HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Diptheria and Tetanus Toxoids Adsorbed safely and effectively. See full prescribing information for Diptheria and Tetanus Toxoids Adsorbed.

Diptheria and Tetanus Toxoids Adsorbed
Suspension for Intramuscular Injection
Initial U.S. Approval: 1997

----------RECENT MAJOR CHANGES----------

Warnings & Precautions:
- Apnea in premature infants (5.5) XX/201X
- Syncope (5.6) XX/201X

----------INDICATIONS AND USAGE----------

Diphtheria and Tetanus Toxoids Adsorbed is a vaccine indicated for active immunization against diphtheria and tetanus. Diphtheria and Tetanus Toxoids Adsorbed is approved for use in children from 6 weeks through 6 years of age (prior to 7th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------

The five dose immunization series consists of an injection administered at 2, 4, 6, 15-18 months and between 4 and 6 years of age. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Suspension for injection, supplied in single dose (0.5 mL) vials (3)

----------CONTRAINDICATIONS----------

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of Diphtheria and Tetanus Toxoids Adsorbed or any other diphtheria toxoid or tetanus toxoid-containing vaccine, or any other component of this vaccine. (4.1)

----------WARNINGS AND PRECAUTIONS----------

- If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Diphtheria and Tetanus Toxoids Adsorbed or any vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Diphtheria and Tetanus Toxoids Adsorbed vaccine. (5.2)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Diphtheria and Tetanus Toxoids Adsorbed, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.5)
- Syncope (fainting) has been reported following vaccination with Diphtheria and Tetanus Toxoids Adsorbed vaccine. Procedures should be in place to prevent falling injury and manage syncopal reactions. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥5%) were crying, fever, and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

----------DRUG INTERACTIONS----------

Immunosuppressive therapies may reduce the response to Diphtheria and Tetanus Toxoids Adsorbed. (7.3)

See 17 for PATIENT COUNSELING INFORMATION
Revised: [XX/201X]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids Adsorbed is a vaccine indicated for active immunization against diphtheria and tetanus. Diphtheria and Tetanus Toxoids Adsorbed is approved for use in children from 6 weeks through 6 years of age (prior to 7th birthday).

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (DTaP) or a DTaP-containing vaccine is recommended for immunization of infants and children 6 weeks through 6 years of age. Diphtheria and Tetanus Toxoids Adsorbed should be used in instances where the pertussis vaccine component is contraindicated.

Diphtheria and Tetanus Toxoids Adsorbed is not to be used for treatment of diphtheria or tetanus infection.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only.

2.1 Dosage and Schedule

Diphtheria and Tetanus Toxoids Adsorbed is approved for administration as a 5 dose series at 2, 4, 6, 15-18 months, and 4-6 years. The first dose of Diphtheria and Tetanus Toxoids Adsorbed may be administered as early as 6 weeks of age.

2.2 Administration

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

After removing the “flip-off” cap, cleanse the vaccine vial stopper with a suitable germicide. Do not remove either the rubber stopper or the metal seal holding it in place. Just before use, shake the vial well until a uniform, white, cloudy suspension results.

Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL dose of Diphtheria and Tetanus Toxoids Adsorbed intramuscularly. Use a separate sterile needle and syringe for each injection. Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. 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.

Diphtheria and Tetanus Toxoids Adsorbed vaccine should not be combined through reconstitution or mixed with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Diphtheria and Tetanus Toxoids Adsorbed is a suspension for injection in 0.5 mL single dose vials.

4 CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Diphtheria and Tetanus Toxoids Adsorbed or any other diphtheria toxoid or tetanus toxoid-containing vaccine, or any other component of this vaccine is a contraindication to administration of Diphtheria and Tetanus Toxoids Adsorbed. [See *Description (11).]*

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine Injection (1:1000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Guillain-Barré Syndrome and Brachial Neuritis

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. (1) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Diphtheria and Tetanus Toxoids Adsorbed vaccine.

5.3 Limitation of Vaccine Effectiveness

Vaccination with Diphtheria and Tetanus Toxoids Adsorbed may not protect all individuals.

5.4 Altered Immunocompetence

If Diphtheria and Tetanus Toxoids Adsorbed vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See *Immunosuppressive Treatments* (*7.3*).]

5.5 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Diphtheria and Tetanus Toxoids Adsorbed, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

5.6 Syncope

Syncope (fainting) has been reported following vaccination with Diphtheria and Tetanus Toxoids Adsorbed vaccine. Procedures should be in place to prevent falling injury and manage syncopal reactions.

6 ADVERSE REACTIONS

The most common adverse reactions (≥5%) were crying, fever, and loss of appetite.

6.1 Clinical Trials Experience

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.

In a clinical trial in Baltimore, 163 infants received Diphtheria and Tetanus Toxoids Adsorbed at 2, 4 and 6 months of age. The results of this trial are presented in Table 1.

Table 1: Percentage of Children Experiencing Local and Systemic Reactions at 24 Hours Following Immunization

Reaction	BALTIMORE * (N=163)		
	Dose 1 (%) (n = 155)	**Dose 2 (%) (n = 145)**	**Dose 3 (%) (n = 136)**
Systemic Reactions			
Fever ≥38°C <39°C (≥100.4°F <102.2°F)	0.7	0.8	6.6
Fever ≥39°C (≥102.2°F)	0	0	0
Crying	13.6	15.2	13.0
Loss of Appetite	3.9	6.2	2.9
Injection Site Reactions			
Redness ≥2.5 cm	0.7	0	3.6
Slight Pain	2.6	2.8	2.2
Moderate Pain	0.7	1.4	0
Hardness ≥2.5 cm	1.3	1.4	3.6

* A total of 163 children received one of the three lots of Diphtheria and Tetanus Toxoids Adsorbed at 2, 4, and 6 months of age, and acellular pertussis vaccine at 3, 5, and 7 months of age. One control group (N=85) received Diphtheria and Tetanus Toxoids Adsorbed concurrently at a separate site with acellular pertussis vaccine at 2, 4 and 6 months of age (data not shown). A second control group (N=85) received commercial DTwP vaccine at 2, 4, and 6 months of age, and a placebo at 3, 5, and 7 months of age (data not shown).

Two clinical trials were conducted in Canada. In the first clinical trial, 52 children aged 17-22 months who had previously received 3 doses of whole-cell DTP Adsorbed vaccine (not licensed in US), received Diphtheria and Tetanus Toxoids Adsorbed with either an acellular pertussis (n = 25) or a whole cell pertussis (n = 27) vaccine (neither licensed in US) given concurrently but

at a separate site. The only reported local reaction was slight pain at the Diphtheria and Tetanus Toxoids Adsorbed injection site in 11% of children.

In a second clinical trial conducted in Canada, 99 children aged 4 to 6 years old who were eligible for the preschool (fifth) dose of DTP received Diphtheria and Tetanus Toxoids Adsorbed in one arm and a whole-cell Monovalent Pertussis vaccine (not licensed in US) in the other. The following local reactions at the Diphtheria and Tetanus Toxoids Adsorbed injection site were reported: redness ≥50 mm - 9%, swelling >50 mm - 51%, tenderness, moderate or severe - 17%, arm mobility “too sore to move” - 9%. (2)

Diphtheria and Tetanus Toxoids Adsorbed evaluated in clinical trials contained thimerosal.

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during the post-marketing use of a Diphtheria and Tetanus Toxoids Adsorbed vaccine manufactured by Sanofi Pasteur Limited that contained thimerosal. Because these events are reported voluntarily from a population of uncertain size, it is not always 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 with Diphtheria and Tetanus Toxoids Adsorbed:

Blood and lymphatic system disorders

Lymphadenopathy

Gastrointestinal disorders

Nausea

General disorders and administration site conditions

Injection site inflammation

Injection site hypersensitivity

Pain

Nervous system disorders

Convulsion

Somnolence

Syncope

Headache

Skin and subcutaneous tissue disorders

Rash

Urticaria

Vascular disorders

Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Administration With Other Vaccines

No safety and immunogenicity data are available on the concomitant administration of Diphtheria and Tetanus Toxoids Adsorbed with other US licensed vaccines.

7.2 Concomitant Administration with Tetanus Immune Globulin (Human)

If passive protection against tetanus is required, TIG (Human) may be administered according to its prescribing information, concomitantly with Diphtheria and Tetanus Toxoids Adsorbed at a separate site with a separate needle and syringe.

7.3 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to Diphtheria and Tetanus Toxoids Adsorbed. [See *Warnings and Precautions (5.2).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Diphtheria and Tetanus Toxoids Adsorbed. It is also not known whether Diphtheria and Tetanus Toxoids Adsorbed can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

8.4 Pediatric Use

Diphtheria and Tetanus Toxoids Adsorbed is not indicated for infants below 6 weeks of age or children 7 years of age or older. Safety and effectiveness of Diphtheria and Tetanus Toxoids Adsorbed in these age groups have not been established.

11 DESCRIPTION

Diphtheria and Tetanus Toxoids Adsorbed is a sterile, cloudy, white, uniform suspension of diphtheria and tetanus toxoids adsorbed on aluminum phosphate and suspended in isotonic sodium chloride solution for intramuscular injection only. Diphtheria and Tetanus Toxoids Adsorbed vaccine does not contain a preservative.

Each 0.5 mL dose is formulated to contain: 25 Lf diphtheria toxoid and 5 Lf tetanus toxoid. Other ingredients per 0.5 mL dose include: 1.5 mg aluminum phosphate and <100 mcg free formaldehyde.

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, uracil, inorganic salts and vitamins.

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.

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

The vial stopper is not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 International Units (IU)/mL is the lowest level giving some degree of protection, and levels of at least 0.1 IU/mL are generally regarded as protective. (3) (4)

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (3) (5)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Diphtheria and Tetanus Toxoids Adsorbed has not been evaluated for carcinogenicity, mutagenic potential, or impairment of fertility.

14 CLINICAL STUDIES

In a clinical study conducted in Baltimore, MD, infants received one of three lots of Diphtheria and Tetanus Toxoids Adsorbed (formulation that contained thimerosal), 0.5 mL, at 2, 4 and 6 months of age. Oral poliovirus vaccine (no longer licensed in the US) was administered concomitantly with Diphtheria and Tetanus Toxoids Adsorbed at 2 and 4 months of age. Diphtheria and tetanus antitoxin levels were evaluated at 8 months of age (see Table 2). Protective levels of diphtheria antitoxin (≥0.01 IU/mL) and tetanus antitoxin (≥0.01 IU/mL) were detected in

99% and 100%, respectively, of the Diphtheria and Tetanus Toxoids Adsorbed recipients after 3 doses. The geometric mean titres (GMT's) for diphtheria and tetanus antitoxin antibodies in recipients of the three Diphtheria and Tetanus Toxoids Adsorbed lots were not significantly different, ranging from 0.25 to 0.35 IU/mL for diphtheria antitoxin antibodies, and from 0.75 to 0.80 IU/mL for tetanus antibodies after the third dose. In a fourth group of 75 infants who received an investigational acellular pertussis vaccine simultaneously with the Diphtheria and Tetanus Toxoids Adsorbed but at separate sites with separate needles and syringes, protective diphtheria and tetanus antitoxin levels developed in 100% of the recipients.

Table 2: Percentage of Children Protected Following Administration of Diphtheria and Tetanus Toxoids Adsorbed

	Post Dose 3 Diphtheria and Tetanus Toxoids Adsorbed
Diphtheria antitoxin ≥0.01 IU/mL	99% (135/136)
Tetanus antitoxin ≥0.01 IU/mL	100% (137/137)

15 REFERENCES

1 Adverse Events Associated with Childhood Vaccines. Institute of Medicine. 1994.

2 Scheifele D, et al. Role of whole-cell pertussis vaccine in severe local reactions to the preschool (fifth) dose of diphtheria-pertussis-tetanus vaccine. Can Med Assoc Journal 1994;150(1).

3 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.

4 Vitek CR, Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W. B. Saunders; 2008. p. 139-56.

5 Wassilak SGF, et al. Tetanus toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W.B. Saunders; 2008. p. 805-39.

16 HOW SUPPLIED/STORAGE AND HANDLING

Diphtheria and Tetanus Toxoids Adsorbed is supplied in:
a 0.5 mL single dose vial: NDC No. 49281-225-58;
in packages of 10 vials: NDC No. 49281-225-10.

The vial stopper is not made with natural rubber latex.

Diphtheria and Tetanus Toxoids Adsorbed 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 vaccine beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

Inform the parent or guardian of the following:

- It is important to complete the immunization series for maximum protection against diphtheria and tetanus.
- Common adverse reactions include local redness, swelling, and tenderness at the injection site, fever, crying, and loss of appetite.
- Other adverse reactions can occur. Call your healthcare provider with any adverse reactions of concern.
- Provide the Vaccine Information Statements (VIS), which are required by the National Childhood Vaccine Injury Act of 1986.

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Toronto Ontario Canada

Distributed by:

231 **Sanofi Pasteur Inc.**

232 Swiftwater PA 18370 USA

233

234 R5-0513 USA

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