

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

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 U.S. Approval: 2005

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

Warnings and Precautions, deleted latex warning 12/2020

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

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

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

For intramuscular injection only.

- Each dose of Adacel is administered as a 0.5 mL injection. (2.1)
- For routine booster vaccination, a first dose of Adacel is administered 5 years or more after the last dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) series or 5 years or more after vaccination with Tetanus and Diphtheria Toxoids Adsorbed (Td). A second dose of Adacel may be administered 8 years or more after the first dose with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).
- Adacel may be administered for tetanus prophylaxis for wound management. For management of a tetanus prone wound, a booster dose of Adacel may be administered if at least 5 years have elapsed since previous receipt of a tetanus toxoid containing vaccine. (2.2)

-----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-----

- 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-----

- Following the first vaccination with Adacel, the most common solicited adverse reactions within 0-14 days of vaccination for Adolescents (11-17 years of age)/Adults (18-64 years of age) were: injection site pain (77.8%/65.7%), headache (43.7%/33.9%), body ache or muscle weakness (30.4%/21.9%), tiredness (30.2%/24.3%), injection site swelling (20.9%/21.0%), and injection site erythema (20.8%/24.7%). (6.1)
- Following a second vaccination with Adacel, the most common solicited reactions occurring within 0-7 days of vaccination for Adults (18-64 years of age) were: injection site pain (87.1%), myalgia (58.1%), headache (41.4%), malaise (33.3%), injection site swelling (6.9%), and injection site erythema (6.4%). (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 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 administered alone. (7.1, 14.4)
- Immunosuppressive therapies may reduce the immune response to Adacel. (7.2)
- Do not mix Adacel with any other vaccine in the same syringe or vial.

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

- Pregnancy Exposure Registry: contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Preparation for Administration
- 2.2 Administration, Dose and Schedule

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity
- 4.2 Encephalopathy

5 WARNINGS AND PRECAUTIONS

- 5.1 Management of Acute Allergic Reactions
- 5.2 Guillain-Barré Syndrome and Brachial Neuritis
- 5.3 Progressive or Unstable Neurologic Disorders
- 5.4 Arthus-Type Hypersensitivity
- 5.5 Altered Immunocompetence
- 5.6 Syncope

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Concomitant Vaccine Administration
- 7.2 Immunosuppressive Treatments

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Immunological Evaluation in Adolescents and Adults, 11 through 64 Years of Age Following a First Vaccination with Adacel
- 14.2 Immunological Evaluation in Adults, 18 through 64 Years of Age Following a Second Vaccination with Adacel
- 14.3 Concomitant Hepatitis B Vaccine Administration
- 14.4 Concomitant Influenza Vaccine Administration

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

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.

Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

Adacel should not be combined through reconstitution or mixed with any other vaccine. Discard unused portion in vial.

2.2 Administration, Dose and Schedule

Adacel is administered as a single 0.5 mL intramuscular injection.

Routine Booster Vaccination

A first dose of Adacel is administered 5 years or more after the last dose of the Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) series or 5 years or more after a dose of Tetanus and Diphtheria Toxoids Adsorbed (Td). A second dose of Adacel may be administered 8 years or more after the first dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

Wound Management

Adacel may be administered for tetanus prophylaxis for wound management. For management of a tetanus prone wound, a booster dose of Adacel may be administered if at least 5 years have elapsed since previous receipt of a tetanus toxoid containing vaccine.

3 DOSAGE FORMS AND STRENGTHS

Adacel is a suspension for injection available in 0.5 mL single-dose vials and prefilled syringes. [See *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. [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.

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 Guillain-Barré Syndrome and Brachial Neuritis

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. A review by the Institute of Medicine found evidence for acceptance of a causal relation between tetanus toxoid and brachial neuritis. (1)

5.3 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.

5.4 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.

5.5 Altered Immunocompetence

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

5.6 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccine, 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 could reveal adverse reactions not observed in clinical trials.

The safety of a first vaccination with Adacel was evaluated in 5 clinical studies. Three of the studies were conducted in the U.S. and 2 were conducted in Canada. Of the study participants, 86% were Caucasian, 8% Black, 3% Hispanic, 1% Asian and 2% of other ethnic origin. 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.

U.S. Adolescent and Adult Study of a First Vaccination with Adacel (Td506)

Clinical study Td506 was a randomized, observer-blind, active-controlled trial that enrolled adolescents 11 through 17 years of age (Adacel N = 1,184; DECAVAC (Tetanus and Diphtheria Toxoids Adsorbed; manufactured by Sanofi Pasteur Inc., Swiftwater, PA) N = 792) and adults 18 through 64 years of age (Adacel N = 1,752; DECAVAC 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 to 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.

The frequency of selected solicited adverse reactions (erythema, swelling, pain and fever) occurring during days 0 to 14 following vaccination with Adacel 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 reactions were reported at a similar frequency in recipients of both Adacel 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 compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel and Td vaccine groups. Among adults, the rates of pain after receipt of Adacel 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 recipients than Td vaccine recipients.

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

Adverse Reactions*		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 manufactured by Sanofi Pasteur Inc., Swiftwater, PA.
- § Adacel 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 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.
- ¶ 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 reactions (days 0-14) are presented in Table 2. The rates of these reactions following a first vaccination with Adacel 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 Reactions for Adolescents and Adults, Days 0-14, Following a First Vaccination with Adacel or Td Vaccine in Study Td506

Adverse Reaction		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 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 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.

Adult Study of a Second Vaccination with Adacel (Td537)

In a randomized, observer-blind, active-controlled, multi-center study (Td537), adults 18 through 64 years of age who had received a first dose of Adacel 8-12 years previously were enrolled and randomized to receive either Adacel (N = 1002) or a US licensed Td vaccine, TENIVAC (Tetanus and Diphtheria Toxoids Adsorbed; manufactured by Sanofi Pasteur, Limited) (N = 328). Subjects were recruited from the primary licensure study Td506 and the Canadian general public and had not received Td or Tdap vaccine since their initial Adacel dose. The demographic characteristics for study participants were similar for both vaccine groups. The mean ages were 28.9 years for the Adacel group and 29.2 years for the Td group. Overall, there were more female participants in both the Adacel group and Td group; 64.5% and 64.6%, respectively. In both vaccine groups, greater than 94% of subjects identified as white and 99% as non-Hispanic or Latino.

Safety data were collected from all participants who received the study vaccine (N = 999 for the Adacel group; N = 328 for the Td group). Solicited local and systemic reactions and unsolicited adverse events were monitored for 7 days post-vaccination using a diary card. Unsolicited adverse events were collected for approximately 28 days post-vaccination. Serious adverse events were collected throughout the study period (up to 6 months post-vaccination).

Solicited adverse reactions reported to occur during days 0-7 following vaccination are presented in Table 3.

Table 3: Frequencies of Solicited Adverse Reactions 0-7 Days Following a Second Vaccination with Adacel Compared to Td Vaccine in Study Td537 - Safety Analysis Set

Adverse Reaction		Adacel (N=999) (%)	Td Adsorbed* (N=328) (%)
Injection site pain	Any	87.1	87.4
	Grade 2 [†]	28.5	31.4
	Grade 3 [‡]	3.6	2.8
Injection site erythema	Any	6.4	5.5
	Grade 2 (≥51 to ≤100 mm)	2.1	2.8
	Grade 3 (>100 mm)	0.2	0.0
Injection site swelling	Any	6.9	8.0
	Grade 2 (≥51 to ≤100 mm)	2.4	2.2
	Grade 3 (>100 mm)	0.3	0.0
Fever	Any	0.9	1.8
	Grade 2 (≥38.5°C to ≤38.9°C or ≥101.2°F to ≤102.0°F)	0.3	0.6
	Grade 3 (≥102.1°F)	0.2	0.3
Headache	Any	41.4	39.1
	Grade 2 [†]	12.4	10.5
	Grade 3 [‡]	2.6	4.0
Malaise	Any	33.3	30.8
	Grade 2 [†]	9.3	9.8
	Grade 3 [‡]	3.0	3.7
Myalgia	Any	58.1	58.2
	Grade 2 [†]	18.7	16.9
	Grade 3 [‡]	3.0	3.1

N = number of participants with available data

* Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

† Some interference with activity

‡ Significant; prevents daily activity

Adult Study of a Second Vaccination with Adacel (Td518)

Study Td518 was a descriptive, open-label, post-marketing, multi-center study evaluating the safety of Adacel readministration in adults 5 years following a previous dose of Adacel. The mean age of subjects was 31.7 years, there were more females (52.2%) than males (47.8%) and 89.9% of subjects were Caucasian. Solicited adverse reactions were collected for 14 days following vaccination. SAEs were monitored for 6 months following vaccination. A total of 545 subjects 16-69 years of age were enrolled. All participants in this study received a first dose of Adacel vaccine as part of Sanofi Pasteur studies Td501, Td502, or Td505. Approximately 90% of the participants had at least one solicited injection site reaction. The most frequently reported injection site reactions were pain in 87.6% of subjects, followed by erythema/redness in 28.6%, and swelling in 25.6%. Approximately 77% of the participants had at least one solicited systemic reaction. The most frequently reported solicited systemic adverse reactions in subjects who received a second dose of Adacel were myalgia (61%), followed by headache (53.2%), malaise (38.2%), and fever (6.5%).

Injection Site and Systemic Reactions Following Adacel Given Concomitantly with Hepatitis B Vaccine

In the concomitant vaccination study with Adacel (first vaccination) and Hepatitis B vaccine [Recombivax HB] (Td501) [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 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 administration site) were similar when Adacel and Hepatitis B vaccine 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 administration site were increased when coadministered. 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 Following Adacel Given Concomitantly with Trivalent Inactivated Influenza Vaccine (TIV)

In the concomitant vaccination study with Adacel (first vaccination) and trivalent inactivated influenza vaccine [Fluzone] (Td502) [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 and TIV. However, pain at the Adacel 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 was similar between the 2 study groups.

Additional Studies

In an additional study (Td505), 1,806 adolescents 11 through 17 years of age received Adacel (first vaccination) as part of the lot consistency study used to support Adacel 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 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 in three supportive Canadian studies (TC9704, Td9707 and TD9805) used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following the first vaccination with Adacel were similar to those reported in the four principal trials in the U.S. 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 recipients in the supportive Canadian studies.

An additional study (Td519) enrolled 1,302 individuals in an open label, two-arm, multicenter trial (651 participants in each group) to evaluate the safety and immunogenicity of a first vaccination with 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

Throughout the 6-month follow-up period following a first vaccination with Adacel in study Td506, SAEs were reported in 1.5% of Adacel recipients and in 1.4% of Td vaccine recipients. Two SAEs in adults were neuropathic events that occurred within 28 days of Adacel 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 following a first vaccination with Adacel in participants up to 64 years of age and no additional neuropathic events were reported.

In study Td537 when a second vaccination of Adacel was administered 8-12 years following the initial vaccination of Adacel, a total of 8 participants (0.8%) in the Adacel group and 1 participant (0.3%) in the Td group reported SAEs during the 6-month follow-up period. All SAEs were considered by the investigator to be unrelated to the study vaccine.

In study Td518, seven participants experienced an SAE, all of which were considered by the investigator to be unrelated to the study vaccine.

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.

- ***Immune system disorders***
Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension)
- ***Nervous system disorders***
Paresthesia, 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, Arthus hypersensitivity

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

When Adacel 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.

Trivalent Inactivated Influenza Vaccine (TIV)

In a clinical study Adacel (first vaccination) was administered concomitantly with a US-licensed trivalent inactivated influenza vaccine (TIV). [See *ADVERSE REACTIONS (6.1)* and *CLINICAL STUDIES (14)*.]

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 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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Adacel during pregnancy. Women who receive Adacel during pregnancy are encouraged to contact directly, or have their healthcare professional contact, Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE).

Risk Summary

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Adacel administration in pregnant women in the U.S.

Available data suggest the rates of major birth defects and miscarriage in women who receive Adacel within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates. (See *Data*)

Two developmental toxicity studies were performed in female rabbits given 0.5 mL (a single human dose) of Adacel twice prior and during gestation. The studies revealed no evidence of harm to the fetus due to Adacel. (See *Data*)

Data

Human Data

An assessment of data from the ongoing pregnancy registry over 12 years (2005-2017) included 1518 reports of exposure to Adacel vaccine from 30 days before or at any time during pregnancy. Of these reports, 543 had known pregnancy outcomes available and were enrolled in the registry prior to the outcomes being known. Among the 543 pregnancies with known outcomes, the timing of Adacel vaccination was not known for 126 of the pregnancies.

Of the prospectively followed pregnancies for whom the timing of Adacel vaccination was known, 374 women received Adacel during the 30 days prior to conception through the second trimester. Outcomes among these prospectively followed pregnancies included 5 infants with major birth defects and 25 cases of miscarriage.

Animal Data

The effect of Adacel on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies in female rabbits. Animals were administered 0.5 mL (a single human dose) of Adacel twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29. 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.

8.2 Lactation

Risk Summary

It is not known whether Adacel vaccine components are excreted in human milk. Data are not available to assess the effect of administration of Adacel on breast-fed infants or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Adacel and any potential adverse effects on the breastfed child from Adacel or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

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

8.5 Geriatric Use

Adacel 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. Based on prespecified criteria, persons 65 years of age and older who received a dose of Adacel 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 *CLINICAL STUDIES (14)* for description of DAPTACEL.]

11 DESCRIPTION

Adacel 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; however, Adacel 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 copurified 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 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 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

The effectiveness of the tetanus toxoid and diphtheria toxoid used in Adacel 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 effectiveness of the pertussis antigens used in Adacel was evaluated based on a comparison of pertussis antibody levels achieved in recipients of Adacel with those obtained in infants after three or four doses of DAPTACEL. For the first dose of Adacel, the comparisons were to infants who received three doses of DAPTACEL in the Sweden I Efficacy trial. For the second dose of Adacel, for the evaluation of FHA, PRN, and FIM antibody levels, the comparisons were to infants who received three doses of DAPTACEL in the Sweden I Efficacy trial; for evaluation of PT antibody levels, the comparison was to infants who received four doses of DAPTACEL in a

US safety and immunogenicity study (Study M5A10). 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 to elicit a booster response (defined as rise in antibody concentration after vaccination) to the tetanus, diphtheria and pertussis antigens following vaccination was evaluated.

14.1 Immunological Evaluation in Adolescents and Adults, 11 through 64 Years of Age Following a First Vaccination with Adacel

Study Td506 was a comparative, multi-center, randomized, observer-blind, controlled trial which enrolled 4,480 participants; 2,053 adolescents (11-17 years of age) and 2,427 adults (18-64 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 or Td vaccine. A total of 4,461 randomized participants were vaccinated. The per-protocol immunogenicity subset included 1,270 Adacel 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 4 and Table 5.) Adacel induced pertussis antibody levels that were non-inferior to those of Swedish infants who received three doses of DAPTACEL vaccine (Sweden I Efficacy Study). (See Table 6.) Acceptable booster responses to each of the pertussis antigens were also demonstrated, ie, the percentage of participants with a booster response exceeded the predefined lower limit. (See Table 7.)

Table 4: Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Tetanus Toxoid Following A First Vaccination with Adacel Vaccine as Compared to Td Vaccine in Adolescents and Adults 11 through 64 Years of Age (Td506)

			Anti-Tetanus toxoid (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 4-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a 2-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 were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel <10%).

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

[¶] Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

Table 5: Pre-vaccination and Post-vaccination Antibody Responses and Booster Response Rates to Diphtheria Toxoid Following A First Vaccination with Adacel as Compared to Td Vaccine in Adolescents and Adults 11 through 64 Years of Age (Td506)

			Anti-Diphtheria toxin (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 4-fold rise in antibody concentration, if the pre-vaccination concentration was equal to or below the cut-off value and a 2-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 were non-inferior to Td vaccine (upper limit of the 95% CI on the difference for Td vaccine minus Adacel <10%).

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

[¶] Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.

Table 6: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs)* Observed One Month Following A First Vaccination with Adacel 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 (Sweden I Efficacy Study)

	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.

[‡] N = 80, number of infants who received DAPTACEL with available data post dose 3 (Sweden Efficacy I).

[§] N = 741, number of adults in the per-protocol population with available data for Adacel.

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

Table 7: Booster Response Rates to the Pertussis Antigens Observed One Month Following a First Vaccination with Adacel in Adolescents and Adults 11 through 64 Years of Age

	Adolescents 11-17 Years of Age		Adults 18-64 Years of Age		Predefined 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 4-fold rise in antibody concentration if the pre-vaccination concentration was equal to or below the cut-off value and a 2-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 a first vaccination with 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 Immunological Evaluation in Adults, 18 through 64 Years of Age Following a Second Vaccination with Adacel

In study Td537 [See *ADVERSE REACTIONS (6.1)*.], subjects 18 to 64 years of age who had received a dose of Adacel 8-12 years previously, were randomized to receive a second dose of Adacel or Td vaccine (Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur, Limited). Blood samples for immunogenicity analyses were obtained from participants pre-vaccination and approximately 28 days post-vaccination. The per-protocol analysis set was used for all immunogenicity analyses, and included 948 participants in the Adacel group and 317 participants in the Td control vaccine group. Of the study participants, 35% were male. Of subjects who reported a racial/ethnic demographic, 95% were Caucasian, 2% Black, 0.5% American Indian or Alaska native, 1% Asian and 1.5% were of mixed or other origin.

A tetanus antitoxoid level of ≥ 0.1 IU/mL, measured by the ELISA used in this study was considered protective. An anti-diphtheria anti-toxin level of ≥ 0.1 IU/mL was considered protective. Pre-vaccination and post-vaccination seroprotection rates and booster response rates are presented in Table 8.

Table 8: Pre-vaccination and Post-vaccination Seroprotection Rates and Booster Response Rates to Tetanus Toxoid and Diphtheria Toxoid Following a Second Vaccination with Adacel Compared to Td Vaccine in Persons 18 through 64 Years of Age, Per Protocol Analysis Set

	Vaccine	N*	Pre-vaccination		1 month post-vaccination		
			≥0.1 IU/mL (95% CI)	≥1.0 IU/mL (95% CI)	≥0.1 IU/mL (95% CI) [†]	≥1.0 IU/mL (95% CI) [‡]	%Booster [§] (95% CI)
Anti-Tetanus Toxoid (ELISA - IU/mL)	Adacel	944-948	97.2 (96.0; 98.2)	62.3 (59.1; 65.4)	100.0 (99.6; 100.0)	99.9 (99.4; 100.0)	74.5 ^{¶#} (71.6; 77.2)
	Td [Ⓟ] Adsorbed	315-317	96.5 (93.8; 98.2)	63.8 (58.2; 69.1)	100.0 (98.8; 100.0)	100.0 (98.8; 100.0)	81.6 ^{¶#} (76.9; 85.7)
Anti-Diphtheria Toxin (ELISA - IU/mL)	Adacel	945-948	84.7 (82.2; 86.9)	29.1 (26.2; 32.1)	99.8 (99.2; 100.0)	94.9 (93.3; 96.2)	83.2 [¶] (80.6; 85.5)
	Td [Ⓟ] Adsorbed	315-317	83.8 (79.3; 87.7)	29.8 (24.8; 35.2)	99.4 (97.7; 99.9)	94.0 (90.8; 96.4)	84.1 [¶] (79.6; 88.0)

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

[†] Seroprotection rates at ≥0.10 IU/mL for Adacel were non-inferior to Td for diphtheria toxin and tetanus toxoid (upper limit of the 95% CI on the difference for Td vaccine minus Adacel <10%).

[‡] Seroprotection rates at ≥1.0 IU/mL were not prospectively defined as a primary or secondary endpoint.

[§] Booster response is defined as a minimum rise in antibody concentration from pre to post-vaccination. The minimum rise is at least 2 times if the pre-vaccination concentration is above the cutoff value, or at least 4 times if it is at or below the cutoff value. The cutoff values for tetanus and diphtheria are 2.7 IU/mL and 2.56 IU/mL, respectively.

[¶] n/M: defines the number n of participants with booster response / the number M of subjects with available data to evaluate booster response. There were (n/M) 703/944, 257/315, 786/945 and 265/315 for Adacel/Tetanus, Td Adsorbed/Tetanus, Adacel/Diphtheria, and Td Adsorbed/Diphtheria, respectively.

[#] Booster response rates for tetanus toxoid in Adacel did not meet the pre-specified non-inferiority criteria.

[Ⓟ] Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

For all pertussis antigens (PT, FHA, PRN and FIM), post-vaccination anti-pertussis GMCs in the Adacel group were non-inferior to GMCs induced by 3 or 4 doses of DAPTACEL in historical studies as are presented in Table 9.

Table 9: Ratio of Pertussis Antibody Geometric Mean Concentrations (GMCs) Observed One Month Following a Second Vaccination with Adacel in Adults Compared with Those Observed in Infants One Month following Vaccination with 3 or 4 Doses of DAPTACEL (Per-Protocol Analysis Set)

Antigen	Adacel			DAPTACEL*			Adacel/DAPTACEL*	
	N	GMC (EU/mL)	(95% CI)	N	GMC (EU/mL)	(95% CI)	GMC Ratio	(95% CI)†
PT	935	102	(94.9; 110)	366	98.1	(90.9; 106)	1.04	(0.92; 1.18)
FHA	948	209	(200; 217)	80	39.9	(34.6; 46.1)	5.22	(4.51; 6.05)
PRN	948	318	(302; 334)	80	108	(91.4; 128)	2.94	(2.46; 3.51)
FIM	948	745	(711; 781)	80	341	(270; 431)	2.18	(1.84; 2.60)

* DAPTACEL: Historical controls who received DAPTACEL in Sanofi Pasteur studies. PT antibody GMC were compared to GMC following 4 doses of DAPTACEL in M5A10. FHA, PRN and FIM antibody GMCs were compared to GMCs following 3 doses of Daptacel in the Sweden I Efficacy trial.

† For each pertussis antigen, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the GMC ratio (Adacel divided by the historical control) was > 0.66.

Booster response rates for PT and FHA were non-inferior in Adacel participants compared to pre-specified criteria for booster response rates, but non-inferiority was not achieved for PRN and FIM booster response rates (See Table 10).

Table 1: Comparison of Booster Response* Rates for Pertussis Antigens Following a Second Vaccination with Adacel (Per-Protocol Analysis Set)

Antigen	Adacel (N=948)		Pre-specified criteria for Booster Response Rates†	Adacel minus Pre-specified Booster Response Rates‡	
	n/M	% (95% CI)	%	Difference (%)	(95% CI)‡
PT	693/894	77.5 (74.6; 80.2)	61.4	16.12	(13.27; 18.73)
FHA	651/945	68.9 (65.8; 71.8)	73.1	-4.21	(-7.23; -1.34)
PRN	617/945	65.3 (62.2; 68.3)	83.9	-18.61	(-21.7; -15.6)
FIM	537/945	56.8 (53.6; 60.0)	75.9	-19.07	(-22.3; -16.0)

N = number of subjects analyzed according to Per-Protocol Analysis Set

M = number of subjects with available data for the considered endpoint

n = number of subjects fulfilling the item listed in the first column

* Booster response is defined as a minimum rise in antibody concentration from pre to post-vaccination. The minimum rise is at least 2-fold if the pre-vaccination concentration is above the cutoff value, or at least 4-fold if it is at or below the cutoff value. The cutoff values for Study Td537 for the pertussis antigens are: 93 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN, and 285 EU/mL for FIM.

† Pre-specified criteria for booster response rates were derived from participants 21 to <65 years of age who received Adacel in Study Td506.

‡ Non-inferiority in booster response rate for each pertussis antigen was demonstrated if the lower limit of the 2-sided 95% CI of the difference of booster response rates between participants receiving Adacel in Study Td537

and expected booster response rates based on Study Td506 was >-10%.

14.3 Concomitant Hepatitis B Vaccine Administration

The concomitant use of Adacel (first vaccination) 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 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 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)*.]

14.4 Concomitant Influenza Vaccine Administration

The concomitant use of Adacel (first vaccination) 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 (N = 361). Sera were obtained prior to and 4-6 weeks after Adacel, 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 prespecified criterion was ≥ 0.67) and influenza antigens (percent of participants with hemagglutination-inhibition [HI] antibody titer $\geq 1:40$ 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)*.]

15 REFERENCES

- 1 Stratton KR, et al, editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington: National Academy Press; 1994. p. 67-117.
- 2 Stainer DW, et al. A simple chemically defined medium for the production of phase I Bordetella pertussis. J Gen Microbiol 1970;63:211-20.
- 3 Mueller JH, et al. Variable factors influencing the production of tetanus toxin. J Bacteriol 1954;67(3):271-7.
- 4 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, MD. DHHS 91-1174. 1991. p. 7-11.

- 5 FDA. Department of Health and Human Services (DHHS). Biological products bacterial vaccines and toxoids; implementation of efficacy review; proposed rule. Fed Reg 1985;50(240):51002-117.
- 6 Wassilak SGF, et al. Tetanus toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: WB Saunders Company; 2008. p. 805-39.
- 7 Vitek CR and Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W.B. Saunders Company; 2008. p. 139-56.
- 8 Gustafsson L, et al. A controlled trial of a two-component acellular, a five-component acellular and a whole-cell pertussis vaccine. N Engl J Med 1996;334(6):349-55.

16 HOW SUPPLIED/STORAGE AND HANDLING

Syringe, without needle, single-dose – NDC 49281-400-89 (not made with natural rubber latex); in package of 5 syringes, NDC 49281-400-20.

Vial, single-dose – NDC 49281-400-58; in package of 5 vials; NDC 49281-400-05. The vial stopper is not made with natural rubber latex. Discard unused portion in vial.

Vial, single-dose – NDC 49281-400-58; in package of 10 vials; NDC 49281-400-10. The vial stopper is not made with natural rubber latex. Discard unused portion in vial.

Not all pack sizes may be marketed.

Adacel should be stored at 2°C to 8°C (35°F 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, healthcare 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 healthcare provider should inform the patient, parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel or other vaccines containing similar components. The healthcare 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 healthcare provider.

Pregnancy Exposure Registry

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

Manufactured by:

Sanofi Pasteur Limited
Toronto Ontario Canada

Distributed by:

Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Adacel® is a registered trademark of Sanofi, its affiliates, and its subsidiaries.

R13-1220 USA

SANOFI PASTEUR 