1] modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. The fimbriae types 2 and 3 are extracted from the bacterial cells and the pertussis toxin, FHA and PRN are prepared from the supernatant. These proteins are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. Pertussis toxin is inactivated with glutaraldehyde and FHA is treated with formaldehyde. The individual antigens are adsorbed separately onto aluminum phosphate.

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

The adsorbed diphtheria, tetanus and acellular pertussis components are combined in a sterile isotonic sodium chloride solution containing 2-phenoxyethanol (not as a preservative).

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

CLINICAL PHARMACOLOGY

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

Diphtheria

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

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

Prior to the widespread use of diphtheria toxoid in the late 1940s, diphtheria disease was common in the US. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5% - 10% of cases were fatal; the highest case-fatality rates were in the very young and the elderly. More recently, reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. After 1979, cutaneous diphtheria was no longer reportable.[4] From 1980 through 2000, only 50 cases of diphtheria were reported in the US. During the period 1980-1996, six fatal cases of diphtheria were reported. Only 1 case of diphtheria was reported each year in 1998-2000 with no fatalities.[7] Of 40 reported cases with known age in 1982-1998, 63% were in persons ≥20 years of age. Most cases have occurred in unimmunized or inadequately immunized persons. Although diphtheria disease is rare in the US, it appears that *C. diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria.[8]

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

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

EVENT	Dose 1 (2 MONTHS) N = 321	Dose 2 (4 MONTHS) N = 317	Dose 3 (6 Months) N = 315
Local			
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
Systemic			
Fever*†			
Any ≥38°C (100.4°F)	11.9	9.9	9.9
≥39°C (102.2°F)	0.3	0.3	0.6
≥40°C (104°F)	0	0	0
Irritability			
Any	72.0	61.2	56.2
Moderate + Severe	33.6	25.2	18.7
Severe	0.3	0.3	0
Anorexia			
Any	26.2	14.8	17.8
Moderate + Severe	5.6	3.8	4.8
Severe	0	0.3	0
Drowsiness			
Any	62.0	44.8	35.6
Moderate + Severe	24.0	8.5	7.3
Severe	0.6	0.3	0
Crying ≥3 Hours	0.3	0	0

N = Number of evaluable subjects
* Rectal temperature
† N = 319, 314 and 313 at 2, 4 and 6 months respectively
Moderate = discomforting enough to interfere with or limit usual daily activity
Severe = disabling, unable to perform daily activities

NIAID sponsored a multicenter Phase I/II clinical trial to compare the safety and immunogenicity of 13 acellular pertussis vaccines with a conventional whole-cell pertussis DTP vaccine in infants in the US. The common local and systemic adverse experiences, after all 3 doses, for DAPTACEL® and the participating acellular vaccines that have subsequently been licensed in the US were generally similar in type and frequency and were reduced in comparison to the whole-cell pertussis DTP vaccine.[29]

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

- As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for several weeks. Sterile abscess formation at the site of injection has been reported.[4,33]
- Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing, hypotension or shock) have been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.[4]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.[34]

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.[35] The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications[36,37] including cochlear lesion, brachial plexus neuropathies,[38] paralysis of the radial nerve,[34] paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).[39,40] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[40]

Onset of infantile spasms has occurred in infants who have recently received whole-cell pertussis DTP or DT. Analysis of data from the National Childhood Encephalopathy Study (NCES) on children with infantile spasms failed to demonstrate that receipt of DT or whole-cell pertussis DTP vaccines was causally related to infantile spasms.[24,41] The incidence of onset of infantile spasms increases at 3-9 months of age, the time period in which the second and third doses of whole-cell pertussis DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of whole-cell pertussis DTP.[4]

Persistent, inconsolable crying lasting ≥3 hours and high-pitched, unusual screaming, 1% and 0.1% respectively, after 15,752 doses of whole-cell pertussis DTP vaccine have been reported.[39] Convulsions and hypotonic-hyporesponsive episodes (HHE) have each been reported to occur at a frequency of about 1:1,750 injections of whole-cell pertussis DTP.[17,27,39] Most convulsions are brief, generalized and self-limited and are usually associated with fever. Neither febrile nor afebrile convulsions associated with whole-cell pertussis DTP vaccine have been shown to be associated with subsequent seizure disorder.[17] Persistent, inconsolable crying ≥3 hours, convulsions and HHE have also been reported following DTaP vaccines, including DAPTACEL®.[5]

In another large study (Sweden II Efficacy Trial), 3 DTaP vaccines and a whole-cell pertussis DTP vaccine, none of which are licensed in the US, were evaluated to assess relative safety and efficacy.[42] This study included HCPDT, a vaccine made of the same components as DAPTACEL® but containing twice the amount of PT and four times the amount of FHA (20 µg pertussis toxoid and 20 µg FHA). Hypotonic-hyporesponsive episodes (HHE) were observed following 29 (0.047%) of 61,220 doses of HCPDT; 16 (0.026%) of 61,219 doses of an acellular pertussis vaccine made by another manufacturer; and 34 (0.056%) of 60,792 doses of a whole-cell pertussis DTP vaccine. There were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of 33 (0.047%) in 69,525 doses.[15,42] (See CONTRAINDICATIONS and PRECAUTIONS.)

Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of whole-cell pertussis DTP and DTaP. Large case-control studies of SIDS in the US have shown that receipt of whole-cell pertussis DTP was not causally related to SIDS.[43,44] It should be recognized that the first 3 immunizing doses of whole-cell pertussis DTP and DTaP (including DAPTACEL®) are usually administered to infants 2-6 months of age and that approximately 85% of SIDS cases occur at ages 1-6 months with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP[17] and acellular pertussis vaccines. A review by a committee of the IOM concluded that available evidence did not indicate a causal relation between whole-cell pertussis DTP vaccine and SIDS.[24]

Whole-cell pertussis DTP vaccine has been associated with acute encephalopathy.[24] A 10-year follow-up to the National Childhood Encephalopathy Study (NCES) of children who experienced acute neurologic disorders in infancy concluded that serious acute neurologic illness increased the risk of chronic neurologic disease or death.[45] A committee of the Institute of Medicine (IOM) has concluded that, because whole-cell pertussis DTP may cause acute neurologic illness, whole-cell pertussis DTP may also cause chronic neurologic disease in the context of the NCES report.[25] However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell pertussis DTP increased the overall risk of chronic neurologic disease.[25]

A bulging fontanel associated with increased intracranial pressure which occurred within 24 hours following whole-cell pertussis DTP immunization has been reported, although a causal relationship has not been established.[46,47,48]

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act (or statute) further requires the health-care professional to report to the Secretary of the US Department of Health and Human Services the occurrence following immunization of any events set forth in the statute or the Vaccine Injury Table, including anaphylaxis or anaphylactic shock within 7 days; encephalopathy or encephalitis within 7 days, brachial neuritis within 28 days; or an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this DAPTACEL® package insert.[17,49]

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[49,50]

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Do NOT administer this product intravenously or subcutaneously.

Immunization Series
A 0.5 mL dose of DAPTACEL® is approved for administration as a 4 dose series at 2, 4 and 6 months of age, at intervals of 6-8 weeks and at 17-20 months of age. (See CLINICAL PHARMACOLOGY.) The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The interval between the third and fourth dose should be at least 6 months. It is recommended that DAPTACEL® be given for all doses in the series because no data on the interchangeability of DAPTACEL® with other DTaP vaccines exist. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL® in children who have previously received 4 doses of DAPTACEL®.[51]

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

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.[18]

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

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

Pre-term infants should be vaccinated according to their chronological age from birth.[17]

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

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

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

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

HOW SUPPLIED
Vial, 1 x 1 Dose - Product No. 49281-286-01
Vial, 5 x 1 Dose - Product No. 49281-286-05
Vial, 10 x 1 Dose - Product No. 49281-286-10

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

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