HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Adacel safely and effectively. See full prescribing information for Adacel.

Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed)
Suspension for Intramuscular Injection
Initial US Approval: 2005

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

Indications and usage. (1)
Warnings and Precautions. (5.7) XX/201X

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

- Adacel is a vaccine indicated for active booster immunization against tetanus, diphtheria and pertussis. Adacel is approved for use as a single dose in persons 10 through 64 years of age. (1)

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

- A single intramuscular injection of 0.5 mL. (2.1)

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

- Single-dose vials and prefilled syringes containing a 0.5-mL suspension for injection. (3)

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

- Severe allergic reaction (eg, anaphylaxis) to any component of Adacel or any other diphtheria toxoid, tetanus toxoid and pertussis antigen-containing vaccine. (4.1)
- Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine. (4.2)

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

- The tip caps of the Adacel prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals. (5.2, 17)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following a subsequent dose of Adacel vaccine. (5.3)
- Progressive or unstable neurologic conditions are reasons to defer Adacel vaccination. (5.4)
- Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive Adacel unless at least 10 years have elapsed since the last dose of a tetanus toxoid-containing vaccine. (5.5)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including Adacel. Procedures should be in place to prevent falling injury and manage syncopal reactions. (5.7)

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

- The most common solicited injection site reactions occurring within 0-14 days following vaccination with Adacel were:
  - For Adolescents 11-17 years of age: pain (77.8%), swelling (20.9%), erythema (20.8%).
  - For Adults 18-64 years of age: pain (65.7%), swelling (21.0%), erythema (24.7%) (6.1).
- The most common solicited systemic reactions occurring within 0-14 days following vaccination with Adacel were:
  - For Adolescents 11-17 years of age: headache (43.7%), body ache or muscle weakness (30.4%), tiredness (15.1%).
  - For Adults 18-64 years of age: headache (33.9%), body ache or muscle weakness (21.9%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

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

- When Adacel vaccine was administered concomitantly with trivalent inactivated influenza vaccine (TIV) to adults 19-64 years of age, a lower antibody response was observed for pertactin antigen as compared to Adacel vaccine administered alone. (7.1, 14.3)
- Immunosuppressive therapies may reduce the immune response to Adacel. (7.2)
- Do not mix Adacel vaccine with any other vaccine in the same syringe or vial.

----------USE IN SPECIFIC POPULATIONS----------

- Safety and effectiveness of Adacel vaccine have not been established in pregnant women. (8.1)
- Pregnancy Surveillance Registry: contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). (8.1)

See 17 PATIENT COUNSELING INFORMATION

Revised: [XX/201X]

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Adacel is a vaccine indicated for active booster immunization against tetanus, diphtheria and pertussis. Adacel vaccine is approved for use as a single dose in individuals 10 through 64 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Just before use, shake the vial or syringe well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

When withdrawing a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Use a separate sterile needle and syringe for each injection. Using a sterile needle and syringe, withdraw the 0.5 mL dose of vaccine from the single-dose vial and administer the vaccine to the individual. 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.

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

2.2 Administration, Dose and Schedule

Adacel vaccine is administered as a single 0.5 mL intramuscular injection into the deltoid muscle of the upper arm.

Do not administer this product intravenously, subcutaneously or intradermally.

There are no data to support repeat administration of Adacel vaccine.

Five years should have elapsed since the recipient’s last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine and the administration of Adacel vaccine.

2.3 Additional Dosing Information

Primary series: The safety and effectiveness of Adacel vaccine used as a primary series or to complete the primary series, for diphtheria, tetanus, or pertussis has not been demonstrated.

Wound management: If tetanus prophylaxis is needed for wound management, Adacel may be given if no previous dose of any Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) has been administered.

3 DOSAGE FORMS AND STRENGTHS

Adacel vaccine is a suspension for injection (0.5 mL dose) available in 0.5 mL single-dose vials and prefilled syringes. [See *DOSAGE AND ADMINISTRATION (2.2) and HOW SUPPLIED/STORAGE AND HANDLING (*16*).*]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (eg, anaphylaxis) after a previous dose of any tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to administration of Adacel vaccine. [See *DESCRIPTION (11).*] Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

4.2 Encephalopathy

Encephalopathy (eg, coma, prolonged seizures, or decreased level of consciousness) within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to administration of any pertussis containing vaccine, including Adacel vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

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

5.2 Latex

The tip caps of the Adacel prefilled syringe may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals. The vial stopper is not made with natural rubber latex. [See *HOW SUPPLIED/STORAGE AND HANDLING* (*16).*]

5.3 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine found evidence for acceptance of 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 a dose of Adacel vaccine.

5.4 Progressive or Unstable Neurologic Disorders

Progressive or unstable neurologic conditions are reasons to defer Adacel. It is not known whether administration of Adacel to persons with an unstable or progressive neurologic disorder might hasten manifestations of the disorder or affect the prognosis. Administration of Adacel to persons with an unstable or progressive neurologic disorder may result in diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination.

5.5 Arthus-Type Hypersensitivity

Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive Adacel unless at least 10 years have elapsed since the last dose of a tetanus toxoid containing vaccine.

5.6 Altered Immunocompetence

If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See *Drug Interactions (7.2).*]

5.7 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including Adacel. Procedures should be in place to prevent falling injury and manage syncopal reactions.

6 ADVERSE REACTIONS

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. As with any vaccine, there is the possibility that broad use of Adacel vaccine could reveal adverse reactions not observed in clinical trials.

The safety of Adacel vaccine was evaluated in 5 clinical studies. A total of 7,143 individuals 10 through 64 years of age inclusive (4,695 adolescents 10 through 17 years of age and, 2,448 adults 18 through 64 years of age) received a single dose of Adacel vaccine.

Clinical study Td506 was a randomized, observer-blind, active controlled trial that enrolled adolescents 11 through 17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and adults 18 through 64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician’s office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician’s office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from participants via telephone contact. At least 96% of participants completed the 6-month follow-up evaluation.

Solicited Adverse Events in the US Adolescent and Adult Study (Td506)

The frequency of selected solicited adverse events (erythema, swelling, pain and fever) occurring during days 0-14 following vaccination with Adacel vaccine or Td vaccine in adolescents 11 through 17 years of age and adults 18 through 64 years of age are presented in Table 1. Most of these events were reported at a similar frequency in recipients of both Adacel vaccine and Td vaccine. Pain at the injection site was the most common adverse reaction in 62.9% to 77.8% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients.

Table 1:Frequencies of Solicited Injection Site Reactions and Fever for Adolescents and Adults, Days 0-14, Following Vaccination With Adacel Vaccine or Td Vaccine in Study Td506

Adverse Event*		Adolescents 11-17 years		Adults 18-64 years	
		Adacel N† = 1,170-1,175 (%)	Td‡ N† = 783-787 (%)	Adacel N† = 1,688-1,698 (%)	Td‡ N† = 551-561 (%)
Injection Site Pain	Any	77.8§	71.0	65.7	62.9
	Moderate**	18.0	15.6	15.1	10.2
	Severe††	1.5	0.6	1.1	0.9
Injection Site Swelling	Any	20.9	18.3	21.0	17.3
	Moderate**				
	1.0 to 3.4 cm	6.5	5.7	7.6	5.4
	Severe††				
	≥3.5 cm	6.4	5.5	5.8	5.5
	≥5 cm (2 inches)	2.8	3.6	3.2	2.7
Injection Site Erythema	Any	20.8	19.7	24.7	21.6
	Moderate**				
	1.0 to 3.4 cm	5.9	4.6	8.0	8.4
	Severe††				
	≥3.5 cm	6.0	5.3	6.2	4.8
	≥5 cm (2 inches)	2.7	2.9	4.0	3.0
Fever	≥38.0°C (≥100.4°F)	5.0§	2.7	1.4	1.1
	≥38.8°C to ≤39.4°C (≥102.0°F to ≤103.0°F)	0.9	0.6	0.4	0.2
	≥39.5°C (≥103.1°F)	0.2	0.1	0.0	0.2

* The study sample size was designed to detect >10% differences between Adacel and Td vaccines for events of 'Any' intensity.

† N = number of participants with available data.

‡ Tetanus and Diphtheria Toxoids Adsorbed for Adult Use manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

§ Adacel vaccine did not meet the non-inferiority criterion for rates of 'Any' Pain in adolescents compared to Td vaccine rates (upper limit of the 95% CI on the difference for Adacel vaccine minus Td vaccine was 10.7% whereas the criterion was <10%). For 'Any' Fever the non-inferiority criteria was met, however, 'Any' Fever was statistically higher in adolescents receiving Adacel vaccine.

** Interfered with activities, but did not necessitate medical care or absenteeism.

†† Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

The frequency of other solicited adverse events (days 0-14) are presented in Table 2. The rates of these events following Adacel vaccine were comparable with those observed with Td vaccine. Headache was the most frequent systemic reaction and was usually of mild to moderate intensity.

Table 2: Frequencies of Other Solicited Adverse Events for Adolescents and Adults, Days 0-14, Following Vaccination With Adacel Vaccine or Td Vaccine in Study Td506

Adverse Event		Adolescents 11-17 years		Adults 18-64 years	
		Adacel N* = 1,174-1,175 (%)	Td† N* = 787 (%)	Adacel N* = 1,697-1,698 (%)	Td† N* = 560-561 (%)
Headache	Any	43.7	40.4	33.9	34.1
	Moderate‡	14.2	11.1	11.4	10.5
	Severe§	2.0	1.5	2.8	2.1
Body Ache or Muscle Weakness	Any	30.4	29.9	21.9	18.8
	Moderate‡	8.5	6.9	6.1	5.7
	Severe§	1.3	0.9	1.2	0.9
Tiredness	Any	30.2	27.3	24.3	20.7
	Moderate‡	9.8	7.5	6.9	6.1
	Severe§	1.2	1.0	1.3	0.5
Chills	Any	15.1	12.6	8.1	6.6
	Moderate‡	3.2	2.5	1.3	1.6
	Severe§	0.5	0.1	0.7	0.5
Sore and Swollen Joints	Any	11.3	11.7	9.1	7.0
	Moderate‡	2.6	2.5	2.5	2.1
	Severe§	0.3	0.1	0.5	0.5
Nausea	Any	13.3	12.3	9.2	7.9
	Moderate‡	3.2	3.2	2.5	1.8
	Severe§	1.0	0.6	0.8	0.5
Lymph Node Swelling	Any	6.6	5.3	6.5	4.1
	Moderate‡	1.0	0.5	1.2	0.5
	Severe§	0.1	0.0	0.1	0.0
Diarrhea	Any	10.3	10.2	10.3	11.3
	Moderate‡	1.9	2.0	2.2	2.7
	Severe§	0.3	0.0	0.5	0.5
Vomiting	Any	4.6	2.8	3.0	1.8
	Moderate‡	1.2	1.1	1.0	0.9
	Severe§	0.5	0.3	0.5	0.2
Rash	Any	2.7	2.0	2.0	2.3

* N = number of participants with available data.

† Tetanus and Diphtheria Toxoids Adsorbed for Adult Use manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

‡ Interfered with activities, but did not necessitate medical care or absenteeism.

§ Incapacitating, prevented the performance of usual activities, may have/or did necessitate medical care or absenteeism.

Injection site and systemic solicited reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most injection site reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two vaccine groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of extensive limb swelling of the injected limb in study Td506, nor in the other three studies which also contributed to the safety database for Adacel vaccine.

Injection Site and Systemic Reactions When Given With Hepatitis B Vaccine

In the concomitant vaccination study with Adacel and Hepatitis B vaccines [see *Clinical Studies (14)*], injection site and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Injection site adverse events were only monitored at site/arm of Adacel vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, ie, up to 6 months post-vaccination.

The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups.

Injection Site and Systemic Reactions When Given With Trivalent Inactivated Influenza Vaccine (TIV)

In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine [see *Clinical Studies (14)*], injection site and systemic adverse events were monitored for

14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, ie, up to 84 days, only events that elicited seeking medical attention were collected.

The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and TIV. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups.

Additional Studies

In an additional study, 1,806 adolescents 11 through 17 years of age received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11 through 17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days.

An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing ‘any’ local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

An additional study, Td519, enrolled 1,302 individuals in an open label, two-arm, multi-center trial (651subjects in each group) to evaluate the safety and immunogenicity of a single dose of Adacel administered to persons 10 to < 11 years of age compared to persons 11 to < 12 years of age. Immediate reactions were monitored for 20 minutes post-vaccination. Solicited local and systemic adverse events were monitored for 7 days post-vaccination using a diary card. Unsolicited and serious adverse events were collected for approximately 30 days post-vaccination. Similar rates of immediate, solicited and unsolicited adverse reactions were reported in each of the two age cohorts. One serious adverse event, not related to vaccination, was reported in the younger age group.

Serious Adverse Events in All Safety Studies

In all the studies, participants were monitored for serious adverse events throughout the duration of the study.

Throughout the 6-month follow-up period in study Td506, serious adverse events were reported in 1.5% of Adacel vaccine recipients and in 1.4% of Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials in participants up to 64 years of age and no additional neuropathic events were reported.

6.2 Postmarketing Experience

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

The following adverse events were included based on one or more of the following factors: severity, frequency of reporting or strength of evidence for a causal relationship to Adacel vaccine.

- **Immune system disorders**

  Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension)

- **Nervous system disorders**

  Paraesthesia, hypoesthesia, Guillain-Barré syndrome, brachial neuritis, facial palsy, convulsion, syncope, myelitis

- **Cardiac disorders**

  Myocarditis

- **Skin and subcutaneous tissue disorders**

  Pruritus, urticaria

- **Musculoskeletal and connective tissue disorders**

  Myositis, muscle spasm

- **General disorders and administration site conditions**

  Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints

  Injection site bruising, sterile abscess

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

When Adacel vaccine is administered concomitantly with other injectable vaccines or Tetanus Immune Globulin, they should be given with separate syringes and at different injection sites. Adacel should not be mixed with any other vaccine in the same syringe or vial.

In clinical studies, Adacel vaccine was administered concomitantly with one of the following US-licensed vaccines: Hepatitis B (10 mcg, two dose regimen) or trivalent inactivated influenza vaccines (TIV). [See *Adverse Reactions (6.1) and CLINICAL STUDIES (14).*]

Hepatitis B Vaccine

Concomitant immunization of Adacel vaccine with Hepatitis B vaccine did not result in reduced antibody responses to any of the antigens from either vaccine.

Trivalent Inactivated Influenza Vaccine (TIV)

No interference in tetanus and diphtheria seroprotection rates and responses to influenza vaccine, detoxified pertussis toxin (PT), fimbriae types 2 and 3 (FIM) or filamentous hemagglutinin (FHA) were observed when Adacel vaccine was administered concomitantly with TIV compared to separate administration. A lower pertactin (PRN) GMC was observed when Adacel vaccine was administered concomitantly with TIV compared to separate administration.

7.2 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 vaccines. [See *Warnings And Precautions (5.6).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed.

Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

Registry of Receipt of Adacel Vaccine During Pregnancy

Sanofi Pasteur Inc. maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. Women who receive Adacel vaccine during pregnancy are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE).

8.3 Nursing Mothers

It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

8.4 Pediatric Use

Adacel vaccine is not approved for individuals less than 10 years of age. Safety and effectiveness of Adacel vaccine in persons less than 10 years of age have not been established.

8.5 Geriatric Use

Adacel vaccine is not approved for use in individuals 65 years of age and older.

In a clinical study, individuals 65 years of age and older received a single dose of Adacel vaccine. Based on pre-specified criteria, persons 65 years of age and older who received a dose of Adacel vaccine had lower geometric mean concentrations of antibodies to PT, PRN and FIM when compared to infants who had received a primary series of DAPTACEL®, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP). [See Section 14 for description of DAPTACEL vaccine.]

11 DESCRIPTION

Adacel vaccine is a sterile isotonic suspension of tetanus and diphtheria toxoids and pertussis antigens adsorbed on aluminum phosphate, for intramuscular injection.

Each 0.5 mL dose contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)].Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative). The antigens are the same as those in DAPTACEL vaccine; however, Adacel vaccine is formulated with reduced quantities of diphtheria and detoxified PT.

The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (2) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and co-purified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde, and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed onto aluminum phosphate.

The tetanus toxin is produced from *Clostridium tetani* grown in modified Mueller-Miller

casamino acid medium without beef heart infusion. (3) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. *Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. (4) After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection. Adacel vaccine does not contain a preservative.

In the guinea pig potency test, 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. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA).

Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tetanus

Tetanus is a disease manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C tetani*.

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 assay is considered the minimum protective level. (5) (6)

Diphtheria

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 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. (5) Levels of 1.0 IU/mL have been associated with long-term protection. (7)

Pertussis

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

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy of the tetanus toxoid and diphtheria toxoid used in Adacel vaccine was based on the immune response to these antigens compared to a US licensed Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) vaccine manufactured by Sanofi Pasteur Inc., Swiftwater, PA. The primary measures for immune response to the diphtheria and tetanus toxoids were the percentage of participants attaining an antibody level of at least 0.1 IU/mL.

The efficacy of the pertussis antigens used in Adacel vaccine was inferred based on a comparison of pertussis antibody levels achieved in recipients of a single booster dose of Adacel vaccine with those obtained in infants after three doses of DAPTACEL vaccine. In the Sweden I Efficacy Trial, three doses of DAPTACEL vaccine were shown to confer a protective efficacy of 84.9% (95% CI: 80.1%, 88.6%) against WHO defined pertussis (21 days of paroxysmal cough with laboratory-confirmed *B pertussis* infection or epidemiological link to a confirmed case). The protective efficacy against mild pertussis (defined as at least one day of cough with laboratory-confirmed *B pertussis* infection) was 77.9% (95% CI: 72.6%, 82.2%). (8)

In addition, the ability of Adacel vaccine to elicit a booster response (defined as rise in antibody concentration after vaccination) to the tetanus, diphtheria and pertussis antigens following vaccination was evaluated. The demonstration of a booster response depended on the antibody concentration to each antigen as established based on the 95th percentile of the pre-vaccination antibody concentrations observed in historical clinical trials with Adacel vaccine.

14.1 Immunological Evaluation in Adolescents and Adults, 10 Through 64 Years of Age

Study Td506 was a comparative, multi-center, randomized, observer-blind, controlled trial which enrolled 4,480 participants; 2,053 adolescents (11 through 17 years of age) and 2,427 adults (18 through 64 years of age). Enrollment was stratified by age to ensure adequate representation across the entire age range. Participants had not received a tetanus or diphtheria toxoid containing vaccine within the previous 5 years. After enrollment participants were randomized to receive one dose of either Adacel vaccine or Td vaccine. A total of 4,461 randomized participants were vaccinated. The per-protocol immunogenicity subset included 1,270 Adacel vaccine recipients and 1,026 Td vaccine recipients. Sera were obtained before and approximately 35 days after

vaccination. [Blinding procedures for safety assessments are described in *ADVERSE REACTIONS (6)*.]

Demographic characteristics were similar within age groups and between the vaccine groups. A total of 76% of the adolescents and 1.1% of the adults reported a history of receiving 5 previous doses of diphtheria-tetanus-pertussis containing vaccines. Anti-tetanus and anti-diphtheria seroprotection rates (≥0.1 IU/mL) and booster response rates were comparable between Adacel and Td vaccines. (See Table 3 and Table 4.) Adacel vaccine induced pertussis antibody levels that were non-inferior to those of Swedish infants who received three doses of DAPTACEL vaccine. (See Table 5.) Acceptable booster responses to each of the pertussis antigens were also demonstrated, ie, the percentage of participants with a booster response exceeded the pre-defined lower limit. (See Table 6.)

Table 3: Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Tetanus Toxoid Following Adacel Vaccine as Compared to Td Vaccine in Adolescents and Adults 11 Through 64 Years of Age

			Tetanus Antitoxin (IU/mL)				
			Pre-vaccination		1 Month Post-vaccination		
Age Group (years)	Vaccine	N*	% ≥0.10 (95% CI)	% ≥1.0 (95% CI)	% ≥0.10 (95% CI)	% ≥1.0 (95% CI)	% Booster† (95% CI)
11-17	Adacel	527	99.6 (98.6, 100.0)	44.6 (40.3, 49.0)	100.0‡ (99.3, 100.0)	99.6§ (98.6, 100.0)	91.7‡ (89.0, 93.9)
	Td**	516	99.2 (98.0, 99.8)	43.8 (39.5, 48.2)	100.0 (99.3, 100.0)	99.4 (98.3, 99.9)	91.3 (88.5, 93.6)
18-64	Adacel	742-743	97.3 (95.9, 98.3)	72.9 (69.6, 76.1)	100.0‡ (99.5, 100.0)	97.8§ (96.5, 98.8)	63.1‡ (59.5, 66.6)
	Td**	509	95.9 (93.8, 97.4)	70.3 (66.2, 74.3)	99.8 (98.9, 100.0)	98.2 (96.7, 99.2)	66.8 (62.5, 70.9)

* N = number of participants in the per-protocol population with available data.

† Booster response is defined as: A four-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for tetanus was 2.7 IU/mL.

‡ Seroprotection rates at ≥0.10 IU/mL and booster response rates to Adacel vaccine were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel vaccine <10%).

§ Seroprotection rates at ≥1.0 IU/mL were not prospectively defined as a primary endpoint.

** Tetanus and Diphtheria Toxoids Adsorbed for Adult Use manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

Table 4:Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Diphtheria Toxoid Following Adacel Vaccine as Compared to Td Vaccine in Adolescents and Adults 11 Through 64 Years of Age

			Diphtheria Antitoxin (IU/mL)				
			Pre-vaccination		1 Month Post-vaccination		
Age Group (years)	**Vaccine**	**N***	**% ≥0.10 (95% CI)**	**% ≥1.0 (95% CI)**	**% ≥0.10 (95% CI)**	**% ≥1.0 (95% CI)**	**% Booster† (95% CI)**
11-17	**Adacel**	**527**	72.5 (68.5, 76.3)	15.7 (12.7, 19.1)	99.8‡ (98.9, 100.0)	98.7§ (97.3, 99.5)	95.1‡ (92.9, 96.8)
	Td**	**515-516**	70.7 (66.5, 74.6)	17.3 (14.1, 20.8)	99.8 (98.9, 100.0)	98.4 (97.0, 99.3)	95.0 (92.7, 96.7)
18-64	**Adacel**	**739-741**	62.6 (59.0, 66.1)	14.3 (11.9, 17.0)	94.1‡ (92.1, 95.7)	78.0§ (74.8, 80.9)	87.4‡ (84.8, 89.7)
	Td**	**506-507**	63.3 (59.0, 67.5)	16.0 (12.9, 19.5)	95.1 (92.8, 96.8)	79.9 (76.1, 83.3)	83.4 (79.9, 86.5)

* N = number of participants in the per-protocol population with available data.

† Booster response is defined as: A four-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off value for diphtheria was 2.56 IU/mL.

‡ Seroprotection rates at ≥0.10 IU/mL and booster response rates to Adacel vaccine were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel vaccine <10%).

§ Seroprotection rates at ≥1.0 IU/mL were not prospectively defined as a primary endpoint.

** Tetanus and Diphtheria Toxoids Adsorbed for Adult Use manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

Table 5: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs)¥ Observed One Month After a Dose of Adacel Vaccine in Adolescents and Adults 11 Through 64 Years of Age Compared With Those Observed in Infants One Month Following Vaccination at 2, 4 and 6 Months of Age in the Efficacy Trial With DAPTACEL Vaccine

	Adolescents 11-17 Years of Age	**Adults 18-64 Years of Age**
	Adacel*/DAPTACEL† **GMC Ratio** **(95% CIs)**	**Adacel‡/DAPTACEL†** **GMC Ratio** **(95% CIs)**
Anti-PT	3.6 (2.8, 4.5)§	2.1 (1.6, 2.7)§
Anti-FHA	5.4 (4.5, 6.5)§	4.8 (3.9, 5.9)§
Anti-PRN	3.2 (2.5, 4.1)§	3.2 (2.3, 4.4)§
Anti-FIM	5.3 (3.9, 7.1)§	2.5 (1.8, 3.5)§

¥ Antibody GMCs, measured in arbitrary ELISA units were calculated separately for infants, adolescents and adults.

* N = 524 to 526, number of adolescents in the per-protocol population with available data for Adacel vaccine.

† N = 80, number of infants who received DAPTACEL vaccine with available data post-dose 3 (Sweden Efficacy I).

‡ N = 741, number of adults in the per-protocol population with available data for Adacel vaccine.

§ GMC following Adacel vaccine was non-inferior to GMC following DAPTACEL vaccine (lower limit of 95% CI on the ratio of GMC for Adacel vaccine divided by DAPTACEL vaccine >0.67).

Table 6: Booster Response Rates to the Pertussis Antigens Observed One Month After a Dose of Adacel Vaccine in Adolescents and Adults 11 Through 64 Years of Age

	Adolescents 11-17 Years of Age		Adults 18-64 Years of Age		Pre-defined Acceptable Rates* % †
	N‡	% (95% CI)	N‡	% (95% CI)	
Anti-PT	524	92.0 (89.3, 94.2)	739	84.4 (81.6, 87.0)	81.2
Anti-FHA	526	85.6 (82.3, 88.4)	739	82.7 (79.8, 85.3)	77.6
Anti-PRN	525	94.5 (92.2, 96.3)	739	93.8 (91.8, 95.4)	86.4
Anti-FIM	526	94.9 (92.6, 96.6)	739	85.9 (83.2, 88.4)	82.4

* The acceptable response rate for each antigen was defined as the lower limit of the 95% CI for the rate being no more than 10% lower than the response rate observed in previous clinical trials.

† A booster response for each antigen was defined as a four-fold rise in antibody concentration if the pre-vaccination concentration was equal to or below the cut-off value and a two-fold rise in antibody concentration if the pre-vaccination concentration was above the cut-off value. The cut-off values for pertussis antigens were established based on antibody data from both adolescents and adults in previous clinical trials.
The cut-off values were 85 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN and 285 EU/mL for FIM.

‡ N = number of participants in the per-protocol population with available data.

Study Td519 assessed the comparative immunogenicity of Adacel administered to adolescents (10 to < 11 years of age and 11 to < 12 years of age) [see *Adverse Reactions* (6.1).] In this study non-inferiority was demonstrated for booster responses to tetanus and diphtheria toxoids, GMCs to the pertussis antigens (PT, FHA, PRN and FIM) and booster responses to the pertussis antigens PT, FHA and PRN. For FIM, non-inferiority was not demonstrated as the lower bound of the 95% CI of the difference in booster response rates (-5.96%) did not meet the predefined criterion (>-5% when the booster response in the older age group was >95%).

14.2 Concomitant Hepatitis B Vaccine Administration

The concomitant use of Adacel vaccine and hepatitis B (Hep B) vaccine (Recombivax HB®, 10 mcg per dose using a two-dose regimen, manufactured by Merck and Co., Inc) was evaluated in a multi-center, open-labeled, randomized, controlled study that enrolled 410 adolescents, 11 through 14 years of age inclusive. One group received Adacel and Hep B vaccines concurrently (N = 206). The other group (N = 204) received Adacel vaccine at the first visit, then 4-6 weeks later received Hep B vaccine. The second dose of Hep B vaccine was given 4-6 weeks after the first dose. Serum samples were obtained prior to and 4-6 weeks after Adacel vaccine administration, as well as 4-6 weeks after the 2nd dose of Hep B for all participants. No interference was observed in the immune responses to any of the vaccine antigens when Adacel and Hep B vaccines were given concurrently or separately. [See *ADVERSE REACTIONS (6.1).*]

14.3 Concomitant Influenza Vaccine Administration

The concomitant use of Adacel vaccine and trivalent inactivated influenza vaccine (TIV, Fluzone®, manufactured by Sanofi Pasteur Inc., Swiftwater, PA) was evaluated in a multi-center, open-labeled, randomized, controlled study conducted in 720 adults, 19-64 years of age inclusive. In one group, participants received Adacel and TIV vaccines concurrently (N = 359). The other group received TIV at the first visit, then 4-6 weeks later received Adacel vaccine (N = 361). Sera were obtained prior to and 4-6 weeks after Adacel vaccine, as well as 4-6 weeks after the TIV. The immune responses were comparable for concurrent and separate administration of Adacel and TIV vaccines for diphtheria (percent of participants with seroprotective concentration ≥0.10 IU/mL and booster responses), tetanus (percent of participants with seroprotective concentration ≥0.10 IU/mL), pertussis antigens (booster responses and GMCs except lower PRN GMC in the concomitant group, lower bound of the 90% CI was 0.61 and the pre-specified criterion was

≥0.67) and influenza antigens (percent of participants with hemagglutination-inhibition [HI] antibody titer ≥1:40 IU/mL and ≥4-fold rise in HI titer). Although tetanus booster response rates were significantly lower in the group receiving the vaccines concurrently versus separately, greater than 98% of participants in both groups achieved seroprotective levels of ≥0.1 IU/mL. [See *ADVERSE REACTIONS (6.1)*.]

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16 HOW SUPPLIED/STORAGE AND HANDLING

Syringe, without needle, 1 dose - NDC No. 49281-400-88; in package of 5 syringes, NDC No. 49281-400-15. The tip caps of the prefilled syringes may contain natural rubber latex. No other components are made with natural rubber latex.

Vial, 1 dose - NDC No. 49281-400-58; in package of 5 vials; NDC No. 49281-400-05. The vial stopper is not made with natural rubber latex.

Vial, 1 dose - NDC No. 49281-400-58; in package of 10 vials; NDC No. 49281-400-10. The vial stopper is not made with natural rubber latex.

Adacel vaccine should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

Before administration of Adacel vaccine, health-care providers should inform the patient, parent or guardian of the benefits and risks of the vaccine and the importance of receiving recommended booster dose unless a contraindication to further immunization exists.

The health-care provider should inform the patient, parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The patient, parent or guardian should be instructed to report any serious adverse reactions to their health-care provider.

Pregnancy Exposure Registry [See *USE IN SPECIFIC POPULATIONS (8.1).]*

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