Tetanus and Diphtheria Toxoids Adsorbed
For Adult Use

℞ only

DESCRIPTION

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is a sterile, cloudy, white, uniform suspension of tetanus and diphtheria toxoids adsorbed on aluminum phosphate and suspended in isotonic sodium chloride solution for intramuscular injection only.

Tetanus toxoid is prepared from the toxin produced during the growth of a selected strain of *Clostridium tetani.* The toxin is converted to toxoid by the addition of formalin, concentrated and then purified. The culture medium consists of a tryptic digest of casein, supplemented with cystine, dextrose, uracil, inorganic salts and vitamins.

Diphtheria toxoid is prepared from the toxin produced during the growth of a selected strain of *Corynebacterium diphtheriae* grown with aeration in submerged culture. The toxin is purified by precipitation, converted to toxoid by the addition of formalin and concentrated by ultrafiltration. The culture medium consists of a tryptic digest of casein, supplemented with cystine, maltose, inorganic salts and vitamins.

Each dose (0.5 mL) is formulated to contain:

tetanus toxoid	5 Lf
diphtheria toxoid	2 Lf

Other ingredients per dose include 3 mg of 2-phenoxyethanol as the preservative, 1.5 mg of aluminum phosphate equivalent to 0.33 mg of aluminum as the adjuvant, and no more than 0.1 mg of residual formaldehyde.

When tested in guinea pigs, the tetanus component induces at least 2 neutralizing units/mL of serum and the diphtheria component induces at least 0.5 neutralizing units/mL of serum.

CLINICAL PHARMACOLOGY

In the United States, immunization against tetanus and diphtheria became widespread in the late 1940s, and resulted in a striking decrease in the incidence of morbidity and mortality from these diseases.

Tetanus

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *Clostridium tetani.* The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. The muscle spasms usually involve the jaw (lockjaw) and neck and then become generalized.

The occurrence of tetanus disease in the US decreased steadily from 560 reported cases in 1947 to an average of 43 cases reported annually during 1998-2000. Among patients with known outcome, the case-fatality ratio during 1998-2000 was 18%, 5 times lower than the case-fatality ratio of 91% reported in 1947. In the mid to late 1990s, the age distribution of reported tetanus cases among adults shifted to a younger age group. Among cases reported during 1998-2000, 9% were <20 years of age, 55% were 20-59 years of age, and 36% were ≥60 years of age. In previous decades, most cases were among persons ≥60 years of age. Adults ≥60 years of age continue to have the highest rates of tetanus and tetanus-related deaths. The majority of tetanus cases during 1998-2000 occurred among persons who were not appropriately vaccinated against tetanus or who had an unknown vaccination history.[1]

Neonatal tetanus occurs among infants born under unhygienic conditions to inadequately vaccinated mothers. Vaccinated mothers confer protection to their infants through transplacental transfer of maternal antibody.[2] From 1998 through 2000, one case of neonatal tetanus was reported in the US.[1]

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the US. Thus, universal primary immunization, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect all age groups.[2] Following adequate immunization with tetanus toxoid, it is thought that protection persists for at least 10 years. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.[3,4] More recently, a level ≥0.1 to 0.2 IU/mL has been considered as protective.[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.* Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal respiratory infections than with cutaneous infections.[2]

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.[2] From 1980 through 2000, 51 cases of diphtheria were reported in the US, an average of 2 or 3 cases per year. Only one case was reported each year in 1998, 1999, and 2000. The case-fatality rate for diphtheria has changed very little since the 1950s. Of 49 reported cases with known age during the period 1980-2000, 55% were in persons ≥20 years of age; 43% were among persons ≥40 years of age.[6] 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.[6]

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in the newly independent states of the former Soviet Union beginning in 1990. This epidemic resulted in approximately 150,000 cases and 5,000 deaths during the years 1990-1998.[7] This outbreak is believed to be due to several factors, including a lack of routine immunization of adults in these countries.[8]

Complete immunization significantly reduces the risk of developing diphtheria and immunized persons who develop disease have milder illness. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum 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] Following adequate immunization with diphtheria toxoid, it is thought that protection persists for ≥10 years.[9] Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheria*e in the pharynx, nose, or on the skin.

Efficacy of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited

The efficacy of tetanus toxoid and diphtheria toxoid used in Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, was determined on the basis of immunogenicity studies.

Primary Immunization

The immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, administered as a series of three doses for primary immunization was evaluated in 17 subjects ages 6 to 56 years in a study conducted in Canada. The first two doses were administered two months apart, followed by a third dose six to eight months after the second dose. Serum tetanus antitoxin levels were measured by an *in vivo* neutralizing assay, and serum diphtheria antitoxin levels were measured by an *in vitro* neutralizing assay. All 17 subjects had serum tetanus and diphtheria antitoxin levels pre-vaccination and 7 days post-vaccination <0.01 IU/mL, consistent with no previous immunization. Four weeks following the second dose of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, all 17 subjects had a serum tetanus antitoxin level >0.1 IU/mL and a

serum diphtheria antitoxin level ≥0.01 IU/mL. Four weeks following the third dose, all 17 subjects had a serum diphtheria antitoxin level >0.1 IU/mL.

Booster Immunization

In two studies conducted in Canada, the immune responses to a dose of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, were evaluated in subjects who were presumed to have previously received primary immunization against tetanus and diphtheria, and had not received tetanus or diphtheria toxoid within 5 years prior to enrollment. Prior to vaccination and 28-35 days following vaccination, serum tetanus antitoxin levels were measured by an ELISA that has been shown to correlate with an *in vivo* neutralizing assay, and serum diphtheria antitoxin levels were measured by an *in vitro* neutralizing assay. The results from these studies are presented in Tables 1 and 2.

TABLE 1: TETANUS ANTITOXIN LEVELS AND BOOSTER RESPONSE RATES IN PRESUMABLY PREVIOUSLY PRIMED ADOLESCENTS AND ADULTS WHO RECEIVED A DOSE OF TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE.

Study/ Age Group	Timing	Percent of Subjects With Specified Levels of Antitoxin and a Booster Response							
		≥0.01 IU/mL		≥0.1 IU/mL		≥1.0 IU/mL		Booster Response[1]	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
Study A									
Adolescents[2]	pre-	97.3	(85.8, 99.9)	89.2	(74.6, 97.0)	10.8	(3.0, 25.4)		
N = 37	post-	100	(90.5, 100)	100	(90.5, 100)	100	(90.5, 100)	100	(90.5, 100)
Adults[3]	pre-	98.9	(96.7, 99.8)	95.1	(91.7, 97.3)	54.4	(48.1, 60.5)		
N = 263	post-	100	(98.6, 100)	99.6	(97.9, 100)	98.9	(96.7, 99.8)	80.6	(75.3, 85.2)
Study B									
Adults[4]	pre-	99.2	(95.5, 100)	92.6	(86.5, 96.6)	59.0	(49.7, 67.8)		
N = 122	post-	100	(97.0, 100)	100	(97.0, 100)	96.7	(91.8, 99.1)	81.2	(73.1, 87.7)

[1] Booster response: ≥4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level, and post-vaccination level ≥0.1 IU/mL

[2] Adolescents ages 12-17 years; 45.9% (17/37) of subjects were female.

[3] Adults ages 18-54 years; 71.5% (188/263) of subjects were female.

[4] Adults ages 19-59 years; 64.8% (79/122) of subjects were female.

Pre-indicates pre-vaccination.

Post-indicates 28-35 days post-vaccination.

TABLE 2: DIPHTHERIA ANTITOXIN LEVELS AND BOOSTER RESPONSE RATES IN PRESUMABLY PREVIOUSLY PRIMED ADOLESCENTS AND ADULTS WHO RECEIVED A DOSE OF TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE

Study/ Age Group	Timing	Percent of Subjects with Specified Levels of Antitoxin and a Booster Response					
		≥0.01 IU/mL		≥0.1 IU/mL		Booster Response[1]	
		%	95% CI	%	95% CI	%	95% CI
Study A							
Adolescents[2] N = 37	pre-	89.2	(74.6, 97.0)	56.8	(39.5, 72.9)		
	post-	100	(90.5, 100)	100	(90.5, 100)	100	(90.5, 100)
Adults[3] N = 263	pre-	78.7	(73.3, 83.5)	38.4	(32.5, 44.6)		
	post-	98.9	(96.7, 99.8)	84.8	(79.9, 88.9)	77.6	(72.0, 82.5)
Study B							
Adults[4] N = 122	pre-	82.8	(74.9, 89.0)	35.2	(26.8, 44.4)		
	post-	98.4	(94.2, 99.8)	89.3	(82.5, 94.2)	83.6	(75.8, 89.7)

[1] Booster response: ≥4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level, and post-vaccination level ≥0.1 IU/mL

[2] Adolescents ages 12-17 years; 45.9% (17/37) of subjects were female.

[3] Adults ages 18-54 years; 71.5% (188/263) of subjects were female.

[4] Adults ages 19-59 years; 64.8% (79/122) of subjects were female.

Pre- indicates pre-vaccination.

Post- indicates 28-35 days post-vaccination.

No immunogenicity data are available on concomitant administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, with other US licensed vaccines.

INDICATIONS

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is indicated for active immunization of persons 7-59 years of age for prevention of tetanus and diphtheria. For immunization of infants and children younger than 7 years of age against tetanus and diphtheria, refer to the manufacturers' package inserts for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and for Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT).

If passive protection against tetanus is required, Tetanus Immune Globulin (Human) (TIG) may be administered at a separate site with a separate needle and syringe. (See DOSAGE AND ADMINISTRATION, Tetanus Prophylaxis in Wound Management.)

Persons who have had tetanus or diphtheria should still be immunized since these clinical infections do not always confer immunity.

As with any vaccine, immunization with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, may not protect 100% of susceptible persons.

CONTRAINDICATIONS

Hypersensitivity to any component of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited (see components listed in DESCRIPTION), is a contraindication to further administration.

It is a contraindication to use this vaccine after anaphylaxis or other serious allergic reaction following a previous dose of this vaccine, any other tetanus or diphtheria toxoid-containing vaccine, or any component of this vaccine. Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with diphtheria or tetanus components should be carried out. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

WARNINGS

A booster dose of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use is recommended at 11-12 years of age if at least 5 years have elapsed since the last dose of tetanus and diphtheria-toxoid containing vaccine.[10] Subsequent routine boosters with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use are recommended every 10 years (see DOSAGE AND ADMINISTRATION).[10] More frequent administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult use is not recommended except under circumstances of wound management or diphtheria prophylaxis (see DOSAGE and ADMINISTRATION) since it may be associated with increased incidence and severity of adverse reactions.[2]

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103°F (39.4°C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Tetanus and Diphtheria Toxoids for Adult Use more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2,11]

If Guillain-Barré Syndrome occurs within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give subsequent doses of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.[5]

Because of the risk of hemorrhage, Tetanus and Diphtheria Toxoids Adsorbed For Adult Use should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer Tetanus and Diphtheria Toxoids Adsorbed For Adult Use in such persons, it should be given with caution, with steps taken to avoid the risk of bleeding and hematoma formation following injection.[5]

The Advisory Committee on Immunization Practices (ACIP) has published guidelines for vaccination of persons with recent or acute illness.[5]

PRECAUTIONS

General

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.[5]

Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's previous immunization history, the presence of any contraindications to immunization, the current health status, and history concerning possible hypersensitivity to the vaccine or a similar vaccine.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response to Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited.

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

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of blood borne infectious agents. A used needle and/or syringe must never be used to re-enter a multidose vial to withdraw vaccine even when it is to be used for inoculation of the same patient. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

Information for Patients

Before administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, health-care providers should inform the patient, parent or guardian of the benefits and risks of immunization and of the importance of completing the primary immunization series or receiving recommended booster doses, as appropriate.

The health-care provider should inform the parent or guardian, or the patient about the potential for adverse reactions that have been temporally associated with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, or other vaccines containing similar components. Parents or guardians, or patients should be instructed to report any serious adverse reactions to their health-care provider.

It is extremely important when the patient returns for a subsequent dose, that the patient, parent or guardian, should be questioned concerning any symptoms and/or signs of an adverse reaction after a previous dose. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

The health-care provider should provide the Vaccine Information Statements (VISs) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization.

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, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[12] The toll-free number for VAERS forms and information is 1-800-822-7967.

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 vaccines. (See PRECAUTIONS, General.)

No information is available regarding concomitant administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, with other US-licensed vaccines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited. It is also not known whether Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited should be given to a pregnant woman only if clearly needed.

The ACIP has published recommendations for use of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use in pregnant women.[5]

Nursing mothers

It is not known whether Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is administered to a nursing woman.

Pediatric Use

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is not indicated for infants and children younger than 7 years of age. For immunization of infants and children younger than 7 years of age against tetanus and diphtheria, refer to the manufacturers' package inserts for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and for Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT).

Geriatric Use

Clinical studies of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, did not include subjects aged 60 years and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

During clinical trials, the most common adverse reactions associated with the administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, were pain, swelling and redness at the injection site.

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.

In a clinical study of primary immunization conducted in Canada, Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, was administered as a three dose primary series to 18 subjects, 8 of whom were 6-9 years of age and 10 of whom were 17-56 years of age. In three booster immunization studies conducted in Canada, Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, was administered to 773 subjects overall, ranging in age from 12-59 years.

In two of the booster immunization studies, one dose of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, was administered to subjects who were presumed to have previously received primary immunization against tetanus and diphtheria, and had not received tetanus or diphtheria toxoid within 5 years prior to enrollment.

Safety data are available for 37 adolescents ages 12-17 years and 263 adults ages 18-54 years from Study A, and for 126 adults ages 19-59 years from Study B. In both studies, telephone questionnaires to inquire about adverse events were administered at approximately 24 hours, 72 hours, and 8-10 days following vaccination. Information on adverse events that occurred after 8-10 days was collected at a subsequent visit, approximately one-month following vaccination. Some study sites distributed worksheets to subjects to assist in recording adverse events, although the use and content of worksheets were not standardized. Frequencies of selected solicited adverse events reported anytime during the first 72 hours following vaccination are presented in Table 3. One subject in Study A reported swelling of the entire injected upper limb.

TABLE 3: FREQUENCIES OF SELECTED SOLICITED ADVERSE EVENTS WITHIN 72 HOURS FOLLOWING A DOSE OF TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE IN PRESUMABLY PREVIOUSLY PRIMED SUBJECTS

Event	Study A		Study B
	Adolescents[1] N = 37	Adults[2] N = 263	Adults[3] N = 126
	%	%	%
Local			
Redness			
Any	5.4	8.4	21.4
≥35 mm	2.7	1.5	3.2
≥50 mm	2.7	1.1	0.0
≥100 mm	0.0	0.4	0.0
Swelling			
Any	16.2	13.3	10.3
≥35 mm	13.5	5.7	7.1
≥50 mm	10.8	3.8	4.0
≥100 mm	2.7	1.5	0.8
Pain			
Any	81.1	84.8	84.9
Moderate[4] or worse	18.9	12.2	15.1
Severe[5]	0.0	0.4	0.8
Systemic			
Fever			
≥38.0°C	2.7	4.2	0.8
≥38.3°C	0.0	0.0	0.0
Chills	8.1	4.6	5.6
Sore or Swollen Joints	8.1	5.3	5.6

[1] Ages 12-17 years; 45.9% (17/37) of subjects were female.
[2] Ages 18-54 years; 71.5% (188/263) of subjects were female.
[3] Ages 19-59 years; 65.1% (82/126) of subjects were female.
[4] Moderate = interfered with activities, but did not require medical care or absenteeism
[5] Severe = incapacitating, unable to perform usual activities, required medical care or absenteeism

No serious adverse events were reported in the one-month period following vaccination with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, among the 426 subjects in Study A or Study B. In another booster immunization study of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, in which adverse events were monitored for 4 days following vaccination, no serious adverse events were reported among 347 subjects ages 17-29 years. In a primary immunization study in which 18 subjects ages 6-56 years received three doses of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, and were monitored for adverse events for 3 days following each dose, no serious adverse events were reported.

Rates of adverse events less common than those reported in Table 3 are not known at this time. As with any vaccine, there is the possibility that broad use of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, could reveal adverse events not observed in clinical trials.

Additional Adverse Reactions

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

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. (See WARNINGS.)[13]

Persistent nodules at the site of injection have been reported following the use of adsorbed products.[2]

Cases of allergic or anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) have been reported after receiving some preparations containing diphtheria and/or tetanus toxoid.[2] Death following vaccine-caused anaphylaxis has been reported.[13]

Certain neurological conditions have been reported in temporal association with some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillian-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, cranial mononeuropathies, and EEG disturbances with encephalopathy (with or without permanent intellectual and/or motor function impairment). The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[13]

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 further requires the health-care professional 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. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; 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 Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited package insert.[12,14,15]

Reporting by parents, guardians or adult patients of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization should be reported by health-care providers to the US Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967. [12,14,15]

Health-care providers also should report these events to the Director of Scientific and Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits. (See DESCRIPTION.)

SHAKE THE VIAL WELL to distribute uniformly the suspension before withdrawing each dose. When administering a dose from a stoppered vial, do not remove either the 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.

Inject 0.5 mL **intramuscularly**. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area.

Do not administer this product intravenously or subcutaneously.

The needle length should be sufficient to deliver the vaccine intramuscularly, but not so long as to involve underlying nerves and blood vessels or bone. The health-care professional should determine the appropriate size and length of the needle for individual patients.

Needles should not be recapped and should be disposed of properly.

Primary Immunization

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is approved for administration in persons 7-59 years of age who have not been immunized previously against tetanus and diphtheria, as a primary immunization series of three 0.5 mL doses, with the first two doses administered two months apart, followed by a third dose six to eight months after the second dose.

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, may be used to complete the primary immunization series for tetanus and diphtheria in children 7 years of age or older who have received one or two doses of whole-cell pertussis DTP, DTaP and/or DT vaccine. However, the safety and efficacy of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, in such children have not been evaluated.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use. There is no need to start the series over again, regardless of the time elapsed between doses.

Routine Booster Immunization

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is approved for booster immunization in persons 7-59 years of age who have completed primary immunization against tetanus and diphtheria. A booster dose of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use is recommended by the ACIP in persons 11-12 years of age if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine.[10] Subsequent routine boosters with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use are recommended every 10 years.[10,16] If a dose is given sooner than 10 years, as part of wound management or on exposure to diphtheria, the next booster is not needed for 10 years thereafter.[2] MORE FREQUENT BOOSTER DOSES ARE NOT RECOMMENDED AND MAY BE ASSOCIATED WITH INCREASED INCIDENCE AND SEVERITY OF ADVERSE REACTIONS[2,5] (see WARNINGS).

Diphtheria Prophylaxis for Case Contacts

The ACIP has published recommendations on vaccination for diphtheria prophylaxis in individuals who have had contact with a person with confirmed or suspected diphtheria.[2]

Tetanus Prophylaxis in Wound Management

The need for active immunization with a tetanus toxoid-containing preparation, with or without passive immunization with TIG (Human) depends on both the condition of the wound and the patient's vaccination history (Table 4).

A thorough attempt must be made to determine whether a patient has completed primary immunization. Individuals who have completed primary immunization against tetanus, and who sustain wounds which are minor and uncontaminated, should receive a booster dose of a tetanus toxoid-containing preparation only if they have not received tetanus toxoid within the preceding 10 years. For tetanus prone wounds (e.g., wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite), a booster is appropriate if the patient has not received a tetanus toxoid-containing preparation within the preceding 5 years. If a booster dose is given sooner than 10 years as part of wound management, the next routine booster should not be given for 10 years thereafter.[2]

Individuals who have not completed primary immunization against tetanus, or whose immunization history is unknown or uncertain, should be immunized with a tetanus toxoid-containing product. Completion of primary immunization thereafter should be ensured. In addition, if these individuals have sustained a tetanus-prone wound, the use of TIG (Human) is recommended. TIG (Human) should be administered at a separate site, with a separate needle and syringe, according to the manufacturer's package insert. If a contraindication to using tetanus toxoid-containing preparations exists in a person who has not completed a primary immunizing course of tetanus toxoid and other than a clean, minor wound is sustained, only passive immunization with TIG (Human) should be given.[2]

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use is the recommended preparation for active tetanus immunization in wound management of patients ≥7 years of age.[2] In such persons, a preparation containing tetanus and diphtheria toxoids is preferred instead of single-antigen tetanus toxoid to enhance diphtheria protection. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is approved for wound management of patients 7-59 years of age.

TABLE 4[2]: SUMMARY GUIDE TO TETANUS PROPHYLAXIS IN ROUTINE WOUND MANAGEMENT FOR PERSONS 7 YEARS OF AGE OR OLDER‡

History of Adsorbed Tetanus Toxoid (doses)	Clean, Minor Wounds		All Other Wounds**	
	Td*	TIG	Td*	TIG
Unknown or <three	Yes	No	Yes	Yes
≥Three¶	No†	No	No§	No

‡ Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, is approved for wound management of patients 7-59 years of age. Tetanus and Diphtheria Adsorbed for Adult Use, manufactured by Aventis Pasteur Limited, is not indicated for individuals 60 years of age or older (see Clinical Pharmacology and Indications).

** Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

* Tetanus and Diphtheria Toxoids Adsorbed For Adult Use.

¶ If only three doses of fluid tetanus toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid should be given.

† Yes, if >10 years since last dose.

§ Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

Concomitant Vaccine Administration

No safety and immunogenicity data are available on the concomitant administration of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited, with other US licensed vaccines.

STORAGE

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard product if exposed to freezing.

Do not use vaccine after expiration date.

HOW SUPPLIED

Vial, 5 mL multidose	Product No. 49281-210-10
Vial, single dose (package of 10)	Product No. 49281-210-11

CPT® Code: 90718

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REFERENCES

1. Pascual FB, et al. Tetanus Surveillance-United States, 1998-2000. In: Surveillance Summaries, June 20, 2003. MMWR 2003;52(No.SS-3):1-8.

2. Centers for Disease Control and Prevention. Diphtheria, Tetanus, and Pertussis: Recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(No. RR-10):1-28.

3. Wassilak SGF, et al. Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 3rd ed. Philadelphia, PA: W.B. Saunders Company;1999:441-474.

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 December 13, 1985;50(240):51002-51117.

5. Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR-2):1-35.

6. Centers for Disease Control and Prevention. Diphtheria. In: Atkinson W and Wolfe C, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* 7th ed. Atlanta, GA: Public Health Foundation. 2002:39-48.

7. Dittmann S, et al. Successful control of epidemic diphtheria in the states of the former Union of Soviet Socialist Republics: Lessons Learned. J Infect Dis 2000;181:S10-S22.

8. Hardy IRB, et al. Current situation and control strategies for resurgence of diphtheria in newly independent states of the former Soviet Union. Lancet 1996;347:1739-1744.

9. Mortimer EA and Wharton M. Diphtheria toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 3rd ed. Philadelphia, PA: W.B. Saunders Company,1999:140-157.

10. Centers for Disease Control and Prevention. Recommended childhood and adolescent immunization schedule-United States, 2003. MMWR 2003;52(04)Q1-Q4.

11. Centers for Disease Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR-12):22-31.

12. Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System United States. MMWR 1990;39:730-733.

13. Institute of Medicine (US). Stratton KR, et al, eds. *Adverse events associated with childhood vaccines: evidence bearing on causality*. Washington (DC): National Academy Press. 1994:67-117.

14. Centers for Disease Control and Prevention. National Childhood Vaccine Injury Act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37:197-200.

15. Food and Drug Administration. New reporting requirements for vaccine adverse events. FDA Drug Bull 1988;18(2):16-18.

16. Centers for Disease Control and Prevention. Recommended adult immunization schedule-United States, 2002-2003. MMWR 2002;51(40):904-908.

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