A.H.F.S. Category 80:08

Tetanus and Diphtheria Toxoids Adsorbed For Adult Use

℞ only

Caution: Federal (USA) law prohibits dispensing without prescription.

DESCRIPTION

Tetanus and Diphtheria Toxoids Adsorbed for Adult Use, for intramuscular use, is a sterile suspension of alum-precipitated (aluminum potassium sulfate) toxoid in an isotonic sodium chloride solution containing sodium phosphate buffer to control pH. The vaccine, after shaking, is a turbid liquid, whitish-gray in color.

Clostridium tetani culture is grown in a peptone-based medium. *Corynebacterium diphtheriae* culture is grown in a modified Mueller and Miller medium.[1] Both toxins are detoxified with formaldehyde. The detoxified materials are then separately purified by serial ammonium sulfate fractionation and diafiltration. Thimerosal (a mercury derivative) 1:10,000 is added as a preservative.

Each 0.5 mL dose is formulated to contain 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid, and not more than 0.28 mg of aluminum by assay. The tetanus and diphtheria toxoids induce at least 2 units and 0.5 units of antitoxin per mL, respectively, in the guinea pig potency test.

CLINICAL PHARMACOLOGY

TETANUS

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*.

The occurrence of tetanus in the United States (US) has decreased dramatically from 560 reported cases in 1947 to a record low of 48 reported cases in 1987. Tetanus in the US is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention (CDC) during 1987 and 1988, 68% were ≥ 50 years of age, while only six were < 20 years of age. Overall, the case-fatality rate was 21%. The age distribution of recent cases and the results of serosurveys indicate that many US adults are not protected against tetanus. Serosurveys undertaken since 1977 indicate that 6% to 11% of adults 18 to 39 years of age and 49% to 66% of those ≥ 60 years of age may lack protective levels of circulating tetanus antitoxin.[2] In 1992, 45 cases were reported of which 82% were ≥ 50 years of age.[3] The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[2]

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition was implicated. Non-acute skin lesions, such as ulcers, or medical conditions such as abscesses, were reported in association with 14% of cases.[2]

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. From 1972 through 1984, 29 cases of neonatal tetanus were reported in the US. No cases of neonatal tetanus were reported in the period 1985 to 1989.[2]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the US.[2] Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of neutralizing antibodies to tetanus toxin that persist for ≥ 10 years.[2]

DIPHTHERIA

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

At one time, diphtheria was common in the US. More than 200,000 cases, primarily among young children, were reported in 1921. Approximately 5% to 10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. 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 a notifiable disease. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons 20 years of age or older.[2]

Diphtheria is currently a rare disease in the US primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥ three doses of diphtheria and tetanus toxoids and pertussis vaccine adsorbed [DTP]) and because of an apparent reduction in the prevalence of toxigenic strains of *C. diphtheriae*. Most cases occur among unvaccinated or inadequately vaccinated persons.[2]

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 illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.[2]

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have milder illness. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.[2]

The potency of tetanus and diphtheria toxoids was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines & Toxoids.[4]

A clinical study to evaluate the serological responses and adverse reactions was performed in 58 individuals 6 years of age and older. The results indicated protective levels of antibody were achieved in greater than 90% of the study population after primary immunization with both components. Booster effects were achieved in 100% of the individuals with pre-existing antibody responses.[5]

INDICATIONS AND USAGE

Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is indicated for active immunization of children 7 years of age or older, and adults, against tetanus and diphtheria. Td is the preparation of choice for vaccination of all persons 7 years of age or older because side effects from higher doses of diphtheria toxoid are more common in this group than they are among younger children. Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) is indicated for active immunization of children up to age 7 years against diphtheria and tetanus.[2]

The Advisory Committee on Immunization Practices (ACIP) recommends the following: *A previously unvaccinated pregnant woman whose child might be born under unhygienic circumstances (without sterile technique) should receive two doses of Td 4 to 8 weeks apart before delivery, preferably during the last two trimesters. Pregnant women in similar circumstances who have not had a complete vaccination series should complete the three-dose series. Those vaccinated more than 10 years previously should have a booster dose. No evidence exists to indicate that tetanus and diphtheria toxoids administered during pregnancy are teratogenic.*[2] (See **PREGNANCY** section)

This vaccine is not to be used for the treatment of tetanus or diphtheria infection.

This vaccine should not be used for immunizing children below 7 years of age. In children below 7 years of age, either Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) – Tripedia®, or Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) (DTP) is recommended. If a contraindication to pertussis immunization exists, the recommended vaccine is Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT).[2]

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

If passive immunization is required, Tetanus Immune Globulin (Human) (TIG) and/or equine Diphtheria Antitoxin are the products of choice for tetanus and diphtheria, respectively (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION** sections).

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL, A MERCURY DERIVATIVE, IS A CONTRAINDICATION FOR FURTHER USE OF THIS VACCINE.

It is a contraindication to use this or any other related vaccine after a serious adverse reaction temporally associated with a previous dose including an anaphylactic reaction.

A history of systemic allergic or neurologic reactions following a previous dose of Td is an *absolute contraindication* for further use.[2]

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 should be given using TIG (Human).[2]

Immunization should be deferred during the course of an acute illness. Vaccination of persons with severe, febrile illness should generally be deferred until these persons have recovered. However, the presence of minor illnesses such as mild upper respiratory infections with or without fever should not preclude vaccination.[2]

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[6]

WARNINGS

This product contains dry natural latex rubber as follows: The stopper to the vial contains dry natural latex rubber. In the case of the syringe, the needle cover and plunger contain dry natural latex rubber.

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 Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.[2]

Intramuscular injections should be given with great care in patients suffering from thrombocytopenia or other coagulation disorders.[2]

A routine booster should not be given more frequently than every ten years. (This guideline should not preclude wound management considerations.)

Deaths have been reported in temporal association with the administration of Td vaccine; however, no causal relationship was proven[7] (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

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

EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

There is an increased incidence of local and systemic reactions to booster doses of tetanus toxoid when given to previously immunized persons. (Refer to **DOSAGE AND ADMINISTRATION** section for timing of recall injections.) Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This should include review of the patient's history with respect to possible sensitivity and any previous adverse reactions (see **CONTRAINDICATIONS** section) to the vaccine or similar vaccine, to possible sensitivity to dry natural latex rubber, and a current knowledge of the literature concerning the use of the vaccine under consideration.

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

Immunosuppressive therapies including radiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic drugs may reduce the immune response to vaccines. Therefore, routine vaccination should be deferred, if possible, while patients are receiving such therapy.[2] If Td has been administered to persons receiving immunosuppressive therapy, or having an immunodeficiency disorder, an adequate antibody response may not be obtained.[2] When possible, immunosuppressive treatment should be interrupted when immunization is required due to a tetanus-prone wound.

Administration of Td is not contraindicated in individuals with HIV infection.[8]

It is advisable to use Td (For Adult Use – 7 years of age and older) in wound prophylaxis instead of tetanus toxoid alone in order to maintain adequate levels of diphtheria immunity.[2]

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

INFORMATION FOR PATIENTS

Prior to administration of Td, health-care personnel should inform the parent, guardian or adult patient the benefits and risks of immunization, and also inquire about the recent health status of the patient to be injected.

As part of the child's or adult's permanent immunization record, the date, lot number and manufacturer of the vaccine administered MUST be recorded.[9,10,11]

The health-care provider should inform the parent, guardian or adult patient about the potential for adverse reactions that have been temporally associated with Td administration. The parent, guardian or adult patient should be instructed to report any serious adverse reactions to their health-care provider.

IT IS EXTREMELY IMPORTANT WHEN THE PARENT, GUARDIAN OR ADULT PATIENT RETURNS FOR THE NEXT DOSE IN THE SERIES, THE PARENT, GUARDIAN, OR ADULT PATIENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE **CONTRAINDICATIONS**; **ADVERSE REACTIONS** SECTIONS).

The health-care provider should inform the parent, guardian or adult patient of the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Materials (VIMs) which are required to be given with each immunization.

DRUG INTERACTIONS

If passive immunization for tetanus is needed, TIG (Human) is the product of choice for tetanus. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG (Human) for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG (Human) are given concurrently, separate syringes and different sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

Diphtheria Antitoxin (equine) is available for treatment of the acute phases of diphtheria. When Td and Diphtheria Antitoxin are used together, they must be given at different sites using separate needles and syringes.

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies may reduce the response to vaccines (see **PRECAUTIONS** – GENERAL section).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No studies have been performed to evaluate carcinogenicity, mutagenic potential, or impact on fertility.

PREGNANCY
REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C
Animal reproduction studies have not been conducted with Tetanus and Diphtheria Toxoids Adsorbed For Adult Use vaccine. It is also not known whether Tetanus and Diphtheria Toxoids Adsorbed For Adult Use vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use vaccine should be given to a pregnant woman only if clearly needed.

Adequate immunization by routine boosters in non-pregnant women of child-bearing age can obviate the need to vaccinate women during pregnancy (see **DOSAGE AND ADMINISTRATION** section).

Physicians generally avoid prescribing unnecessary drugs and biologics for pregnant women.

However, the ACIP recommends the following: *A previously unvaccinated pregnant woman whose child might be born under unhygienic circumstances (without sterile technique) should receive two doses of Td 4 to 8 weeks apart before delivery, preferably during the last two trimesters. Pregnant women in similar circumstances who have not had a complete vaccination series should complete the three-dose series. Those vaccinated more than 10 years previously should have a booster dose. No evidence exists to indicate that tetanus and diphtheria toxoids administered during pregnancy are teratogenic.*[2]

It has been reported that tetanus toxoid administered to pregnant women prevents neonatal tetanus in newborns.[12,13] However, the data reported on the safety of tetanus toxoid when so used is inconclusive because the incidence of neonatal deaths in New Guinea was significantly higher than in the United States.[12] A prospective study in the United States has not been done to confirm these reports.

PEDIATRIC USE
SAFETY AND EFFECTIVENESS OF TETANUS AND DIPHTHERIA TOXOIDS ADSORBED FOR ADULT USE VACCINE BELOW 7 YEARS OF AGE HAVE NOT BEEN ESTABLISHED.

In children below 7 years of age, either Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) – Tripedia®, or Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed USP (For Pediatric Use) (DTP) is recommended. If a contraindication to pertussis immunization exists, the recommended vaccine is Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT).[2]

ADVERSE REACTIONS
BODY SYSTEM AS A WHOLE
Adverse reactions may be local and include redness, warmth, edema, induration with or without tenderness as well as urticaria, and rash. Malaise, transient fever, pain, hypotension, nausea and arthralgia may develop in some patients after the injection. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection) may occur, particularly in persons who have received multiple prior boosters.[2]

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) and death have been reported after receiving preparations containing tetanus and diphtheria antigens.[2]

In a clinical study involving 58 individuals 6 years of age and older, 19% of the individuals noted local reactions consisting of erythema, tenderness and induration at the injection site and 2% systemic reactions consisting of headache, malaise and temperature elevations.[5]

Deaths have been reported in temporal association with the administration of tetanus toxoid containing vaccines. On rare occasions, anaphylaxis has been reported following administration of products containing tetanus toxoid. Upon review, a report by the Institute of Medicine (IOM) concluded the evidence established a causal relationship between tetanus toxoid and anaphylaxis.[7]

NERVOUS SYSTEM
The following neurologic illnesses have been reported as temporally associated with vaccines containing tetanus toxoid: neurological complications[14] including cochlear lesion,[15] brachial plexus neuropathies,[14,16] paralysis of the radial nerve,[17] paralysis of the recurrent nerve,[15] accommodation paresis, Guillain-Barré syndrome (GBS), and EEG disturbances with encephalopathy. The IOM following review of the reports of neurologic events following vaccination with tetanus toxoid, Td or DT, concluded the evidence favored acceptance of a causal relationship between tetanus toxoid and brachial neuritis and GBS.[7,18]

CARDIOVASCULAR SYSTEM
Acute anaphylatic reactions may occur rarely following administration of tetanus and diphtheria antigens which may cause acute hives and cardiovascular collapse.

Adverse reactions to diphtheria toxoid in adults are minimized by the small amount of the antigen (not more than 2 Lf units per dose), contained in Td.[19–23]

EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

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 and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[9,10,11]

Reporting by parents, guardians or adult patients of all adverse events occurring after vaccine administration should be encouraged. Patients experiencing adverse events following immunization who require a visit to a health-care provider should be reported by health-care providers to the US Department of Health and Human Services (DHHS) 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.[9,10,11]

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

DOSAGE AND ADMINISTRATION[2]

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

SHAKE VIAL WELL *before withdrawing each dose*. Discard vial of vaccine if it cannot be resuspended.

Inject 0.5 mL intramuscularly in the area of the vastus lateralis (mid-thigh laterally) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

The following guidelines are derived from the Advisory Committee on Immunization Practices (ACIP).[2]

Primary Immunization for Children over 7 Years of Age and Adults:

A series of three doses of 0.5 mL each of Td should be given intramuscularly; the second dose of 0.5 mL is given 4 to 8 weeks after the first dose; and the third dose of 0.5 mL is given 6 to 12 months after the second dose. Td is the agent of choice for immunization of all individuals 7 years of age and older, because side effects from higher doses of diphtheria toxoid are more common in older children and adults.

Children who remain incompletely immunized after their seventh birthday should be counted as having prior exposure to tetanus and diphtheria toxoids (e.g., a child who previously received two doses of DTP needs only one dose of Td to complete the primary series for tetanus and diphtheria).

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

Routine Recall Injections:

To maintain adequate protection a booster dose of 0.5 mL every 10 years thereafter is recommended.

Recall Injection After Injury:

A thorough attempt must be made to determine whether a patient has completed primary immunization. Patients with unknown or uncertain previous immunization histories should be considered to have no previous tetanus toxoid doses. Persons who had military service since 1941 can be considered to have received at least one dose. Although most people in the military since 1941 may have completed a primary series of tetanus toxoid, this cannot be assumed for each individual. Patients who have not completed a primary series may require tetanus toxoid and passive immunization at the time of wound cleaning and debridement (Table 1).[2]

Available evidence indicates that complete primary vaccination with tetanus toxoid provides long-lasting protection ≥ 10 years for most recipients. Consequently, after complete primary tetanus vaccination, boosters, even for wound management, need to be given only every 10 years when wounds are minor and uncontaminated. For other wounds, a booster is appropriate if the patient has not received tetanus toxoid within the preceding five years. Persons who have received at least two doses of tetanus toxoid rapidly develop antitoxin antibodies.[2]

Td is the preferred preparation for active tetanus immunization in wound management of patients ≥ 7 years of age. Because a large proportion of adults are susceptible, this plan enhances diphtheria protection. Thus, by taking advantage of acute health-care visits, such as for wound management, some patients can be protected who otherwise would remain susceptible. For inadequately vaccinated patients of all ages, completion of primary vaccination at the time of discharge or at follow-up visits should be ensured.[2]

TABLE 1[2] **SUMMARY GUIDE TO TETANUS PROPHYLAXIS IN ROUTINE WOUND MANAGEMENT, 1991***

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

* Important details are in the text of the insert.

** 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.

† 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.)

If passive immunization for tetanus is needed, TIG (Human) is the product of choice. It provides longer protection than antitoxin of animal origin and causes few adverse reactions. The currently recommended prophylactic dose of TIG (Human) for wounds of average severity is 250 units intramuscularly. When tetanus toxoid and TIG (Human) are given concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.[2]

HOW SUPPLIED

Syringe, 0.5 mL (10 x 0.5 mL syringes per package) – Product No. 49281-271-10
Vial, 5 mL – Product No. 49281-271-83

STORAGE

Store between 2° - 8°C (35° - 46°F). DO NOT FREEZE.

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