INDICATIONS AND USAGE

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

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)

DOSE 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 of 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

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

ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

DRUG INTERACTIONS

When Adacel was administered concomitantly with Influenza Vaccine (IV) to adults 18-64 years of age, a lower antibody response was observed for pertussis 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. (7.4)

Pregnancy Exposure Registry: contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VAC-CINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

Revised: 12/2020

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.

USE IN SPECIFIC POPULATIONS

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
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 an increase 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 immunsuppressive 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 syncope 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 population 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, 85% 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 = 1,752; DECAVAC (T etanus and Diphtheria T oxoids Adsorbed; manufactured by Sanofi Pasteur Inc., Swiftwater, PA) N = 792) and adults 18 through 64 years of age (Adacel N = 1,175, 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 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 interview. 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 adolescent recipients 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 38.5°C and higher was uncommon, although in the adolescent age group it occurred significantly more frequently in adolescent recipients than Td vaccine recipients.
as were the rates of unsolicited adverse events from day 28 through 6 months. There were no 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.

**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 [Hecombivac HB] (Td501) [See CLINICAL STUDIES (14)], injection site and systemic 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 through-out 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 2.

**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 (continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adolescents 11-17 years</th>
<th>Adults 18-64 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adacel (N = 1,174-1,117) (%)</td>
<td>Td (N = 787) (%)</td>
</tr>
<tr>
<td>Sore and Swollen Joints</td>
<td>Any</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>Moderate†</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Severe‡</td>
<td>0.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>Any</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Moderate†</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Severe‡</td>
<td>1.0</td>
</tr>
<tr>
<td>Lymph Node Swelling</td>
<td>Any</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>Moderate†</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Severe‡</td>
<td>0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Any</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>Moderate†</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Severe‡</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Any</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>Moderate†</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Severe‡</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>Any</td>
<td>2.7</td>
</tr>
</tbody>
</table>

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 (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adacel (N=999) (%)</th>
<th>Td Adsorbed’ (N=328) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (&gt;38.5°C to &lt;38.9°C or ≥101.2°F to ≤102.0°F)</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Grade 3 (&gt;102.1°F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>12.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>33.3</td>
<td>30.8</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>18.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

N = number of participants with available data.

†Tetanus and Diphtheria Toxoids Adsorbed manufactured by Sanofi Pasteur Inc., Swiftwater, PA.
‡Some interference with activity
§Significant; prevents daily activity

**Injection Site and Systemic Reactions Following Adacel Given Concomitantly with Trivalent Inactivated Influenza Vaccine [Fluzone](Td505)**

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. 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, i.e., 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 higher in participants who received Adacel and Hepatitis B vaccine than in those who received Adacel alone. The rates of generalized body aches were statistically higher rates following concurrent administration (66.6%) versus separate administration (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.

**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 following a single dose of vaccination. 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 adverse event occurring in approximately 44% of all participants. Sore and/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, TC9707 and TC9805) 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 transient 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 (Td919) 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 neurologic 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 severe 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 neurologic 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 Td517, eight 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 to 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.

- **Immun system disorders**
  - Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension)
- **Nervous system disorders**
  - Paresthesia, hypoesthesia, Guillain-Barré syndrome, brachial neuritis, facial palsy, convulsion, syncope, myeltis
- **Cardiac disorders**
  - Myocarditis
- **Skin and subcutaneous tissue disorders**
  - Pruritus, urticaria
- **Musculoskeletal and connective tissue disorders**
  - Myositis, myalgia
- **General disorders and administration site conditions**
  - Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

When Adacel is administered concomitantly with other injectable vaccines or TdT 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), tetanus toxoid (T), and pertussis antigens [2.5 mcg detoxified 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 (0.8% v/v) 2-phenoxethanol (not as a preservative). The antigens are the same as those in DAPTACEIL, 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 and FHA are isolated from the supernatant culture medium and purified by ammonium sulfate fractionation and diafiltration. The individual antigens are adsorbed on aluminum phosphate, for intramuscular injection. 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 and purified by ammonium sulfate fractionation and diafiltration. Corynebacterium diphtheriae is grown in modified MV medium. Pertactin is generated by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. The adesorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxethanol (not as a preservative) and water for injection. Adacel does not contain a preservative.

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 provider contact, the Vaccine Safety Datalink at 1-888-822-2963 (1-888-VACCINE) / For Risk Summary

All pregnancies are at risk for 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 3%, and live birth rate is 98% to 99%. 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 to and during gestation. The studies revealed no evidence of harm to the fetus due to Adacel. [See Data]

8.2 Lactation

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.

8.3 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 the lower geometric mean concentrations of antibodies to PT, PRN and FHA when compared to infants who had received a primary series of DAPTACEIL, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP). [See CLINICAL STUDIES (14) for description of DAPTACEIL.]

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 UF tetanus toxoid (T), 2.1 UF diphtheria toxoid (D), and acellular pertussis vaccines: 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 (0.8% v/v) 2-phenoxethanol (not as a preservative). The antigens are the same as those in DAPTACEIL; 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 and FHA are isolated from the supernatant culture medium and purified by ammonium sulfate fractionation and diafiltration. The individual antigens are adsorbed on aluminum phosphate, for intramuscular injection. 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 and purified by ammonium sulfate fractionation and diafiltration. Corynebacterium diphtheriae is grown in modified MV medium. Pertactin is generated by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. The adesorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxethanol (not as a preservative) and water for injection. Adacel does not contain a preservative.

In the guinea pig cotinine 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 FHA as measured by enzyme-linked immunosorbent assay (ELISA). Diphtheria and tetanus toxoids are individually adsorbed on 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 0.1 U/mL measured by neutralization assay is considered the minimum protective level. [5] (6) Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxicogenic strains of C. diphtheriae. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.1 U/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 U/mL are generally regarded as protective. [5] Levels of 1.0 U/mL have been associated with long-term protection. [7] Pertussis

Pertussis (whooping cough) is a respiratory disease caused by B. pertussis. This Gram-negative coccolobacillus 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 DAPTACEEL 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 DAPTACEEL in the Sweden I Efficacy trial; for evaluation of PT antibody levels, the comparison was to infants who received four doses of DAPTACEEL in a US safety and immunogenicity study (Study USA101). In the Sweden I Efficacy Trial, three doses of DAPTACEEL 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%).

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 vaccination and 1 month following a first vaccination with Adacel in Adolescents and Adults 11 through 64 Years of Age as Compared to Td Vaccine in Adolescents and Adults 11 through 64 Years of Age (Td506).

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)

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Vaccine</th>
<th>% ≥0.10 (95% CI)</th>
<th>% ≥1.0 (95% CI)</th>
<th>% ≥0.10 (95% CI)</th>
<th>% ≥1.0 (95% CI)</th>
<th>% Booster (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-17</td>
<td>Adacel</td>
<td>99.6</td>
<td>44.6</td>
<td>100.0</td>
<td>99.6</td>
<td>91.7</td>
</tr>
<tr>
<td></td>
<td>Td</td>
<td>99.2</td>
<td>43.8</td>
<td>100.0</td>
<td>99.4</td>
<td>91.2</td>
</tr>
<tr>
<td>18-64</td>
<td>Adacel</td>
<td>97.7</td>
<td>72.9</td>
<td>100.0</td>
<td>97.7</td>
<td>63.4</td>
</tr>
<tr>
<td></td>
<td>Td</td>
<td>95.9</td>
<td>70.3</td>
<td>99.6</td>
<td>92.8</td>
<td>66.8</td>
</tr>
</tbody>
</table>

*Anti-Tetanus toxoid (IU/mL)

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)

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Vaccine</th>
<th>% ≥0.10 (95% CI)</th>
<th>% ≥1.0 (95% CI)</th>
<th>% ≥0.10 (95% CI)</th>
<th>% ≥1.0 (95% CI)</th>
<th>% Booster (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-17</td>
<td>Adacel</td>
<td>72.5</td>
<td>15.7</td>
<td>99.8</td>
<td>98.7</td>
<td>95.1</td>
</tr>
<tr>
<td></td>
<td>Td</td>
<td>70.7</td>
<td>17.3</td>
<td>98.9</td>
<td>97.4</td>
<td>95.0</td>
</tr>
<tr>
<td>18-64</td>
<td>Adacel</td>
<td>82.6</td>
<td>14.3</td>
<td>94.1</td>
<td>78.0</td>
<td>87.4</td>
</tr>
<tr>
<td></td>
<td>Td</td>
<td>506-507</td>
<td>16.0</td>
<td>95.1</td>
<td>79.9</td>
<td>83.4</td>
</tr>
</tbody>
</table>

*Anti-Diphtheria toxoid (IU/mL)

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 DAPTACEEL (Sweden I Efficacy Study)

<table>
<thead>
<tr>
<th>Age Adults 11-17 Years of Age</th>
<th>GMC Ratio (95% CIs)</th>
<th>GMC Ratio (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adacel/DAPTACEEL</td>
<td>Anti-PT: 3.6 (2.8, 4.5)</td>
<td>2.1 (1.6, 2.7)</td>
</tr>
<tr>
<td></td>
<td>Anti-FHA: 5.4 (4.5, 6.5)</td>
<td>4.8 (3.9, 5.9)</td>
</tr>
<tr>
<td></td>
<td>Anti-PRN: 3.2 (2.4, 4.1)</td>
<td>3.2 (2.3, 4.4)</td>
</tr>
<tr>
<td></td>
<td>Anti-FIM: 5.3 (3.9, 7.4)</td>
<td>2.5 (1.8, 3.5)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Age Adults 11-17 Years of Age</th>
<th>Booster Response Rates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PT: 524 (89.3, 94.2)</td>
<td>739 (81.6, 87.0)</td>
</tr>
<tr>
<td>Anti-FHA: 526 (82.3, 88.4)</td>
<td>739 (81.8, 87.0)</td>
</tr>
<tr>
<td>Anti-PRN: 525 (91.8, 95.4)</td>
<td>739 (81.8, 87.0)</td>
</tr>
</tbody>
</table>
1.5% were of mixed or other origin.

Of the study participants, 35% were male. Of subjects who reported a racial/ethnic background, seroprotection rates were evaluated approximately 28 days post-vaccination. The per-protocol analysis set was used for all immunogenicity analyses.

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%.

In this study non-inferiority was demonstrated for booster responses to tetanus and diphtheria toxoids, for all 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 (-5.36%) did not meet the predefined criterion (<5%) when the booster response in the older age group was ≥95%.

### 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 (continued)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>N</th>
<th>GMC (EU/mL) (95% CI)</th>
<th>%</th>
<th>Antigen</th>
<th>N</th>
<th>GMC (EU/mL) (95% CI)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>935</td>
<td>(94.9; 100) 366</td>
<td>98.1</td>
<td>(90.9; 106) 104</td>
<td>(0.92; 1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td>948</td>
<td>(200; 217) 80</td>
<td>39.9</td>
<td>(34.6; 46.1) 5.22</td>
<td>(4.51; 6.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td>948</td>
<td>(302; 334) 80</td>
<td>108</td>
<td>(91.4; 128) 2.94</td>
<td>(2.46; 3.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIM</td>
<td>948</td>
<td>(71; 781) 80</td>
<td>341</td>
<td>(270; 431) 2.18</td>
<td>(1.84; 2.60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PT, FHA, PRN and FIM, anti-diphtheria anti-toxin level of 2.7 IU/mL and 2.56 IU/mL, respectively.

| *N* = number of subjects analyzed according to Per-Protocol Analysis Set |
| --- | --- | --- | --- |
| 431 | 80 | 108 (91.4; 106) | 2.18 | (1.84; 2.60) |

*Adacel (N=945) |

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Pre-specified criteria or Booster Response Rates†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>63/3/94</td>
</tr>
<tr>
<td>FHA</td>
<td>651/945</td>
</tr>
<tr>
<td>PRN</td>
<td>517/945</td>
</tr>
<tr>
<td>FIM</td>
<td>537/945</td>
</tr>
</tbody>
</table>

**Adacel minus pre-specified Booster Response Rates†**

### 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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Pre-vaccination</th>
<th>1 month post-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-FIM</td>
<td>526</td>
<td>94.9 (92.6; 96.6) 739</td>
<td>85.9 (83.2; 88.4) 82.4</td>
</tr>
</tbody>
</table>

*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.

### 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)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>N</th>
<th>GMC (EU/mL) (95% CI)</th>
<th>%</th>
<th>Antigen</th>
<th>N</th>
<th>GMC (EU/mL) (95% CI)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>935</td>
<td>(94.9; 100) 366</td>
<td>98.1</td>
<td>(90.9; 106) 104</td>
<td>(0.92; 1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td>948</td>
<td>(200; 217) 80</td>
<td>39.9</td>
<td>(34.6; 46.1) 5.22</td>
<td>(4.51; 6.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td>948</td>
<td>(302; 334) 80</td>
<td>108</td>
<td>(91.4; 128) 2.94</td>
<td>(2.46; 3.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIM</td>
<td>948</td>
<td>(71; 781) 80</td>
<td>341</td>
<td>(270; 431) 2.18</td>
<td>(1.84; 2.60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ADVERSE REACTIONS (6.1)

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

Study Td537 assessed the comparative immunogenicity of a first vaccination with Adacel administered to adolescents (10 <11 years of age and 11 to <12 years of age) [See ADVERSE REACTIONS (6.1)]. In this study non-inferiority was defined 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 (-5.36%) did not meet the predefined criterion (<5%) when the booster response in the older age group was ≥95%.
What is Adacel vaccine?

Adacel vaccine is a vaccine that helps protect against tetanus, diphtheria, and pertussis diseases in people who are 10 through 64 years of age. It cannot cause tetanus, diphtheria, or pertussis. Adacel vaccine is not made with natural rubber latex. Discard unused portion in vial.

What are the possible side effects of Adacel vaccine?

The most common side effects of Adacel vaccine are:

- pain,
- redness and swelling where you got the shot
- headache
- body aches
- tiredness
- fever

These are not all the possible side effects of Adacel vaccine. You may ask your healthcare provider for a list of side effects that is available to healthcare professionals.

If you or your child experience side effects that concern you, call your healthcare provider for medical advice. You may report side effects to VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

What ingredients are in Adacel vaccine?

Adacel vaccine contains noninfectious tetanus, diphtheria, and pertussis proteins, aluminum phosphate, 2-phenoxyethanol, and residual amounts of formaldehyde and glutaraldehyde. Adacel vaccine does not contain preservatives.

Patient Information Sheet

Adacel®

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Please read this information before vaccination with Adacel vaccine. This summary is not intended to take the place of talking with your healthcare provider. If you have questions or would like more information, please talk with your healthcare provider.

What is Adacel vaccine?

Adacel vaccine is a vaccine that helps protect against tetanus, diphtheria, and pertussis diseases in people who are 10 through 64 years of age. It cannot cause tetanus, diphtheria, or pertussis. Adacel vaccine may not protect all people getting the vaccine.

Tetanus, also called “lockjaw”, can cause severe muscle spasms making it difficult for a person to open their mouth or swallow. You can get tetanus through a cut or wound.

Diphtheria can cause throat, lung and skin infections leading to severe complications that affect the lungs, heart and nervous system.

Pertussis, also called “whooping cough,” causes coughing fits that can affect breathing. Diphtheria and pertussis are spread from person to person.

Who should not get Adacel vaccine?

You should not get Adacel vaccine if you:

- had a severe allergic reaction to a previous tetanus vaccine, diphtheria vaccine, pertussis vaccine, or any component of Adacel vaccine.
- had severe injection site pain or swelling after a prior tetanus, diphtheria, or pertussis vaccination.
- had Guillain-Barré syndrome, a nerve disease causing severe muscle weakness, after getting a vaccine.
- have a brain disorder or brain disease that is not stable.
- are pregnant or nursing.
- had a tetanus, diphtheria, or pertussis vaccine within the last 5 years.

Fainting can occur around the time of vaccination with Adacel or other vaccines. Tell your healthcare provider if you or your child has fainted in connection with any previous vaccination.

How is Adacel vaccine given?

Adacel is a single shot that is given into the muscle of the upper arm.

USE IN SPECIFIC POPULATIONS (8.1)

[See ]

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

Patient Information Sheet

Adacel®

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Please read this information before vaccination with Adacel vaccine. This summary is not intended to take the place of talking with your healthcare provider. If you have questions or would like more information, please talk with your healthcare provider.

What is Adacel vaccine?

Adacel vaccine is a vaccine that helps protect against tetanus, diphtheria, and pertussis diseases in people who are 10 through 64 years of age. It cannot cause tetanus, diphtheria, or pertussis. Adacel vaccine may not protect all people getting the vaccine.

Tetanus, also called “lockjaw”, can cause severe muscle spasms making it difficult for a person to open their mouth or swallow. You can get tetanus through a cut or wound.

Diphtheria can cause throat, lung and skin infections leading to severe complications that affect the lungs, heart and nervous system.

Pertussis, also called “whooping cough,” causes coughing fits that can affect breathing. Diphtheria and pertussis are spread from person to person.

Who should not get Adacel vaccine?

You should not get Adacel vaccine if you:

- had a severe allergic reaction to a previous tetanus vaccine, diphtheria vaccine, pertussis vaccine, or any component of Adacel vaccine.
- were told you have an “encephalopathy”, which is a kind of brain disease or malfunction, after receiving a previous dose of a pertussis vaccine.
- are younger than 10 years old or older than 64 years of age.

What should I tell my healthcare provider before I or my child gets Adacel vaccine?

Tell your healthcare provider if you or your child:

- had severe injection site pain or swelling after a prior tetanus, diphtheria, or pertussis vaccination.
- had Guillain-Barré syndrome, a nerve disease causing severe muscle weakness, after getting a vaccine.
- have a brain disorder or brain disease that is not stable.
- are pregnant or nursing.
- had a tetanus, diphtheria, or pertussis vaccine within the last 5 years.

Fainting can occur around the time of vaccination with Adacel or other vaccines. Tell your healthcare provider if you or your child has fainted in connection with any previous vaccination.

How is Adacel vaccine given?

Adacel is a single shot that is given into the muscle of the upper arm.

What are the possible side effects of Adacel vaccine?

The most common side effects of Adacel vaccine are:

- pain, redness and swelling where you got the shot
- headache
- body ache
- tiredness
- fever

These are not all the possible side effects of Adacel vaccine. You may ask your healthcare provider for a list of side effects that is available to healthcare professionals.

If you or your child experience side effects that concern you, call your healthcare provider for medical advice. You may report side effects to VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

What ingredients are in Adacel vaccine?

Adacel vaccine contains noninfectious tetanus, diphtheria, and pertussis proteins, aluminum phosphate, 2-phenoxyethanol, and residual amounts of formaldehyde and glutaraldehyde. Adacel vaccine does not contain preservatives.

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada

Distributed by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

R13-1220 USA

TRDAP-FPLR-SL-DEC20 Rx Only