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)
- immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months 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 (DTP) 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)
- To provide protection against pertussis in infants younger than 2 months of age, administer Adacel during the third trimester of pregnancy

Dosage Forms and Strengths

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

CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of Adacel or any other diphtheria toxoid, tetanus toxoid and pertussis antigen-containing vaccine. (4.1)
- Encephalopathy (e.g., 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 (77.6%/85.7%), 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 0-7 days of vaccination for Adults (18-64 years of age) were: injection site pain (67.1%), 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: 05/2023
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.
- Immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months 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.

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 5 years or more after the first dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

Vaccination During the Third Trimester of Pregnancy
To prevent pertussis in infants younger than 2 months of age, administer Adacel to pregnant individuals during the third trimester of pregnancy.

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 (e.g., 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 (e.g., coma, prolonged seizures, or decreased level of consciousness) 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 is a contraindication to further 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.

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 Immune competency
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, 6% 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 82.9% 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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Adolescents 11-17 years</th>
<th>Adults 18-64 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adacel</td>
<td>Td</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>N = 1,170</td>
<td>N = 1,688</td>
</tr>
<tr>
<td>N(%)</td>
<td>N(%)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain, Any</td>
<td>77.8</td>
<td>65.7</td>
</tr>
<tr>
<td>Injection Site Pain, Moderate</td>
<td>18.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Injection Site Pain, Severe</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Injection Site Swelling, Any</td>
<td>20.9</td>
<td>21.0</td>
</tr>
<tr>
<td>Injection Site Swelling, Moderate</td>
<td>6.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Injection Site Swelling, Severe ≥3.5 cm</td>
<td>6.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Injection Site Swelling, Severe ≥5 cm (2 inches)</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Injection Site Swelling, Any</td>
<td>20.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Injection Site Swelling, Moderate</td>
<td>5.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Injection Site Swelling, Severe ≥3.5 cm</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Injection Site Swelling, Severe ≥5 cm (2 inches)</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Fever, ≥38.0°C (±100.4°F)</td>
<td>5.0©</td>
<td>1.4</td>
</tr>
</tbody>
</table>

© Fever ≥38.0°C (±100.4°F)
*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 rates 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adolescents 11-17 years Adacel N = 1,174-1,175 (%)</th>
<th>Adolescents 11-17 years Td N = 787 (%)</th>
<th>Adults 18-64 years Adacel N = 1,697-1,698 (%)</th>
<th>Adults 18-64 years Td N = 560-561 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, Any</td>
<td>43.7</td>
<td>40.4</td>
<td>33.9</td>
<td>34.1</td>
</tr>
<tr>
<td>Headache, Moderate</td>
<td>14.2</td>
<td>11.1</td>
<td>11.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Headache, Severe</td>
<td>2.0</td>
<td>1.5</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Body Ache or Muscle Weakness, Any</td>
<td>30.4</td>
<td>29.9</td>
<td>21.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Body Ache or Muscle Weakness, Moderate</td>
<td>8.5</td>
<td>6.9</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Body Ache or Muscle Weakness, Severe</td>
<td>1.3</td>
<td>0.9</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Tiredness, Any</td>
<td>30.2</td>
<td>27.3</td>
<td>24.3</td>
<td>20.7</td>
</tr>
<tr>
<td>Tiredness, Moderate</td>
<td>9.8</td>
<td>7.5</td>
<td>6.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Tiredness, Severe</td>
<td>1.2</td>
<td>1.0</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Chills, Any</td>
<td>15.1</td>
<td>12.6</td>
<td>8.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Chills, Moderate</td>
<td>3.2</td>
<td>2.5</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Chills, Severe</td>
<td>0.5</td>
<td>0.1</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Sore and Swollen Joints, Any</td>
<td>11.3</td>
<td>11.7</td>
<td>9.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Sore and Swollen Joints, Moderate</td>
<td>2.6</td>
<td>2.5</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Sore and Swollen Joints, Severe</td>
<td>0.3</td>
<td>0.1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea, Any</td>
<td>13.3</td>
<td>12.3</td>
<td>9.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Nausea, Moderate</td>
<td>3.2</td>
<td>3.2</td>
<td>2.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Nausea, Severe</td>
<td>1.0</td>
<td>0.6</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Lymph Node Swelling, Any</td>
<td>6.6</td>
<td>5.3</td>
<td>6.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Lymph Node Swelling, Moderate</td>
<td>1.0</td>
<td>0.5</td>
<td>1.2</td>
<td>0.5</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 NCT01439165 - Safety Analysis Set

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adacel (N=999) (%)</th>
<th>Td Adsorbed' (N=328) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain, Any</td>
<td>87.1</td>
<td>87.4</td>
</tr>
<tr>
<td>Injection site pain, Grade 1</td>
<td>38.5</td>
<td>31.4</td>
</tr>
<tr>
<td>Injection site pain, Grade 2</td>
<td>28.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Injection site erythema, Any</td>
<td>6.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Injection site erythema, Grade 2</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Injection site erythema, Grade 3</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Injection site swelling, Any</td>
<td>8.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Injection site swelling, Grade 2</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Injection site swelling, Grade 3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fever, Any</td>
<td>0.9</td>
<td>1.8</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 NCT01439165 - 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, Grade 2 (≥38.5°C to &lt;38.9°C or ≥101.2°F to ≤102.0°F)</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Fever, Grade 3 (≥102.1°F)</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Headache, Any</td>
<td>41.4</td>
<td>39.1</td>
</tr>
<tr>
<td>Headache, Grade 2†</td>
<td>12.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Headache, Grade 3‡</td>
<td>2.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Malaise, Any</td>
<td>33.3</td>
<td>30.8</td>
</tr>
<tr>
<td>Malaise, Grade 2†</td>
<td>9.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Malaise, Grade 3‡</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Myalgia, Any</td>
<td>58.1</td>
<td>58.2</td>
</tr>
<tr>
<td>Myalgia, Grade 2†</td>
<td>18.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Myalgia, Grade 3‡</td>
<td>3.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Number of participants with available data

†Significant; prevents daily activity
‡Some interference with activity

### ADVERSE REACTIONS

In an additional study (NCT00347958), injection site and systemic adverse events were monitored daily for 14 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.

### Adult Study of a Second Vaccination with Adacel (NCT00347958)

Study NCT00347958 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, 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, 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 1.6 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, i.e., 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.

### 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 NCT01439165 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 NCT00347958, 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, hypoten-sion, vomiting, diarrhea, urticaria, anaphylactic shock or anaphylactoid reaction)
- **Nervous system disorders**
  - Paresthesia, hyposthesia, 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

### 7. DRUG INTERACTIONS

#### 7.1 Concomitant Vaccine Administration

When Adacel is administered concomitantly with other injectable vaccines or Tetanus toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

- If given concurrently with other injectable vaccines or Tetanus toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.

- If given concurrently with other injectable vaccines or Tetanus toxoids Adsorbed manufactured by Sanofi Pasteur Limited, Toronto, Ontario, Canada.
bacterium 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-phenoxethanol (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 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 pertussis toxin released by C. diphtheriae.

Protection against disease is due to the development of neutralizing antibodies to tetanus toxoid. A serum tetanus toxoid level of at least 0.1 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 toxoid. A serum diphtheria toxoid 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, rod-shaped bacterium produces a variety of biologically active compounds, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

13 NONCLINICAL TOXICITY

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 immunogenicity were the percentage of participants with antibody levels defined as protective. (5) (6)

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 DAPTECIEL, in the Sweden I Efficacy trial. For the second dose of Adacel, the evaluation for FHA, PRN, and FIM antibody levels, the comparisons were to infants who received three doses of DAPTECIEL in the Sweden I Efficacy trial; for evaluation of PT antibody levels, the comparison was to infants who received four doses of DAPTECIEL in the US safety and immunogenicity study (Study NCT00255047). In the Sweden I Efficacy trial, three doses of DAPTECIEL 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

The clini-cally First Vaccination with Adacel (Td506). 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 vaccine recipients and 1,026 Td vaccine recipients. Sera were obtained before and approximately 35 days after vaccination. (6)

Blinding procedures for safety assessments are described in ADVERSE REACTIONS (6). (6)

Demographic characteristics were similar within age groups and between the vaccine groups. A total of 76% of the adolescents and 71.1% of the adults reported a history of receiving 5 previous doses of diphtheria-tetanus-pertussis containing vaccines. Anti-tetanus and anti-diptheria 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 DAPTECIEL vaccine in the Sweden I Efficacy Study. (See Table 6.) Acceptable booster responses to each of the pertussis antigens were also demonstrated, i.e., 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)

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Vaccine</th>
<th>Anti-Tetanus toxoid (IU/mL) Pre-vaccination</th>
<th>Anti-Tetanus toxoid (IU/mL) 1 Month Post-vaccination</th>
<th>Anti-Tetanus toxoid (IU/mL) 1 Month Post-vaccination Booster</th>
<th>N = number of participants in the per-protocol population with available data</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-17</td>
<td>Adacel</td>
<td>527</td>
<td>99.6 (98.6, 100.0)</td>
<td>100.2 (99.3, 100.0)</td>
<td>99.9 (98.6, 100.0)</td>
</tr>
<tr>
<td></td>
<td>Td†</td>
<td>516</td>
<td>99.2 (98.0, 99.8)</td>
<td>100.0 (99.3, 100.0)</td>
<td>99.4 (98.3, 99.9)</td>
</tr>
<tr>
<td>18-64</td>
<td>Adacel</td>
<td>742-743</td>
<td>97.3 (95.9, 98.3)</td>
<td>100.0 (99.5, 100.0)</td>
<td>97.8 (96.5, 98.8)</td>
</tr>
<tr>
<td></td>
<td>Td†</td>
<td>509</td>
<td>99.9 (93.8, 97.4)</td>
<td>99.8 (98.9, 100.0)</td>
<td>98.2 (96.7, 99.2)</td>
</tr>
</tbody>
</table>

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 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)

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Vaccine</th>
<th>Anti-Diphtheria toxoid (IU/mL) Pre-vaccination</th>
<th>Anti-Diphtheria toxoid (IU/mL) 1 Month Post-vaccination</th>
<th>Anti-Diphtheria toxoid (IU/mL) 1 Month Post-vaccination Booster</th>
<th>N = number of participants in the per-protocol population with available data</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-17</td>
<td>Adacel</td>
<td>527</td>
<td>98.7 (98.1, 99.3)</td>
<td>99.2 (98.3, 99.9)</td>
<td>96.5 (95.9, 96.6)</td>
</tr>
<tr>
<td></td>
<td>Td†</td>
<td>515-516</td>
<td>92.7 (91.6, 93.8)</td>
<td>92.9 (92.1, 93.7)</td>
<td>93.5 (92.9, 94.7)</td>
</tr>
<tr>
<td>18-64</td>
<td>Adacel</td>
<td>739-741</td>
<td>62.6 (59.0, 66.1)</td>
<td>94.1 (92.1, 96.1)</td>
<td>74.6 (74.8, 75.4)</td>
</tr>
<tr>
<td></td>
<td>Td†</td>
<td>506-507</td>
<td>63.3 (59.0, 67.5)</td>
<td>96.1 (92.8, 99.3)</td>
<td>78.4 (76.1, 80.3)</td>
</tr>
</tbody>
</table>

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 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 2.4 and 6 Months of Age in the Efficacy Trial with DAPTACEEL (Sweden I Efficacy Study)

<table>
<thead>
<tr>
<th>Age in the Efficacy Trial with DAPTACEEL (Sweden I Efficacy Study)</th>
<th>Adolescents 11-17 Years of Age</th>
<th>Adults 18-64 Years of Age</th>
<th>GMC Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PT</td>
<td>3.6 (2.8, 4.5)†</td>
<td>2.1 (1.6, 2.7)†</td>
<td></td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>5.4 (4.5, 6.5)†</td>
<td>1.8 (3.9, 5.0)†</td>
<td></td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>3.2 (2.5, 4.1)†</td>
<td>3.2 (2.3, 4.4)†</td>
<td></td>
</tr>
<tr>
<td>Anti-FIM</td>
<td>5.3 (3.9, 7.1)†</td>
<td>2.5 (1.8, 3.5)†</td>
<td></td>
</tr>
</tbody>
</table>

*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 DAPTACEEL 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 DAPTACEEL (lower limit of 95% CI on the ratio of GMC for Adacel divided by DAPTACEEL >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

<table>
<thead>
<tr>
<th>Age in the Efficacy Trial with DAPTACEEL (Sweden I Efficacy Study)</th>
<th>Adolescents 11-17 Years of Age</th>
<th>Adults 18-64 Years of Age</th>
<th>Predetermined Acceptable Rates‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PT</td>
<td>524</td>
<td>739</td>
<td>84.4 (81.6, 87.0)</td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>526</td>
<td>739</td>
<td>82.7 (79.8, 85.3)</td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>525</td>
<td>739</td>
<td>93.8 (91.8, 95.4)</td>
</tr>
<tr>
<td>Anti-FIM</td>
<td>526</td>
<td>739</td>
<td>85.9 (83.2, 88.4)</td>
</tr>
</tbody>
</table>

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

Study NCT01311557 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 (−0.56%) did not meet the predefined criterion (>−5%) when the booster response in the older age group was non-inferior.

14.2 Immunological Evaluation in Adults, 16 through 64 Years of Age Following a Second Vaccination with Adacel

In study NCT01439165 [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 846 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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Pre-vaccination ≥0.1 IU/mL (95% CI)</th>
<th>Pre-vaccination ≥1.0 IU/mL (95% CI)</th>
<th>1 month post-vaccination ≥0.1 IU/mL (95% CI)</th>
<th>1 month post-vaccination ≥1.0 IU/mL (95% CI)</th>
<th>Booster ≥1.0 IU/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Tetanus Toxoid (ELISA - IU/mL)</td>
<td>Adacel</td>
<td>944-948</td>
<td>97.2 (96.0; 98.2)</td>
<td>62.3 (59.1; 65.4)</td>
<td>100.0 (99.6; 100.0)</td>
<td>99.9 (99.4; 100.0)</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Td Ad-absorbed</td>
<td>315-317</td>
<td>96.5 (93.8; 98.2)</td>
<td>63.8 (58.2; 69.1)</td>
<td>100.0 (98.8; 100.0)</td>
<td>98.8 (98.0; 100.0)</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Adacel</td>
<td>945-948</td>
<td>84.7 (82.2; 86.8)</td>
<td>29.1 (26.2; 32.1)</td>
<td>99.8 (99.2; 100.0)</td>
<td>94.9 (93.3; 95.2)</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Td Ad-absorbed</td>
<td>315-317</td>
<td>83.8 (79.3; 87.7)</td>
<td>29.8 (24.8; 35.2)</td>
<td>99.4 (97.7; 99.9)</td>
<td>94.0 (90.8; 96.4)</td>
</tr>
</tbody>
</table>

*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>Booster ≥1.0 IU/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Tetanus Toxoid (ELISA - IU/mL)</td>
<td>Adacel</td>
<td>944-948</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Td Ad-absorbed</td>
<td>315-317</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Adacel</td>
<td>945-948</td>
</tr>
<tr>
<td>Anti-Diphtheria Toxoid (ELISA - IU/mL)</td>
<td>Td Ad-absorbed</td>
<td>315-317</td>
</tr>
</tbody>
</table>

N = number of participants in the per-protocol population with available data. *Seroprotection rates at ≥0.1 IU/mL for Adacel were non-inferior to Td for diphtheria toxoid 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 rates are 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.

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)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>N</th>
<th>Adacel GMC (EU/mL) (95% CI)</th>
<th>Adacel (95% CI)</th>
<th>DAP-TACEL GMC (EU/mL)</th>
<th>DAP-TACEL (95% CI)</th>
<th>DAP-TACEL/GMC Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>935</td>
<td>102 (94.9; 110)</td>
<td>366</td>
<td>98.1 (90.9; 106)</td>
<td>1.04 (0.92; 1.18)</td>
<td></td>
</tr>
<tr>
<td>FHA</td>
<td>948</td>
<td>209 (200; 217)</td>
<td>80</td>
<td>39.9 (34.6; 46.1)</td>
<td>5.22 (4.51; 6.05)</td>
<td></td>
</tr>
<tr>
<td>PRN</td>
<td>948</td>
<td>318 (302; 334)</td>
<td>80</td>
<td>108 (91.4; 128)</td>
<td>2.94 (2.46; 3.51)</td>
<td></td>
</tr>
</tbody>
</table>

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 NCT01439165 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. †For each pertussis antigen, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference of booster response rates between Adacel and DAPTACEL was >-10%. ‡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 Td506 and expected booster response rates based on Study Td506 was >-10%.

14.3 Study in Pregnant Women

The effectiveness of Adacel immunization during the third trimester of pregnancy to prevent pertussis among infants younger than 2 months of age was assessed based on a re-analysis of the Adacel-relevant data (Study NCT03049082) from an observational study of Tdap vaccine effectiveness in the United States (9). This matched case-control study included pertussis cases reported from 2011 through 2014 in infants born at ≥37 weeks gestation ≥2 days of age whose case of pertussis was defined as the onset of cough illness and at least one of the following: laboratory-confirmed (culture or PCR) of pertussis, epidemiological linkage to a laboratory-confirmed case, or clinically-compatible illness (cough ≥2 weeks with paroxysms, inspiratory whoop or post-tussive vomiting) in an infant ≥2 months old. Tdap-40 cases included a total of 586 infants (179 cases of pertussis and 417 controls without pertussis), the mean age was 4.2 (SD, 2.5) weeks, and 45.7% were non-Hispanic. For the vaccine effectiveness re-analysis, a conditional logistic regression model controlling for infant’s age and maternal education, was fit to data from 101 cases (including 5 infants whose mothers received Adacel during the third trimester and ≥14 days before delivery) and 171 controls (including 27 infants whose mothers received Adacel during the third trimester and ≥14 days before delivery) matched by birth hospital. This resulted in a vaccine effectiveness estimate of 88.0% (95% CI: 43.8; 97.4) for vaccination during the third trimester and ≥14 days before delivery.

14.4 Immune Responses to Pertussis Vaccination in Infants Born to Mothers Who Received Adacel During Pregnancy

Published studies have reported diminished immune responses to pertussis antigens in Tdap-containing vaccines administered to infants whose mothers received Adacel during the third trimester of pregnancy compared with infants whose mothers did not receive Adacel during the third trimester of pregnancy (10, 11). Whether the diminished immune responses observed in vaccinated infants whose mothers received Adacel during pregnancy result in diminished effectiveness of pertussis vaccination in infants is unknown.
14.5 Concomitant Hepatitis B Vaccine Administration

The concomitant use of Adacel (first vaccination) and trivalent inactivated hepatitis 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).]

14.6 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 = 369). 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 ≥10.10 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 ≥1:40 IU/mL and 24-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 ≥0.10 IU/mL. [See ADVERSE REACTIONS (6.1).]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
Syringe, without needle, single-dose – NDC 49281-400-88 (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 consult 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

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R16-0123 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.

Adacel vaccine given during the third trimester of pregnancy helps the pregnant woman create antibodies against the bacteria that cause whooping cough (pertussis) that are passed to her baby before birth. These antibodies help protect the baby against whooping cough during the first few months of life.

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 vaccine.
• had Guillain-Barre 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:
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Swiftwater PA 18370 USA

R13-1220 USA

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