PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ADACEL®

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Suspension for Injection

Each 0.5 mL dose contains Tetanus Toxoid (5 Lf); Diphtheria Toxoid (2 Lf); Acellular Pertussis [Pertussis Toxoid (PT), 2.5 mcg; Filamentous Haemagglutinin (FHA), 5 mcg; Pertactin (PRN), 3 mcg and Fimbriae Types 2 and 3 (FIM), 5 mcg].

(For immunization against Tetanus, Diphtheria and Pertussis)

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Recent Major Label Changes

1 Indications	**09/2020** **10/2021**
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	**09/2020**
7 Warnings and Precautions	**09/2020** **10/2021**

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PART I: HEALTH PROFESSIONAL INFORMATION

1. Indications

ADACEL® is indicated for:

- Active booster immunization for the prevention of tetanus, diphtheria and pertussis (whooping cough) in persons 4 years of age and older.

- Vaccination during pregnancy for passive immunization against pertussis disease in young infants. (See 4 Dosage And Administration, 4.1 Dosing Considerations, 7 Warnings And Precautions, 7.1 Special Populations , 7.1.1 Pregnant Women , And Part Ii: Scientific Information, 14 Clinical Trials , Immunogenicity In Pregnancy).

In children 4 through 6 years of age, ADACEL® may be considered as an alternative for the fifth dose of tetanus, diphtheria and acellular pertussis vaccine (DTaP). These children should also receive a separate booster with Inactivated Poliomyelitis Vaccine (IPV) to complete the vaccination series for this age, when indicated.

Persons who have had tetanus, diphtheria or pertussis should still be immunized since these clinical infections do not always confer immunity. Human Immunodeficiency Virus (HIV)-infected persons, both asymptomatic and symptomatic, should be immunized against tetanus, diphtheria and pertussis according to standard schedules.

Tetanus Prophylaxis in Wound Management

The need for active immunization with a tetanus toxoid-containing preparation such as Td Adsorbed vaccine or ADACEL®, with or without passive immunization with Tetanus Immune Globulin, depends on both the condition of the wound and the patient's vaccination history. (See 4 Dosage And Administration).

2. Contraindications

Adacel® is contraindicated in patients who are hypersensitive to this vaccine or to a vaccine containing one or more of the same components after previous administration (because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered) or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition And Packaging .

Acute Neurological Disorders
Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis-containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with any pertussis-containing vaccine, including ADACEL®.

4. Dosage And Administration

4.1. Dosing Considerations

Administration Route Related Precautions:

Do not administer ADACEL® by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Intradermal or subcutaneous routes of administration are not to be utilized.

ADACEL® should not be administered into the buttocks.

4.2. Recommended Dose and Dosage Adjustment

ADACEL® (0.5 mL) should be administered as a booster injection by the intramuscular route.

Re-dosing with ADACEL® can be used to boost immunity to diphtheria, tetanus and pertussis at 5- to10-year intervals. For re-dosing see 8 Adverse Reactions , 8.2 Clinical Trial Adverse Reactions for safety at 5 and 10 years and Part Ii: Scientific Information , 14 Clinical Trials , 14.2 Study Results , Study Td526 for immunogenicity at 10 years.

The preferred site is into the deltoid muscle.

Fractional doses (doses <0.5 mL) should not be given. The effect of fractional doses on the safety and efficacy has not been determined.

If ADACEL® is administered to a pregnant woman, it should ideally be done during the third trimester of pregnancy or according to recommendations from the National Advisory Committee on Immunization (NACI).

Health-care professionals should also refer to the NACI recommendations for tetanus prophylaxis in routine wound management shown in Table 1 .

Table 1: NACI Recommended Use of Immunizing Agents in Wound Management

History of Tetanus Immunization	Clean, Minor Wounds		All Other Wounds	
	Td*	TIG † (Human)	Td*	TIG† (Human)
Uncertain or <3 doses of an immunization series‡	Yes	No	Yes	Yes
≥3 doses received in an immunization series‡	No§	No	No**	No††

* Adult-type tetanus and diphtheria toxoid.
† Tetanus immune globulin, given at a separate site from the Td.
‡ Primary immunization is at least 3 doses at age appropriate intervals.
§ Yes, if >10 years since last booster.
** Yes, if >5 years since last booster.

†† Yes, if persons are known to have a significant humoral immune deficiency state (e.g., HIV, agammaglobulinemia) since immune response to tetanus toxoid may be suboptimal.

A thorough attempt must be made to determine whether a patient has completed primary immunization. Persons who have completed primary immunization against tetanus and who sustain wounds that are minor and uncontaminated, should receive a booster dose of a tetanus toxoid-containing preparation if they have not received tetanus toxoid within the preceding 10 years. For tetanus-prone wounds (e.g., wounds contaminated with dirt, feces, soil and saliva, puncture wounds, avulsions and wounds resulting from missiles, crushing, burns or frostbite), a booster is appropriate if the patient has not received a tetanus toxoid-containing preparation within the preceding 5 years.

4.4. Administration

Inspect for extraneous particulate matter and/or discolouration before use. (See 6 Dosage Forms, Strengths, Composition And Packaging , Description). If these conditions exist, the product should not be administered.

Shake the vial well until a uniform, cloudy, suspension results. Cleanse the vial stopper with a suitable germicide prior to withdrawing the dose. Do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual recipient, to prevent disease transmission. Needles should not be recapped but should be disposed of according to biohazard waste guidelines. (See 7 Warnings And Precautions).

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. Administer the total volume of 0.5 mL **intramuscularly** (I.M.). The preferred site of injection is the deltoid muscle.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

5. Overdosage

For management of a suspected drug overdose, contact your regional poison control centre.

6. Dosage Forms, Strengths, Composition And Packaging

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Suspension for injection Each 0.5 mL dose is formulated to contain: **Active Ingredient:** Tetanus Toxoid, Diphtheria Toxoid and Acellular Pertussis [Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN), Fimbriae Types 2 and 3 (FIM)]	2-phenoxyethanol, Aluminum Phosphate (adjuvant), Manufacturing Process Residuals: Formaldehyde and glutaraldehyde are present in trace amounts.

Description

ADACEL® is supplied as a sterile uniform, cloudy, white suspension in a vial.

Each dose (0.5 mL) is formulated to contain: Tetanus Toxoid (5 Lf); Diphtheria Toxoid (2 Lf); Acellular Pertussis [Pertussis Toxoid (PT), 2.5 mcg; Filamentous Haemagglutinin (FHA), 5 mcg; Pertactin (PRN), 3 mcg and Fimbriae Types 2 and 3 (FIM), 5 mcg].

The non-medicinal ingredients are as follows: Aluminum Phosphate (1.5 mg) and 2-phenoxyethanol (0.6% v/v).

Packaging

ADACEL® is supplied in 0.5 mL single dose glass vials.

The vials are made of Type 1 glass. The container closure system of ADACEL® is free of latex (natural rubber).

ADACEL® is available in a package of:
1 single dose vial
5 single dose vials
10 single dose vials

7. Warnings And Precautions

General

ADACEL® is not to be used for the treatment of disease caused by *Bordetella pertussis*, *Corynebacterium diphtheriae* or *Clostridium tetani* infections.

Before administration of ADACEL®, health-care providers should inform the recipient or the parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements regarding information to be provided to the recipient/guardian before immunization.

It is extremely important that the recipient, parent or guardian be questioned concerning any signs or symptoms of an adverse reaction after a previous dose of vaccine. (See 2 Contraindications and 8 Adverse Reactions).

The rates and severity of adverse events in recipients of tetanus toxoid are influenced by the number of prior doses and level of pre-existing antitoxins.

Syncope (fainting) can occur following, or even before, administration of injectable vaccines, including ADACEL®. Procedures should be in place to prevent falling injury and manage syncopal reactions.

As with any vaccine, ADACEL® may not protect 100% of vaccinated persons.

Febrile and Acute Disease: Vaccination should be postponed in cases of an acute or febrile disease. However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

Hematologic

Because any intramuscular injection can cause an injection site hematoma in persons with any bleeding disorders, such as hemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with ADACEL® should not be administered to such persons unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection.

Immune

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Hypersensitivity reactions may occur following the use of ADACEL® even in persons with no prior history of hypersensitivity to the product components.

As with all other products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.

Immunocompromised persons (whether from disease or treatment) may not achieve the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. Nevertheless, vaccination of persons with chronic immunodeficiency such as HIV infection is recommended even if the immune response might be limited.

Neurologic

ADACEL® should not be administered to individuals with progressive or unstable neurological disorders, uncontrolled epilepsy or progressive encephalopathy until a treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk.

If Guillain-Barré syndrome (GBS) occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give ADACEL® or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

Skin

Local reactions at injection site such as pain, swelling and erythema/redness may occur. See .

7.1. Special Populations

7.1.1 Pregnant Women

ADACEL® vaccination during pregnancy for passive immunization against pertussis in early infancy has been evaluated in published studies. Safety data from 4 randomized controlled trials (outcomes for 310 pregnancies) and 6 observational studies (outcomes for 125,356 pregnancies) of women who received ADACEL® or ADACEL®-POLIO during pregnancy (the majority in the 3rd trimester) have shown no vaccine-related adverse effect on pregnancy or on the health of the fetus/newborn child. These studies support the administration of ADACEL® during pregnancy (See 14 Clinical Trials, Immunogencity in pregnancy).

7.1.2 Breast-feeding

The effect of administration of ADACEL® during lactation has not been assessed. As ADACEL® is inactivated, any risk to the mother or the infant is improbable. However, the effect on breast-fed infants of the administration of ADACEL® to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunize a nursing woman.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety of ADACEL® was evaluated in a total of 5,818 participants who received a single dose of ADACEL® in 6 clinical trials (298 children ≥4 years of age, 1,508 adolescents, 2,842 adults <65 years of age and 1,170 adults ≥65 years of age).

Pain at the injection site was the most common solicited injection site reaction. Most injection site reactions occurred within 3 days following vaccination and their mean duration was less than 3 days. The most frequent systemic reaction was tiredness in children and headache in adolescents and adults (18 - 64 years). Myalgia was the most frequently reported systemic reaction among older adults ≥65 years of age. Fever was reported in less than 10% of vaccinees. These reactions were usually transient and of mild to moderate intensity. In addition, in adolescents and all adults the incidence of injection site and systemic reactions following ADACEL® was comparable to those observed with a Td vaccine booster. In children the observed frequencies of injection site reactions and fever following ADACEL® were significantly lower than those observed with QUADRACEL® (DTaP IPV) when administered as a booster at 4 to 6 years of age. Except for fever, the observed rates for the systemic reactions were comparable between the two vaccines.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The frequency of the solicited injection site and systemic reactions reported in three clinical trials are shown in Table 3 .

Two serious adverse events were reported during Study Td506 which were considered related to the vaccination: a case of severe migraine with unilateral facial paralysis, and a diagnosis of nerve compression in the neck and left arm. Both of these conditions resolved spontaneously or with treatment.

Table 3: Frequency (%) of Solicited Reactions Observed Within 0 to 14 Days in Clinical Trials in Children, Adolescents and Adults, Following a Single Dose With ADACEL®

Solicited Reactions	Children 4 - 6 years (N = 298)	Adolescents 11 - 17 years (N = 1,184)	Adults 18 - 64 years (N = 1,752)	Adults ≥65 years (N = 1,153)
Injection Site Reactions				
Pain	39.6	77.8	65.7	43.0
Swelling	24.2	20.9	21.0	18.1
Erythema	34.6	20.8	24.7	24.3
Systemic Reactions				
Fever (≥38.0°C)	8.7	5.0	1.4	0.5
Headache	16.4	43.7	33.9	18.2
Nausea	9.4	13.3	9.2	N.S.*
Diarrhea	14.4	10.3	10.3	N.S.*
Vomiting	8.1	4.6	3.0	N.S.*
Anorexia	21.5	N.S.*	N.S.*	N.S.*
Rash	8.4	2.7	2.0	N.S.*
Body Ache or Muscle Weakness † / Myalgia‡	6.4	30.4	21.9	28.4
Sore or Swollen Joints	4.0	11.3	9.1	N.S.*
Tiredness§ / Malaise**	31.5	30.2	24.3	17.2
Chills	7.1	15.1	8.1	N.S.*
Axillary Lymph Node Swelling	5.4	6.6	6.5	N.S.*

* Not Solicited

† Body ache or muscle weakness was the solicited term in the trials in children, adolescents and adults 18 - 64 years of age.

‡ Myalgia was the solicited term in the trial in adults ≥65 years of age.

§ Tiredness was the solicited term in the trials in children, adolescents and adults 18 - 64 years of age.

** Malaise was the solicited term in the trial in adults ≥65 years of age.

Table 4: Frequency (%) of Solicited Reactions Observed in Adolescents and Adults Following Re-administration of ADACEL® at 5 and 10 years Respectively

Solicited Reactions	Re-administration of ADACEL	
	After 5 years*	After 10 years§
	Adolescents and Adults 16- 69 years (N= 544)	Adults 20 – 72 years (N= 361)
Injection Site Reactions		
Pain	87.6	87.8
Erythema/ Redness	28.6	23.1
Swelling	25.6	20.5
Systemic Reactions		
Fever	6.5	4.2
Headache	53.2	40.6
Myalgia	61.0	60.1
Malaise	38.2	29.4

* Adverse reactions observed within 0 to 14 days after vaccination

§ Adverse reactions observed within 0 to 7 days after vaccination

8.5. Post-Market Adverse Reactions

The following additional adverse events have been spontaneously reported during the post-marketing use of ADACEL®. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to ADACEL®.

Immune System Disorders

Hypersensitivity (anaphylactic) reaction (angioedema, edema, rash, hypotension)

Nervous System Disorders

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

Cardiac Disorders

Myocarditis

Skin and Subcutaneous Tissue Disorders

Pruritus, urticaria

Musculoskeletal and Connective Tissue Disorders

Myositis, muscle spasm

General Disorders and Administration Site Conditions

Large injection site reactions (>50 mm) and extensive limb swelling from the injection site beyond one or both joints have been reported after administration of ADACEL® in adolescents and adults. These reactions usually start within 24 - 72 hours after vaccination, may be associated with erythema, warmth, tenderness or pain at the injection site and resolve spontaneously within 3 - 5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine.

Injection site bruising, injection site nodule, sterile abscess

9. Drug Interactions

9.4. Drug-Drug Interactions

Vaccine-Drugs Interactions:

Immunosuppressive treatments may interfere with the development of the expected immune response. (See 7 Warnings And Precautions).

Concomitant Vaccine Administration:

ADACEL® may be administered concurrently with a dose of trivalent inactivated influenza vaccine and with a dose of hepatitis B vaccine in 11 to 12 year-olds.

The concomitant use of ADACEL® and trivalent inactivated influenza vaccine was evaluated in a clinical trial involving 696 adults 19 to 64 years of age. The safety and immunogenicity profiles in adults that received the vaccines concomitantly were comparable to those observed when the vaccines were given on separate occasions one month apart.

The concomitant use of ADACEL® and hepatitis B vaccine was evaluated in a clinical trial involving 269 adolescents 11 to 12 years of age. The safety and immunogenicity profiles in adolescents that received the vaccines concomitantly were comparable to those observed when the vaccines were given on separate occasions one month apart. No interference was observed in the immune responses to any of the vaccine antigens when ADACEL® and hepatitis B vaccines were given concurrently or separately.

Vaccines administered simultaneously should be given using separate syringes at separate injection sites and preferably in separate limbs. ADACEL® should not be mixed in the same syringe with other parenterals.

10. Clinical Pharmacology

10.1. Mechanism of Action

Tetanus and Diphtheria: Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C. tetani*. The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. Protection against disease attributable to *C. tetani* is due to the development of neutralizing antibodies to tetanus toxin.

Strains of *C. diphtheriae* that produce diphtheria toxin can cause severe or fatal illness characterized by membranous inflammation of the upper respiratory tract and toxin-induced damage to the myocardium and nervous system. Protection against disease attributable to *C. diphtheriae* is due to the development of neutralizing antibodies to diphtheria toxin.

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

10.2. Pharmacodynamics

Tetanus and Diphtheria:

A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. A tetanus antitoxin level of at least 0.1 IU/mL as measured by the ELISA used in clinical studies of ADACEL® is considered as protective for tetanus. Levels of 1.0 IU/mL have been associated with long-term protection.

A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. Levels of 1.0 IU/mL have been associated with long-term protection.

Pertussis:

In a clinical trial in Sweden (Sweden I Efficacy Trial), the same pertussis components as in ADACEL® (i.e., PT, FHA, PRN and FIM) have been shown to prevent pertussis in infants with a protective efficacy of 85.2% using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiological link to a confirmed case). In the same study, the protective efficacy against mild disease was 77.9%. A household contact study that was nested in this efficacy trial demonstrated that there were statistically significant correlations between clinical protection and the presence of antibodies against PT, PRN and FIM in pre-exposure sera.

Minimum serum antibody levels to specific pertussis vaccine components that confer protection against the development of clinical pertussis have not been identified. Nevertheless, a number of studies have demonstrated a correlation between the presence of serum antibody responses to pertussis vaccine components and protection against clinical disease. In ADACEL® clinical trials, in children, adolescents and adults <65 years of age, post-vaccination Geometric Mean Concentrations (GMCs) for all pertussis antibodies were consistently above those of TRIPACEL® in the Sweden I Efficacy Trial. Older adults (≥65 years of age) vaccinated with a single dose of ADACEL® achieved lower GMCs for some of the pertussis antibodies than did infants who had received 3 or 4 doses of TRIPACEL®. Nevertheless, their post-

immunization anti-pertussis antibody levels were 4.4- to 15.1-fold higher than pre-immunization levels, suggested an improved degree of protection against pertussis.

10.3. Pharmacokinetics

Duration of Effect

Long-term follow-up of serum antibody levels in adolescents and adults who received a single dose of ADACEL® show that protective levels for tetanus antitoxin (≥0.01 EU/mL) and diphtheria antitoxin (≥0.01 IU/mL) persist in 99.2% and 92.6% of participants, respectively, 10 years post-vaccination. While protective levels against pertussis have not yet been clearly defined, pertussis antibody levels remain 2 to 9 fold higher than pre-immunization levels after 5 years. However at 10 years post-vaccination pertussis antibody levels were observed to decline towards pre-vaccination levels.

Tetanus and diphtheria toxoid boosters are recommended every 10 years. The serology follow-up and redosing data for ADACEL® suggest that it can be used instead of tetanus and diphtheria toxoid vaccine for boosting at 10-year intervals in adults.

11. Storage, Stability And Disposal

Store at 2° to 8°C (35° to 46°F). **Do not freeze**. Discard product if exposed to freezing (≤ 0°C).

ADACEL® has been shown to remain stable at temperature above 8°C and up to 25°C, for a maximum of 3 days (72 hours). These data are not recommendations for shipping or storage, but may guide decision for use in case of temporary temperature excursions.

12. Special Handling Instructions

Do not use after expiration date.

Part Ii: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Product Characteristics:

ADACEL® is a sterile, uniform, cloudy, white suspension of tetanus and diphtheria toxoids adsorbed on aluminum phosphate, combined with acellular pertussis vaccine and suspended in water for injection. This acellular pertussis vaccine is composed of five purified pertussis antigens (PT, FHA, PRN, FIM).

C. diphtheriae is grown in modified Mueller's growth medium. After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. *C. tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The 5 acellular pertussis vaccine components are obtained from *B. pertussis* cultures grown in Stainer-Scholte medium modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. Pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) are isolated separately from the supernatant culture medium. Fimbriae types 2 and 3 (FIM) are extracted from the bacterial cells. These antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde and FHA is treated with formaldehyde and the residual aldehydes are removed by diafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (as excipient) and water for injection.

The potency of tetanus and diphtheria toxoids are measured by in vitro antigenicity enzyme-linked immunosorbent assays (ELISA), which detects immunologically relevant epitopes. Alternatively, the potency can be assessed in guinea pigs, with the tetanus toxoid inducing at least 2 neutralizing units/mL of serum and the diphtheria toxoid inducing 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 PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA).

14. Clinical Trials

14.1. Trial Design and Study Demographics

Table 5: Summary of Demographics and Study Design of the Trials with ADACEL®

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects* (N = ITT†)	Age Range	Gender
TC9704	Randomized, controlled, double-blind, multicentre comparative trial with Td used as control.	1 Dose 0.5 mL I.M.	Adolescents (N = 55) Adults (N = 394)	12.6 - 54.7 years	Males (N = 145) Females (N = 304)
Td508	Randomized, controlled, modified double-blind, multicentre comparative trial with DTaP-IPV used as control.	1 Dose 0.5 mL I.M.	Children (N = 298)	4.0 - 6.6 years	Males (N = 144) Females (N = 154)
Td506	Randomized, controlled, double-blind, multicentre comparative trial with Td used as control.	1 Dose 0.5 mL I.M.	Adolescents (N = 1,184) Adults (N = 1,752)	11.0 - 64.9 years	Males (N = 1,202) Females (N = 1,734)
Td515	Randomized, controlled, modified double-blind, multicentre safety and immunogenicity trial in persons ≥65 years of age.	1 Dose 0.5 mL I.M.	Adults (N = 1,170)	65 - 95 years	Males (N = 591) Females (N = 579)
TD9805	Randomized, controlled, open-label, single centre trial with concomitant Hepatitis B Vaccine.	1 Dose 0.5 mL I.M.	Adolescents (N = 269)	11.0 - 11.8 years	Males (N = 145) Females (N = 124)
Td502	Randomized, controlled, open-label, multicentre trial with concomitant Influenza Vaccine.	1 Dose 0.5 mL I.M.	Adults (N = 696)	19.1 - 64.7 years	Males (N = 281) Females (N = 415)
Td526	Phase IV, open-label, multicenter study assessing immunogenicity and safety in adults following re-dosing 10 years after a previous dose of Tdap or Tdap-IPV vaccine	0.5 mL I.M.	Adults (N=743)	20.0 – 72.0 years	Males (N=297) Females (N=446)

* All studies required participants to be in good health and not have been vaccinated against diphtheria, tetanus, or pertussis within the last 5 years.

† Intent-to-Treat (ITT) population includes all participants who were randomized and received ADACEL®.

14.2. Study Results

Efficacy

Serological correlates of protection have been defined for diphtheria and tetanus. The efficacy of the tetanus toxoid and diphtheria toxoid used in ADACEL® was inferred by the demonstration that the immune responses to these antigens attain levels previously established as protective (≥0.1 IU/mL). Evidence of efficacy was also measured by demonstrating that the diphtheria and tetanus seroresponses for ADACEL® were non-inferior to those observed in Td506 with Td vaccines.

The efficacy of the pertussis antigens used in ADACEL® was inferred based on a comparison of pertussis antibody levels achieved in recipients of a single booster dose of ADACEL® with those obtained in infants after a 3-dose primary series with TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed - DTaP]. In the Sweden I Efficacy Trial, TRIPACEL® was shown to confer a protective efficacy of 85.2% (95% CI: 80.6%, 88.8%) against WHO-defined pertussis (21 days of paroxysmal cough with laboratory-confirmed *B. pertussis* infection). 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%). The acellular pertussis formulations for ADACEL® and TRIPACEL® differ only in the amount of PT (2.5 mcg in ADACEL® versus 10 mcg in TRIPACEL®). The pertussis antibody responses in the 5 clinical studies conducted in children, adolescents and adults 19 - 64 years of age, demonstrate that a booster dose of ADACEL® results in robust antibody responses to all pertussis antigens and post-immunization antibody levels that are several-fold higher than those found to be protective in the Sweden I Efficacy Trial (i.e., >86.6 EU/mL for anti-PT, >40.0 EU/mL for anti-FHA, >108 EU/mL for anti-PRN and >341 EU/mL for anti-FIM as measured in a subset of sera from the Sweden I Efficacy Trial tested contemporaneously with samples from Clinical Trial Td506 in the same laboratory using the same validated assay). Older adults (≥65 years of age) vaccinated with a single dose of ADACEL® achieved lower GMCs for some of the pertussis antibodies than did infants who had received 3 or 4 doses of TRIPACEL®. Nevertheless, their post-immunization anti-pertussis antibody levels were 4.4- to 15.1-fold higher than pre-immunization levels, suggested an improved degree of protection against pertussis.

Evaluation of Safety

Safety was evaluated by comparing the rates of solicited injection site and systemic reactions, as well as unsolicited adverse events between vaccine groups. Participants were monitored for clinical safety immediately after the immunization and for 1 to 6 months post-immunization. Comparability of the safety profiles was evaluated using the rates of solicited injection site and systemic reactions that occurred within designated intervals post-vaccination. In TC9704 and TD9805 these intervals were 0 to 24 hours, 24 to 72 hours (3 days), and >72 hours (3 days) to 14 days post-vaccination (8 days in TC9704). For Td506, Td502 and Td508 the intervals consisted of 0 to 3 days, 4 to 14 days and 0 to 14 days. For Td515 the intervals consisted of 0 to 3 days, 0 to 7 days and 0 to 14 days. Each type of adverse event was classified according to the degree of severity.

TC9704: Comparison of ADACEL® with Td Vaccine

In TC9704, a total of 749 persons were randomized to 5 treatment groups: 449 (55 adolescents 12 to 17 years of age and 394 adults 18 to 54 years of age) received a single dose of 1 to 3 clinical trial lots of ADACEL®; 151 (20 adolescents and 131 adults) were given a single dose of Td Adsorbed (manufactured by Sanofi Pasteur Limited) at Day 0 and monovalent Acellular Pertussis given separately 1 month later; while 149 (17 adolescents and 132 adults) received the Acellular Pertussis and Td in the reverse order. A subset of adult and adolescent vaccines were followed-up at 1 (N = 200), 3 (N = 208), 5 years (N = 189), 8 (N= 162) and 10 years (N= 144) after receiving a single dose of ADACEL®, for assessment of antibody persistence.

Immunogenicity and Antibody Persistence

All ADACEL® recipients (100%) achieved tetanus antitoxin levels ≥0.1 IU/mL, whereas over 85% had diphtheria antitoxin levels ≥0.1 IU/mL. No differences were observed in immune responses to Tetanus or Diphtheria Toxoids between Td and ADACEL® vaccine groups. The long-term antibody profile suggested that protection against diphtheria and tetanus is maintained for at least 10 years following a booster ADACEL® administration in both adolescents and adults. The pertussis response to ADACEL® was also robust, and antibodies persisted at detectable levels higher than pre-immunization levels for 10 years. Table 6 summarizes the findings for diphtheria and tetanus and Table 7 the findings for pertussis.

Table 6: Diphtheria and Tetanus - Persistence of Seroprotection Rates at Levels ≥0.01 UI/mL and ≥0.10 IU/mL, in Study TC9704

Antigen	Visit	≥0.01 (IU/mL)*		% ≥0.10 (IU/mL)*	
		N*	%	N*	%
Diphtheria	Pre-	449	81.1	449	28.3
	1 Month Post	446	98.0	446	85.0
	1 Year Post	198	97.0	198	67.7
	3 Years Post	203	97.0	203	60.1
	5 Years Post	178	93.3	178	52.2
	8 Years Post	151	94.7	151	53.0
	10 Years Post	135	92.6	135	48.9
Tetanus	Pre-	448	98.9	448	96.9
	1 Month Post	446	100.0	446	100.0
	1 Year Post	196	100.0	196	100.0
	3 Years Post	201	100.0	201	100.0
	5 Years Post	174	100.0	174	99.4
	8 Years Post	146	99.3	146	98.6
	10 Years Post	131	99.2	131	99.2

* IU/mL for diphtheria; EU/mL for tetanus

† Per-Protocol population

Table 7: Pertussis Antigens - Geometric Mean Concentrations (GMCs) Persistence in ADACEL® Recipients in Study TC9704

Antigen	Visit	N*	GMC
PT (EU/mL)	Pre-	439	8.92
	1 Month Post	445	144.02
	1 Year Post	200	55.14
	3 Years Post	208	49.12
	5 Years Post	189	43.85
	8 Years Post	150	23.47
	10 Years Post	123	20.60
FHA (EU/mL)	Pre-	449	23.68
	1 Month Post	446	332.62
	1 Year Post	200	112.44
	3 Years Post	208	63.70
	5 Years Post	189	47.46
	8 Years Post	161	60.37
	10 Years Post	142	39.63
PRN (EU/mL)	Pre-	449	5.09
	1 Month Post	446	278.58
	1 Year Post	200	78.45
	3 Years Post	207	78.56
	5 Years Post	189	38.17
	8 Years Post	159	42.59
	10 Years Post	144	40.38
FIM (EU/mL)	Pre-	449	20.09
	1 Month Post	446	985.27
	1 Year Post	200	300.08
	3 Years Post	207	229.44
	5 Years Post	189	194.90
	8 Years Post	161	152.45
	10 Years Post	143	128.43

* Per-Protocol population – pooled groups

Td506: Comparison of ADACEL® with Td Vaccine in a large scale trial

In Td506, 4,480 participants were stratified into 5 age ranges (11 to 13, 14 to 17, 18 to 28, 29 to 48, 49 to 64 years) and then randomized to receive ADACEL® or Td Adsorbed (manufactured by Sanofi Pasteur Limited) licensed in the U.S. A modified double-blind ("observer blind") design was used in Td506, as ADACEL® is supplied in single dose vials while Td Adsorbed was supplied in multidose vials. A total of 4,301 participants were vaccinated in 2 treatment groups: 2,936 (1,184 adolescents 11 to 17 years of age and 1,752 adults 18 to 64 years of age) received a single dose of ADACEL®; and, 1,365 (792 adolescents 11 to 17 years of age and 573 adults 18 to 64 years of age) received a single dose of Td vaccine.

Immunogenicity

For both the adolescent and adult population, diphtheria and tetanus post-vaccination seroprotection rates (% ≥0.1 IU/mL) achieved with ADACEL® were demonstrated to be non-inferior to those with Td vaccine (i.e., the lower limits of the two-sided 95% CIs for differences in seroconversion rates at >0.1 IU/mL, ADACEL® minus Td vaccine, within each age group are >-10%). All (100%) adolescent and adult ADACEL® vaccinees achieved tetanus antitoxin seroprotective levels, while diphtheria seroprotection rates were 99.8% and 94.1%, in adolescents and adults, respectively. (See Table 8 and Table 9).

Table 8: Tetanus Antitoxin Levels and Booster Response Rates for Adolescents and Adults in Study Td506

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

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

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

‡ Seroprotection rates at ≥0.10 IU/mL and booster response rates to ADACEL® were non-inferior to Td vaccine (the lower limits of the two-sided 95% CIs for differences in seroconversion rates at >0.1 IU/mL, ADACEL® minus Td vaccine, within each age group are >-10%).

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

Table 9: Diphtheria Antitoxin Levels and Booster Response Rates for Adolescents and Adults in Study Td506

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

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

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

‡ Seroprotection rates at ≥0.10 IU/mL and booster response rates to ADACEL® were non-inferior to Td vaccine (the lower limits of the two-sided 95% CIs for differences in seroconversion rates at >0.1 IU/mL, ADACEL® minus Td vaccine, within each age group are >-10%).

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

Seroepidemiological studies have shown a clear effect of increasing age on decreasing antibody levels to diphtheria and tetanus. This age-related trend was observed for diphtheria using pre- and post-vaccination seroprotection rates (≥0.1 IU/mL) and GMCs and was similar for both ADACEL® and Td vaccine recipients. For tetanus, seroprotection rates did not decrease with increasing age. All participants who received ADACEL® and all but 1 participant who received Td vaccine achieved tetanus seroprotective levels (≥0.1 IU/mL) post-vaccination.

GMCs for the pertussis antigens PT, FHA, PRN and FIM, before vaccination and at 1-month post-vaccination are presented in Table 10 . Adolescents achieved somewhat higher post-vaccination GMCs and booster response rates than adults. Younger adults (18 - 48 years) tended to achieve higher post-vaccination GMCs and booster response rates than older adults (49 - 64 years). However, for the entire 11 to 64 year-old population, pertussis GMCs for each antigen showed robust rises following vaccination with ADACEL®.

Pertussis antibody GMCs for ADACEL® were consistently higher than Sweden I Efficacy Trial levels for all pertussis antigens, both for adults and adolescents, as well as for the entire study population, 11 to 64

years. (See Table 11).

Table 10: Pertussis Antibody GMCs in Adolescents and Adults Receiving ADACEL® in Study Td506

	Age Group (Years)	Pre-Vaccination		Post-Vaccination	
		N	GMCs (EU/mL)	N	GMCs (EU/mL)
Anti-PT	**Adolescents**	527	14.5	524	309
	Adults	741	12.5	741	179
Anti-FHA	**Adolescents**	527	19.5	526	215
	Adults	741	18.1	741	193
Anti-PRN	**Adolescents**	526	10.0	526	345
	Adults	741	8.5	741	342
Anti-FIM	**Adolescents**	527	25.8	526	1,792
	Adults	741	28.6	741	853

Table 11: Ratio of Pertussis Antibody GMCs¥ Observed One Month After a Dose of ADACEL® in Adolescents and Adults Compared with Those Observed in Infants One Month Following Vaccination at 2, 4 and 6 Months of Age in the Efficacy Trial with TRIPACEL®

	Adolescents	Adults
	ADACEL®*/TRIPACEL® † GMCs Ratio (95% CIs)	ADACEL®‡/TRIPACEL® † GMCs Ratio (95% CIs)
Anti-PT	3.6 (2.8, 4.5)§	2.1 (1.6, 2.7)§
Anti-FHA	5.4 (4.5, 6.5)§	4.8 (3.9, 5.9)§
Anti-PRN	3.2 (2.5, 4.1)§	3.2 (2.3, 4.4)§
Anti-FIM	5.3 (3.9, 7.1)§	2.5 (1.8, 3.5)§

¥ Antibody GMCs, measured in 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 TRIPACEL® with available data post-dose 3 (sera from the Sweden I Efficacy Trial tested contemporaneously with samples from Clinical Trial Td506).

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

§ GMCs following ADACEL vaccine were non-inferior to GMCs following TRIPACEL® (lower limit of 95% CI on the ratio of GMCs for ADACEL® divided by TRIPACEL® >0.67).

Table 12: Booster Responses to the Pertussis Antigens Observed One Month After a Dose of ADACEL® in Adolescents and Adults

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

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

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

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

Antibody Persistence

In Study Td506, 299 adolescents (aged 11 - 17 years) and 349 adults (aged 18 - 64 years) vaccinated with ADACEL® and 282 adolescents and 287 adults vaccinated with Td Vaccine were followed for 1 year and 3 years post-vaccination to measure the persistence of antibody levels against the vaccine antigens. At 1-year post-vaccination, seroprotection rates for tetanus and diphtheria remained very high, almost 100% for all age groups. For pertussis antibodies, levels are also consistently high, exceeding pre-vaccination titres, and are suggestive of continued protective effectiveness. Although there continued to be a decline for all antibodies between 1- and 3-years post-vaccination, seroprotection rates for tetanus and diphtheria remained high (>95% at a level of antibodies ≥0.01 IU/mL for all age groups) at 3-years post-vaccination. For pertussis, antibody levels at 3-years post-vaccination are still substantially higher than pre-vaccination levels. The long-term antibody profile observed in this study indicates that protection against diphtheria, tetanus, and pertussis is maintained at 1- and 3-years following the administration of a single booster dose to adolescents (11 - 17 years old) and adults (18 - 64 years old) of ADACEL®. Table 13 summarizes the findings for diphtheria and tetanus. Table 14 summarizes the findings for pertussis antigens.

Table 13: Diphtheria and Tetanus – Persistence of Seroprotection Rates at Levels ≥0.01 IU/mL and ≥0.1 IU/mL, in Study Td506

Antigen	Time	Age in Years	ADACEL®			Td Vaccine		
			N*	% ≥0.01 IU/mL	% ≥0.1 IU/mL	N*	% ≥0.01 IU/mL	% ≥0.1 IU/mL
Diphtheria	Pre-	11 - 17	227	100.0	70.5	186	100.0	76.3
		18 - 64	225	89.3	60.9	182	91.2	59.3
	1-Month	11 - 17	227	100.0	100.0	186	100.0	100.0
		18 - 64	225	97.8	93.3	182	98.4	91.8
	1-Year	11 - 17	227	100.0	99.6	186	100.0	100.0
		18 - 64	225	96.9	88.4	182	98.4	90.7
	3-Year	11 - 17	227	100.0	96.9	186	100.0	97.8
		18 - 64	225	95.6	81.3	182	97.3	84.1
Tetanus	Pre-	11 - 17	227	100.0	99.6	186	100.0	98.9
		18 - 64	225	100.0	97.3	182	99.5	95.1
	1-Month	11 - 17	227	100.0	100.0	186	100.0	100.0
		18 - 64	225	100.0	100.0	182	100.0	100.0
	1-Year	11 - 17	227	100.0	100.0	186	100.0	100.0
		18 - 64	224	100.0	100.0	182	100.0	100.0
	3-Year	11 - 17	227	100.0	100.0	186	100.0	100.0
		18 - 64	225	100.0	98.7	182	100.0	100.0

* Per-Protocol population

Table 14: Pertussis Antigens - Geometric Mean Concentrations (GMCs) Persistence in ADACEL® Recipients in Study Td506

Antigen	Time	Age in Years	N*	GMC
PT (EU/mL)	Pre-	11 – 17	227	13.53
		18 – 64	225	11.39
	1-Month	11 – 17	227	303.93
		18 – 64	225	151.92
	1-Year	11 – 17	227	115.28
		18 – 64	224	64.88
	3-Year	11 – 17	227	65.87
		18 – 64	225	48.29
FHA (EU/mL)	Pre-	11 – 17	227	19.59
		18 – 64	225	18.61
	1-Month	11 – 17	227	196.38
		18 – 64	225	184.60
	1-Year	11 – 17	227	95.32
		18 – 64	225	87.07
	3-Year	11 – 17	227	52.22
		18 – 64	225	59.15
PRN (EU/mL)	Pre-	11 – 17	226	9.50
		18 – 64	225	8.68
	1-Month	11 – 17	227	322.27
		18 – 64	225	357.99
	1-Year	11 – 17	227	131.94
		18 – 64	225	163.02
	3-Year	11 – 17	227	82.70
		18 - 64	225	113.05
FIM (EU/mL)	Pre-	11 – 17	227	24.76
		18 – 64	225	26.05
	1-Month	11 - 17	227	1,818.85
		18 – 64	225	698.07
	1-Year	11 – 17	227	706.99
		18 – 64	225	309.36
	3-Year	11 – 17	227	352.77
		18 – 64	225	184.64

* Per-Protocol population

Safety

Solicited injection site and systemic reactions were monitored for 14 days post-vaccination using a diary card. Participants were monitored for 28 days for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, hospitalization and serious adverse events.

The rates of solicited injection site and systemic reactions following ADACEL® were comparable to those observed with Td. The frequency of solicited reactions occurring at Days 0 to 14 following one dose of ADACEL® or Td are presented in Table 15.

Most of these reactions were reported at a similar frequency in recipients of both ADACEL® and Td. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63-78% of all vaccinees. The overall rates of pain were statistically different between adolescent recipients of ADACEL® and Td vaccines but rates of moderate and severe pain did not significantly differ. Rates did not significantly differ for adults. Most injection site reactions occurred within the first 3 days after vaccination and were of short duration (mean duration was less than 3 days). Headache was the most frequent systemic reaction and was usually transient and of mild to moderate intensity.

Table 15: Frequency (%) of Solicited Reactions Reported in Adolescents and Adults in Study Td506 From Day 0 to 14 After a Single Dose with ADACEL® or Td Vaccine

Solicited Reactions	Severity	Adolescents		Adults	
		ADACEL® (N = 1,184)	Td (N = 792)	ADACEL® (N = 1,752)	Td (N = 573)
Injection Site*					
Pain	Any	77.8	71.0	65.7	62.9
	Severe†	1.5	0.6	1.1	0.9
Swelling	Any	20.9	18.3	21.0	17.3
	≥35 mm	6.4	5.5	5.7	5.5
Erythema	Any	20.8	19.7	24.7	21.6
	≥35 mm	6.0	5.3	6.2	4.8
Systemic‡					
Headache	Any	43.7	40.4	33.9	34.1
	Severe	2.0	1.5	2.8	2.1
Body Ache or Muscle Weakness	Any	30.4	29.9	21.9	18.8
	Severe	1.3	0.9	1.2	0.9
Tiredness	Any	30.2	27.3	24.3	20.7
	Severe	1.2	1.0	1.3	0.5
Chills	Any	15.1	12.6	8.1	6.6
	Severe	0.5	0.1	0.7	0.5

Solicited Reactions	Severity	Adolescents		Adults	
		ADACEL® (N = 1,184)	**Td (N = 792)**	**ADACEL® (N = 1,752)**	**Td (N = 573)**
Nausea	Any	13.3	12.3	9.2	7.9
	Severe	1.0	0.6	0.8	0.5
Sore or Swollen Joints	Any	11.3	11.7	9.1	7.0
	Severe	0.3	0.1	0.5	0.5
Diarrhea	Any	10.3	10.2	10.3	11.3
	Severe	0.3	0.0	0.5	0.5
Lymph Node Swelling	Any	6.6	5.3	6.5	4.1
	Severe	0.1	0.0	0.1	0.0
Fever	≥38.0°C	5.0	2.7	1.4	1.1
	≥39.5°C	0.2	0.1	0.0	0.2
Vomiting	Any	4.6	2.8	3.0	1.8
	Severe	0.5	0.3	0.5	0.2
Rash	Any	2.7	2.0	2.0	2.3

* All reaction rates (except for 'Any' pain in adolescents) following ADACEL® were non-inferior to rates following Td Vaccine (upper limited of the 95% CI on the difference for ADACEL® minus Td vaccine was 10.7% whereas the criterion was <10%).

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

‡ All solicited systemic reaction rates following ADACEL® were non-inferior to rates following Td Vaccine (upper limit of the 95% CI for the difference in rates of ADACEL® minus Td vaccine <10%).

Two serious adverse events were reported during Study Td506 which were considered related to the vaccination: a case of severe migraine with unilateral facial paralysis, and a diagnosis of nerve compression in the neck and left arm. Both of these conditions resolved spontaneously or with treatment.

Td508: Comparison of ADACEL® with QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine]

In Td508, 593 children 4 to 6 years of age who had previously received a total of 4 doses, including primary immunization, with PENTACEL® [Haemophilus b Conjugate Vaccine (Tetanus Protein Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine - DTaP-IPV combined with Hib] at approximately 2, 4, 6 and 18 months of age, were randomized to receive ADACEL® or QUADRACEL® (DTaP-IPV). A modified double-blind ("observer blind") design was used in Td508, as ADACEL® is supplied in single dose vials while QUADRACEL® was supplied in ampoules. A total of 590 participants were vaccinated in the 2 treatment groups: 298 received a single dose of ADACEL®; and 292 received a single dose of QUADRACEL®.

Immunogenicity

The diphtheria and tetanus post-vaccination seroprotection rates following vaccination with ADACEL® were shown to be non-inferior to those obtained with QUADRACEL®. All vaccinees (100%) achieved diphtheria and tetanus antitoxin levels of ≥0.1 IU/mL. Post-vaccination GMCs for diphtheria were lower in the ADACEL® group compared to the QUADRACEL® group, consistent with the lower diphtheria content in ADACEL®. (See Table 16).

Table 16: Tetanus and Diphtheria Seroprotection Rates Observed in Children 4 to 6 Years of Age Following a Single Dose of ADACEL® or QUADRACEL® in Study Td508

Antitoxin	Vaccine	Pre-Vaccination			Post-Vaccination		
		N	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)	N	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)
Tetanus	ADACEL®	265	95.5	26.4	265	100.0	100.0
	QUADRACEL®	252	96.4	23.8	254	100.0	99.6
Diphtheria	ADACEL®	265	86.0	34.7	265	100.0	97.7
	QUADRACEL®	253	87.4	33.2	253	100.0	98.0

GMCs for the pertussis antigens PT, FHA, PRN and FIM, before vaccination and at 1-month post-vaccination are presented in Table 17. Post-vaccination pertussis antibody GMCs for each antigen showed robust rises following vaccination for each antigen in all vaccinees. The post-vaccination GMCs and four-fold rise rates were generally comparable between both vaccine groups, although anti-PT and anti-FHA were slightly higher in QUADRACEL® vaccinees consistent with higher PT and FHA content of QUADRACEL®, while anti-PRN and anti-FIM were slightly higher in those that received ADACEL®. Pertussis antibody GMCs following ADACEL® were consistently higher than those observed in the Sweden I Efficacy Trial.

Table 17: Pertussis Antibody GMCs Observed in Children 4 to 6 Years of Age Following a Single Dose of ADACEL® or QUADRACEL® in Study Td508

	Vaccine	Pre-Vaccination		Post-Vaccination	
		N	GMCs (EU/mL)	N	GMCs (EU/mL)
Anti-PT	**ADACEL®**	263	19.9	262	297
	QUADRACEL®	251	19.3	254	331
Anti-FHA	**ADACEL®**	263	15.1	263	198
	QUADRACEL®	251	15.4	254	258
Anti-PRN	**ADACEL®**	263	16.3	263	304
	QUADRACEL®	251	16.3	254	243
Anti-FIM	**ADACEL®**	263	52.3	263	1,177
	QUADRACEL®	251	52.6	254	738

Safety

Solicited injection site and systemic reactions were monitored for 14 days post-vaccination using a diary card. Participants were monitored for 28-42 days for unsolicited adverse events, for visits to an emergency room, unexpected visits to an office physician, hospitalization and serious adverse events.

The rates of injection site reactions and fever following the administration of ADACEL® were shown to be non-inferior to those observed after QUADRACEL® and significantly lower in ADACEL® recipients compared to QUADRACEL® recipients. Except for fever, the observed rates for the systemic reactions were comparable between the two vaccines. (See Table 18). There were no unsolicited reports of whole-limb swelling in either vaccine group.

Table 18: Frequency (%) of Solicited Reactions Reported in Children 4 to 6 Years of Age From Day 0 to 14 After a Single Dose with ADACEL® or QUADRACEL® in Study Td508

Solicited Reactions	Severity	ADACEL® (N = 298)	QUADRACEL® (N = 290)
Injection Site*			
Pain	Any	39.6	67.2
	Severe†	0.3	1.0
Swelling	Any	24.2	33.8
	≥35 mm	10.1	17.2
Erythema	Any	34.6	51.7
	≥35 mm	11.7	29.0
Systemic			
Headache	Any	16.4	16.9
	Severe	0.0	0.7
Body Ache or Muscle Weakness	Any	6.4	8.3
	Severe	0.0	0.7
Tiredness	Any	31.5	36.6
	Severe	0.3	3.1
Chills	Any	7.1	10.0
	Severe	0.0	0.3
Nausea	Any	9.4	10.0
	Severe	0.0	0.3
Sore or Swollen Joints	Any	4.0	4.5
	Severe	0.0	0.0
Diarrhea	Any	14.4	9.7
	Severe	0.7	0.7
Lymph Node Swelling	Any	5.4	8.3
	Severe	0.0	0.0
Fever	≥38.0°C	8.7	16.9
	≥39.5°C	1.7	1.4
Vomiting	Any	8.1	10.0
	Severe	1.3	0.0
Rash	Any	8.4	14.1
Anorexia	Any	21.5	22.1

Solicited Reactions	Severity	ADACEL® (N = 298)	QUADRACEL® (N = 290)
	Severe	0.7	2.1

* All injection site reaction rates following ADACEL® were non-inferior to rates following QUADRACEL® (upper limited of the 95% CI for the difference in rates of ADACE ® minus QUADRACEL® <10%).

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

Td515: Comparison of ADACEL® with Tetanus and Diphtheria Toxoids Adsorbed for Adult Use

Study Td515 was conducted in order to evaluate the safety and immunogenicity of ADACEL® in adults ≥65 years of age. This comparative, multi-center, randomized, double-blind controlled trial enrolled 1,563 participants, including 519 aged ≥75. Enrollment was stratified by age to ensure adequate representation across the entire age range. Participants in study Td515 had not received a tetanus or diphtheria toxoid containing vaccine within the previous 5 years and were considered not to have received any previous pertussis vaccination. Participants in study Td515 had no documented history of previous tetanus, diphtheria or pertussis diseases. After enrollment participants were randomized to receive one dose of either ADACEL® or Td vaccine. The per-protocol immunogenicity subset included 1,094 ADACEL® recipients and 371 Td vaccine recipients. Sera were obtained before and approximately 35 days after vaccination. Demographic characteristics were similar between the vaccine groups.

Immunogenicity

As in adolescents and younger adults, anti-tetanus and anti-diphtheria seroprotection rates (≥0.1 IU/mL) and booster response rates in adults ≥65 years of age were at least as high in ADACEL® recipients as in Td vaccine recipients. (See Table 19). When compared to pertussis antibody levels observed in infants after a 3- or 4-dose primary vaccination series with TRIPACEL®, older adults ≥65 years of age vaccinated with a single dose of ADACEL® achieved lower GMCs for some of the pertussis antigens. Nevertheless, the serum level of all four pertussis antibodies increased by at least 4.4-fold compared to the pre-immunization levels, suggesting an improved degree of protection against pertussis. (See Table 20). ADACEL® elicited booster responses in acceptable proportions (criterion: ≥60%) of participants for all pertussis antigens (70.0 to 76.7%), with the exception of PT, for which 52.9% of participants achieved a booster response.

Table 19: Tetanus and Diphtheria Seroprotection Rates Observed in Adults ≥65 Years of Age Following a Single Dose of ADACEL® or Td Vaccine in Study Td515

Antitoxin	Vaccine	Pre-Vaccination			Post-Vaccination	
		N	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)
Tetanus	ADACEL®	1,075 - 1,089	79.9	47.4	98.4	93.8
	Td	368	78.8	43.2	98.1	91.8
Diphtheria	ADACEL®	1,092 - 1,093	38.7	10.6	77.4	52.7

Antitoxin	Vaccine	Pre-Vaccination			Post-Vaccination	
		N	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)	% ≥0.10 (IU/mL)	% ≥1.0 (IU/mL)
	Td	370 - 371	41.4	12.2	79.2	47.4

Table 20: Geometric Mean Fold Rise (GMFR) for Pertussis Antigens Observed in Adults ≥65 Years of Age Following a Single Dose of ADACEL® in Study Td515

Antigen (EU/mL)	Pre-Vaccination			Post-Vaccination			
	N	GMC*	95% CI	GMC*	95% CI	GMFR†	95% CI
PT	957	11.7	(10.8; 12.6)	59.8	(55.4; 64.5)	4.4	(4.1; 4.7)
FHA	1,091	25.5	(23.9; 27.1)	195.9	(184.7; 207.7)	7.6	(7.1; 8.1)
PRN	1,090	4.6	(4.3; 4.9)	69.5	(61.8; 78.1)	10.4	(9.3; 11.5)
FIM	1,021	8.7	(7.8; 9.6)	182.0	(162.3; 204.1)	15.1	(13.5; 16.8)

* For GMCs, values below LLOQ were imputed to be 0.5 x LLOQ, where LLOQ is 3 EU/mL for FHA and 4 EU/mL for PT, PRN and FIM.

† For fold-rises, a pre-vaccination value below LLOQ was imputed to be LLOQ and a post-vaccination value below LLOQ was imputed to be 0.5 x LLOQ.

Safety

Solicited injection site and systemic reactions were monitored for 14 days post-vaccination using a diary card. Participants were monitored for 6 months for unsolicited adverse events, for visits to an emergency room, unexpected visits to an office physician, hospitalization and serious adverse events.

The observed rates for both the injection site reactions and the systemic reactions were comparable between ADACEL® and Td vaccines. (See Table 21).

Table 21: Frequency (%) of Solicited Reactions Reported in Adults ≥65 Years of Age From Day 0 to 14 After a Single Dose with ADACEL® or Td Vaccine in Study Td515

Solicited Reactions	Severity	ADACEL® (N = 1,153)	Td (N = 387)
Injection Site*			
Pain	Any	43.0	42.1
	Severe†	0.5	0.3
Erythema	Any	24.3	22.2
	≥35 mm	4.5	4.9
Swelling	Any	18.1	15.2
	≥35 mm	3.5	4.4
Systemic			
Myalgia	Any	28.4	27.9
	Severe	1.5	1.6
Headache	Any	18.2	19.6
	Severe	0.6	1.0
Malaise	Any	17.2	16.3
	Severe	1.1	1.6
Fever	Any	0.5	0.5
	Severe	<0.1	0.0

* All injection site reaction rates following ADACEL® were non-inferior to rates following Td (upper limit of the 95% CI for the difference in rates of ADACEL® minus Td <10%).

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

TD9805: Concomitant Hepatitis B Vaccine

In Clinical Trial TD9805, 269 adolescents 11 to 12 years of age were randomized to two treatment groups. A total of 269 participants were vaccinated as follows: 135 received a single 0.5 mL dose of ADACEL® given alone (followed by the first dose of hepatitis B [Recombivax HB®, manufactured by Merck and Co., Inc.] one month later); 134 were given a single 0.5 mL dose of ADACEL® concurrently with the first dose of a 3-dose primary series (0, 1 and 6 months) with hepatitis B vaccine.

Immunogenicity

Seroprotection rates for Tetanus or Diphtheria serum antitoxin at 1 month post-vaccination were 100% in the 2 vaccine groups. (See Table 22).

Table 22: Tetanus and Diphtheria Seroprotection Rates Observed in Adolescents 1 Month Following A Single Dose with ADACEL® alone or Concomitantly with Hepatitis B Vaccine in Study TD9805

Vaccine	Tetanus Antitoxin		Diphtheria Antitoxin	
	N*	% ≥0.10 (EU/mL)	N*	% ≥0.10 (IU/mL)
ADACEL®	118	100.0	118	100.0
ADACEL® + Hep B	129	100.0	129	100.0

* Per-Protocol population

At 1 month post-vaccination antibody responses to pertussis antigen were comparable between the 2 groups and the GMCs were several fold higher than those observed in the Sweden I Efficacy Trial. (See Table 23).

Table 23: Pertussis Antibody GMCs Observed in Adolescents with ADACEL® Alone or Concomitantly with Hepatitis B Vaccine in Study TD9805

	Vaccine	Pre-Vaccination		Post-Vaccination	
		N	GMCs (EU/mL)	N	GMCs (EU/mL)
Anti-PT	**ADACEL®**	118	12.1	118	169
	ADACEL® + Hep B	129	10.4	129	144
Anti-FHA	**ADACEL®**	118	32.7	118	445
	ADACEL® + Hep B	129	33.8	129	375
Anti-PRN	**ADACEL®**	118	9.5	118	280
	ADACEL® + Hep B	129	7.9	129	303
Anti-FIM	**ADACEL®**	118	45.0	118	1,033
	ADACEL® + Hep B	129	44.6	129	1,130

Virtually all participants (100% in the sequential versus 99.2% in the concomitant vaccine group) achieved seroprotective levels (≥10 mIU/mL) for hepatitis B antibody. Concurrent administration with ADACEL® therefore did not appear to interfere with the immunogenicity of hepatitis B vaccine.

Antibody Persistence

In Study TD9805, 267 adolescents aged 11 - 14 years at the beginning of the study provided serum samples at 1 (N = 154), 3 (N = 165), 5 (N = 165), and 10 years (N=150) after vaccination with ADACEL®, for assessment of antibody persistence. Table 24 summarizes the findings for diphtheria and tetanus, and Table 25 , the findings for pertussis. The long-term antibody profile suggested that seroprotection against diphtheria and tetanus is maintained for at least 5 years following a booster with ADACEL® administered either alone or concurrently with Hepatitis B Vaccine in adolescents. The pertussis response to ADACEL® was robust and antibodies persisted at levels 2 to 5-fold higher than pre-vaccination. At 10 years post-vaccination, GMCs further declined, in particular for PT and FHA antigens for which antibody levels almost decreased to pre-vaccination levels.

Table 24: Diphtheria and Tetanus - Persistence of Seroprotection Rates at Levels ≥0.01 IU/mL and ≥0.10 IU/mL, in Study TD9805

Antigen	Visit	≥0.01 (IU/mL)*		% ≥0.10 (IU/mL)*	
		N†	%	N†	%
Diphtheria	Pre-	267	100.0	267	82.8
	1 Month Post	267	100.0	267	100.0
	1 Year Post	154	100.0	154	98.7
	3 Years Post	165	100.0	165	98.8
	5 Years Post	163	100.0	163	75.5
	10 Years Post	149	99.3	149	66.4
Tetanus	Pre-	267	99.3	267	98.9
	1 Month Post	267	100.0	267	100.0
	1 Year Post	154	100.0	154	100.0
	3 Years Post	164	100.0	164	100.0
	5 Years Post	161	100.0	161	100.0
	10 years Post	148	100.0	148	99.3

* IU/mL for diphtheria; EU/mL for tetanus

† Per-Protocol population – pooled groups

Table 25: Pertussis Antigens - Geometric Mean Concentrations (GMCs) Persistence in ADACEL® Recipients in Study TD9805

Antigen	Visit	N*	GMC
PT (EU/mL)	**Pre-**	267	11.13
	1 Month Post	267	153.32
	1 Year Post	154	51.70
	3 Years Post	165	36.40
	5 Years Post	165	28.24
	10 Years Post	139	12.38
FHA (EU/mL)	**Pre-**	267	33.02
	1 Month Post	267	396.74
	1 Year Post	154	106.71
	3 Years Post	165	80.84
	5 Years Post	165	64.74
	10 Years Post	150	40.39
PRN (EU/mL)	**Pre-**	267	8.36
	1 Month Post	267	285.40
	1 Year Post	154	75.95
	3 Years Post	165	54.36
	5 Years Post	165	45.74
	10 Years Post	150	26.44
FIM (EU/mL)	**Pre-**	267	45.48
	1 Month Post	267	1,058.62
	1 Year Post	154	324.84
	3 Years Post	165	181.93
	5 Years Post	165	157.79
	10 Years Post	150	116.41

* Per-Protocol population – pooled groups

Safety

There were no clinically important differences in the rates of injection site or systemic reactions at 0 to 24 hr, 24 to 72 hr and 3 to 14 days after immunization with ADACEL® alone or ADACEL® given concurrently with hepatitis B vaccine. There was a trend for slightly increased injection site reaction rates when ADACEL® was administered concurrently with Hepatitis B vaccine. (See Table 26).

Table 26: Frequency (%) of Solicited Reactions of Any Severity Reported in Adolescents in Study TD9805 Day 0 to 14 After ADACEL® Given Alone or Concomitantly with Hepatitis B Vaccine (Hep B)

Solicited Reactions	0 - 24 hours		24 - 72 hours		3 - 14 days	
	ADACEL® (N = 135)	ADACEL® + Hep B (N = 134)	ADACEL® (N = 135)	ADACEL® + Hep B (N = 134)	ADACEL® (N = 135)	ADACEL® + Hep B (N = 134)
Injection Site						
Pain	69.6	75.4	44.0	52.2	8.2	15.7
Swelling	15.6	20.1	11.9	18.8	5.2	9.7
Redness	9.6	12.7	7.5	14.2	2.2	0.7
Systemic						
Tiredness	37.0	31.3	16.3	15.7	13.3	12.7
Headache	28.1	23.9	17.0	17.9	22.2	17.2
Sore or Swollen Joints	19.3	12.7	9.6	7.5	4.4	5.2
Body Ache or Muscle Weakness	18.5	19.4	9.6	10.4	9.6	8.2
Chills	12.6	13.4	3.0	5.2	5.2	4.5
Nausea	12.6	12.7	5.2	2.2	8.9	8.2
Diarrhea	4.4	3.0	4.4	3.7	6.7	9.7
Axillary Lymph Node Swelling	2.2	0.0	2.2	3.7	0.7	1.5
Fever	0.7	1.5	0.7	1.5	4.4	1.5
Vomiting	0.0	1.5	0.0	0.0	4.4	5.2

Td502: Concomitant Inactivated Influenza Vaccine

In Td502, the concomitant use of ADACEL® and trivalent inactivated influenza vaccine (FLUZONE®, Influenza Virus Vaccine Trivalent Types A and B, Zonal Purified, Subvirion, manufactured by Sanofi Pasteur Inc., Swiftwater, PA) was evaluated in a multi-centre, open-labeled, randomized, controlled study involving 696 adult vaccinees, 19 to 64 years of age inclusive. In one group, participants received ADACEL® and influenza vaccines concurrently (N = 356). The other group received influenza vaccine at the first visit, followed by ADACEL® (N = 340) at the second visit, 4 to 6 weeks later.

Immunogenicity

The concomitant vaccine administration diphtheria and tetanus seroprotection rates (% serum antitoxin ≥0.1 IU/mL) were shown to be non-inferior to ADACEL® administration alone in adults 19 to 64 years. The post-vaccination rates demonstrated a substantial rise over the pre-vaccination levels. (See Table 27). Booster response rates for diphtheria were non-inferior when ADACEL® was administered concurrently with influenza vaccine compared to separate administration. Although tetanus booster response rates did not meet the non-inferiority criterion, greater than 98% of participants in both groups achieved seroprotective levels of ≥0.1 IU/mL.

Table 27: Tetanus and Diphtheria Seroprotection Rates in Adults with ADACEL® Alone or Concomitantly with Trivalent Inactivated Influenza Vaccine in Study Td502

Antitoxin	Vaccine	Pre-Vaccination		Post-Vaccination	
		N	% ≥0.10 (IU/mL)	N	% ≥0.10 (IU/mL)
Tetanus	**ADACEL®**	323	86.1	324	98.1
	ADACEL® + Flu	353	89.5	354	99.7
Diphtheria	**ADACEL®**	323	32.5	324	87.0
	ADACEL® + Flu	354	36.4	354	86.2

Post-vaccination pertussis antibody GMCs for both vaccine groups were robust, and non-inferiority was achieved for PT, FHA and FIM. For PRN, the lower limit of the 90% CI of the GMC ratio was slightly lower (0.61) as compared to the non-inferiority criterion of >0.67. The GMC values for all pertussis antigens (Table 28), including PRN, exceeded those achieved after 3 doses of TRIPACEL® in the Sweden I Efficacy Trial.

Table 28: Pertussis Antibody GMCs in Adults with ADACEL® Alone or Concomitantly with Trivalent Inactivated Influenza Vaccine in Study Td502

	Vaccine	Pre-Vaccination		Post-Vaccination	
		N	GMCs (EU/mL)	N	GMCs (EU/mL)
Anti-PT	**ADACEL®**	321	12.6	322	235
	ADACEL® + Flu	354	12.8	352	186
Anti-FHA	**ADACEL®**	322	15.7	323	242
	ADACEL® + Flu	354	16.7	354	201
Anti-PRN	**ADACEL®**	322	6.7	323	260
	ADACEL® + Flu	354	6.9	354	192
Anti-FIM	**ADACEL®**	322	29.6	323	1,136
	ADACEL® + Flu	354	30.9	354	926

Administration of ADACEL® concomitantly with trivalent inactivated influenza vaccine did not interfere with the influenza antibody responses.

Safety

The rates of fever and injection site redness and swelling were similar for recipients of concurrent and separate administration. However, pain at the ADACEL® injection site occurred at a statistically higher rate during the 0 to 14 days following concurrent administration (66.6%) versus separate administration (60.8%). The incidence of other solicited adverse events were similar between the 2 study groups. (See Table 29).

Table 29: Frequency (%) of Solicited Reactions of 'Any' Severity Reported in Adults Day 0 to 14 After ADACEL® Given Alone or Concomitantly with Trivalent Inactivated Influenza Vaccine in Study Td502

Solicited Reactions	ADACEL® (N = 340)	ADACEL® + Flu (N = 356)
Injection Site		
Pain	60.8	66.6
Erythema	12.4	10.8
Swelling	10.3	15.3
Solicited Reactions	**ADACEL® (N = 340)**	**ADACEL® + Flu (N = 356)**
Systemic		
Headache	37.8	39.8
Tiredness	31.6	32.7
Body Ache or Muscle Weakness	21.8	29.3
Nausea	13.9	13.4
Chills	13.6	14.5
Diarrhea	11.5	15.1
Sore or Swollen Joints	9.4	12.5
Axillary Lymph Node Swelling	3.8	5.7
Vomiting	3.8	3.4
Fever	2.4	4.3

Td526: Re-dosing with ADACEL® 10 years after a previous dose of a ADACEL® or ADACEL®-POLIO (Tdap-IPV) vaccine

In an open-label, non-randomized clinical trial (Td526), 743 adults 20 to over 50 years of age were recruited and divided in two treatment groups for the evaluation of immunogenicity and safety following re-dosing with ADACEL®. Group1 comprised 324 persons who previously received ADACEL® or ADACEL®-POLIO vaccines as part of study TD9707 and TD9805. Group 2 consisted of age-balanced Tdap vaccine naïve subjects who had not received any tetanus, diphtheria or pertussis-containing vaccine in the past 10 years.

Immunogenicity

Seroprotective tetanus antitoxin levels ≥ 0.10 IU/mL were achieved by 100% and 99.7% of ADACEL® vaccinees in Groups 1 and 2, respectively. Seroprotective diphtheria antitoxin levels ≥0.10 IU/mL were attained by 98.5% and 96.1% in Groups 1 and 2, respectively. (See Table 30) .

Table 30: Tetanus and Diphtheria Antitoxin Seroprotection Rates in Adults in Study Td526

IU/mL			Group 1 (N=324)		Group 2 (N=381)	
			N*	% 95%CI	N*	% 95%CI
Anti-Tetanus	Pre-vaccination	≥0.10	324	97.5 (95.2; 98.9)	379	93.1 (90.1, 95.5)
		≥1.0	324	44.8 (39.3, 50.3)	379	49.1 (43.9, 54.2)
	Post-vaccination	≥0.10	324	100.0† (98.9, 100.0)	381	99.7 (98.5, 100.0)
		≥1.0	324	100.0 (98.9, 100.0)	381	97.6 (95.6, 98.9)
Anti-Diphtheria	Pre-vaccination	≥0.10	324	73.5 (68.3, 78.2)	381	65.9 (60.9, 70.6)
		≥1.0	324	24.7 (20.1, 29.8)	381	21.8 (17.7, 26.3)
	Post-vaccination	≥0.10	324	98.5 (96.4, 99.5)	381	96.1 (93.6, 97.8)
		≥1.0	324	87.3 (83.2, 90.8)	381	83.5 (79.3, 87.1)

* N: Number of subjects in the Per-Protocol Analysis Set

† Non inferiority for seroprotection rates at ≥0.10 IU/mL was achieved (the lower bound of the two sided 95% CI is greater than -10% (-5% if P_{Group2} > 95%))

GMCs and booster response rates for the pertussis antigens PT, FHA, PRN and FIM pre and post re-dosing with ADACEL® in adults are presented in Table 31 . Non inferiority for Group 1 (Tdap redose) compared to Group 2 (Tdap standard of care) was achieved for PT, FHA and PRN. Although non-inferiority was not achieved for FIM, the lower limit of the confidence interval was marginally inferior (0.66) to non-inferiority criterion.

Table 31: Anti-pertussis GMCs and Booster Response Rates in Adults in Study Td526

Group		Pre-Vaccination		Post-Vaccination		Booster response rates*	
		N†	GMCs (95% CI)	N†	GMCs (95% CI)	N†	(%)
Anti-PT (EU/mL)	Group 1	291	15.1 (12.9; 17.6)	318	116‡ (105; 129)	285	87.7 (83.3; 91.3)
	Group 2	353	9.42 (8.20; 10.8)	357	89.2 (80.2; 99.3)	330	84.2 (79.9; 88.0)
Anti-FHA (EU/mL)	Group 1	324	34.8 (31.2; 38.7)	324	214‡ (199; 231)	324	88.0 (83.9; 91.3)
	Group 2	380	20.0 (17.7; 22.5)	380	249 (229; 272)	379	93.9 (91.0; 96.1)
Anti-PRN (EU/mL)	Group 1	324	28.2 (24.4; 32.7)	324	266‡ (243; 292)	324	90.4 (86.7; 93.4)
	Group 2	381	8.54 (7.41; 9.85)	381	216 (188; 247)	381	92.7 (89.6; 95.1)
Anti-FIM (EU/mL)	Group 1	324	124 (111; 139)	324	779 (720; 843)	324	84.3 (79.8; 88.0)
	Group 2	374	37.8 (32.7; 43.7)	378	1015 (894; 1154)	371	93.0 (89.9; 95.4)

* Booster response is defined as subjects whose post-vaccination antibody concentrations are ≥ 4 xLLOQ, if the pre-vaccination concentration was < LLOQ; ≥ 4 x the pre-vaccination antibody concentration, if the pre-vaccination concentration was ≥ LLOQ but < 4 x LLOQ; ≥ 2 x the pre-vaccination antibody concentration, if the pre-vaccination concentration was ≥ 4 x LLOQ.

LLOQ: PT=4 EU/mL; FHA=3 EU/mL; PRN=4 EU/mL; FIM=4 EU/mL.

† N: Number of subjects with available data

‡ Non inferiority for GMCs was achieved (the lower bound of the two sided 95% CI is greater than 0.67

Safety

Solicited injection site reactions and systemic reactions were monitored within 7 days post vaccination. Unsolicited adverse events were reported up to 30 days post vaccination. The most frequently reported injection-site reaction was pain 87.8% in Group 1 and 84.4% in Group 2. The most frequently reported systemic reaction was myalgia, 60.1% in Group 1 and 53.5% in Group 2. The majority of the injection-site reactions and systemic reactions were mild in intensity (Grade 1) and resolved within 3 days of vaccination. The frequency and intensity of the solicited injection-site and systemic reactions reported are presented in Table 32 .

Table 32: Frequency (%) of Solicited Injection Site and Systemic Reactions reported in Adults in study Td526 within 7 days after re-dosing with ADACEL®

Injection site reactions	Severity	Group 1 N*=361		Group 2 N*=407	
		%	95%CI	%	95%CI
Pain	Any	87.8	(83.9; 91.0)	84.4	(80.5; 87.8)
	Grade 3†	2.6	(1.2; 4.8)	1.7	(0.7; 3.5)
Erythema	Any	23.1	(18.8; 27.8)	29.7	(25.3; 34.4)
	Grade 3†	2.0	(0.8; 4.1)	1.7	(0.7; 3.5)
Swelling	Any	20.5	(16.4; 25.1)	23.3	(19.3; 27.8)
	Grade 3†	2.6	(1.2; 4.8)	1.7	(0.7; 3.5)
Systemic reactions					
Fever	Any	4.2	(2.4; 6.9)	4.9	(3.0; 7.5)
	Grade 3†	0.0	(0.0; 1.0)	0.0	(0.0; 0.9)
Headache	Any	40.6	(35.4; 45.9)	37.6	(32.9; 42.5)
	Grade 3†	1.7	(0.6; 3.7)	2.0	(0.9; 3.9)
Malaise	Any	29.4	(24.7; 34.5)	29.0	(24.6; 33.7)
	Grade 3†	2.0	(0.8; 4.1)	2.0	(0.9; 3.9)
Myalgia	Any	60.1	(54.8; 65.3)	53.5	(48.5; 58.4)
	Grade 3†	2.3	(1.0; 4.4)	1.5	(0.5; 3.2)

* Total number of subjects who received the study vaccine (Full Analysis Set)

† Grade 3 definitions: Pain= Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism; Erythema = ≥ 5cm; Swelling = ≥ 5cm; Fever = > 39.0°C; Headache = Prevents daily activities; Malaise= Prevents daily activities; Myalgia= Prevents daily activities.

Additional Relevant Information

Tetanus and Diphtheria

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C. tetani*. The organism is ubiquitous and its occurrence in nature cannot be controlled. Immunization is highly effective, provides long-lasting protection and is recommended for the whole population. Between 1980 and 2004, the number of cases reported annually in Canada ranged from 1 to 10, with an average of 4 per year.

Diphtheria is a serious communicable disease caused by toxigenic strains of *C. diphtheriae*. The organism may be harboured in the nasopharynx, skin or other sites of asymptomatic carriers, making eradication of the disease difficult. Routine immunization against diphtheria in infancy and childhood

has been widely practiced in Canada since 1930. In Canada, there are 0 to 5 cases reported each year. The case-fatality rate remains at 5 to 10%, with the highest death rates in the very young and elderly. The disease occurs most frequently in unimmunized or partially immunized persons.

Pertussis

Pertussis (whooping cough) results from an acute infection of the respiratory tract by *B. pertussis*. The most serious complications and deaths occur in young infants, particularly those who have not yet had the opportunity to be immunized or are not yet fully immunized (e.g., 1 or 2 doses).
Despite widespread use in Canada of pertussis vaccines in childhood, there was a resurgence in the incidence of pertussis disease in the 1990s. This resurgence was likely due to a combination of factors, including the low efficacy of the combined adsorbed diphtheria-tetanus-whole-cell pertussis whole-cell vaccine used in children in Canada between 1980 and 1997, waning immunity among adolescents and adults, as well as increased physician awareness and improved diagnosis and reporting of pertussis disease. A pattern of steadily increasing age of cases and higher incidence among adolescents and adults has been observed. Pertussis is a frequent cause of cough illness with significant morbidity in adolescents and adults who are a source of transmission to infants. In one study, household members were responsible for 76 – 83% of transmission of pertussis to infants; parents account for 55% of source cases. Sources of infection for adult cases of pertussis include work colleagues (32%), relatives (14%) and friends (6%). Therefore, adolescent and adult vaccination against pertussis may contribute to substantially reduce the burden of infant pertussis, if high average rates among those in contact with young infants can be achieved. According to NACI, pertussis vaccination of adolescents and adults will not only help to prevent the disease in these vaccinees, but may also provide indirect benefits for susceptible infants by reducing their potential exposure to infected adolescents or adults.

Immunogenicity in pregnancy

The assessment of pertussis antibody responses in pregnant women and newborn infants is based on 4 published randomized controlled studies

Maternal antibody directed against pertussis antigens persists for at least 2 months after birth and may be associated with blunting of the infant immune response to active immunization against pertussis. The clinical relevance of the blunting of the immune response is unknown.

The effectiveness of vaccine in infants whose mothers were vaccinated with ADACEL® or ADACEL®-POLIO during pregnancy was evaluated in three published observational studies in UK and US. The vaccine was administered during the third trimester of pregnancy for passive protection against pertussis in infants below 3 months of age.

14.4. Immunogenicity

For information on Immunogenicity, refer to 14 Clinical Trials , 14.2 Study Results of each clinical trial.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

Available data in animals revealed no unexpected findings and no target organ toxicity.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ADACEL®

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Read this carefully before you receive **ADACEL®**. This leaflet is a summary and will not tell you everything about **ADACEL®**. Talk to your doctor or pharmacist if you have any questions about this vaccine.

What is ADACEL® used for?

ADACEL® is a vaccine that is used to boost the body's protection against Tetanus, Diphtheria, and Pertussis (whooping cough). This vaccine may be given to children, adolescents and adults 4 years of age and older. ADACEL® may be used as an alternative to the usual paediatric vaccine in children 4 to 6 years of age who are due for their pre-school booster against diphtheria, tetanus and pertussis. These children should also receive a separate booster with inactivated polio vaccine, when a polio booster is routinely recommended for this age group.

The majority of persons who are vaccinated with ADACEL® will produce enough antibodies to protect them against these 3 diseases. However, as with all vaccines, 100% protection cannot be guaranteed.

ADACEL® may be given to a pregnant woman to help protect her baby against whooping cough.

How does ADACEL® work?

ADACEL® causes your body to produce its own natural protection against tetanus, diphtheria and pertussis (whooping cough). After you receive the vaccine, your body begins to make substances called antibodies. Antibodies help your body to fight disease. If a vaccinated person comes into contact with one of the germs that cause these diseases, the body is usually ready to destroy it.

What are the ingredients in ADACEL®?

Medicinal ingredients: tetanus toxoid, diphtheria toxoid, pertussis toxoid, filamentous haemagglutinin, pertactin and fimbriae types 2 and 3.

Non-medicinal ingredients: Aluminum phosphate, 2-phenoxyethanol. Residual formaldehyde and glutaraldehyde are present in trace amounts.

ADACEL® comes in the following dosage forms:

ADACEL® is a liquid vaccine that is injected into a muscle. A single dose is 0.5 mL.

Do not use ADACEL® if:

- You are known to have a severe allergy to any ingredient in the vaccine or its container, or have had a severe allergic reaction after receiving a vaccine that contained similar ingredients.
- You have had a serious nervous system disorder within 7 days after a previous pertussis vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADACEL®. Talk about any health conditions or problems you may have, including:

- **A high fever or serious illness.** Delay the vaccination until the person is better.
- **An allergy to any component of the vaccine or the container.**
- **A serious nervous system adverse event following a previous tetanus vaccination.**
- **A progressive nervous system disorder or uncontrolled epilepsy.** Vaccination may be considered only after a treatment has been established and the condition is stabilized.
- **Pregnant or nursing mothers.** It is important that you understand the risks and benefits of vaccination. Tell the person giving you the injection if you are pregnant or breast-feeding. The health care professional will recommend whether you should receive ADACEL®.
- **A weakened immune system**. The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems. If possible, try to postpone the vaccination until after you have completed the treatment that affects your immune system.
- **A bleeding disorder or taking blood-thinning medications.** Tell the person giving you the injection about your condition. The injection must be done carefully to prevent excessive bleeding.
- **Have fainted with a previous injection.** Fainting can occur following vaccination. Appropriate measures should be taken to prevent falling injury.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ADACEL®:

DO NOT mix ADACEL® with other vaccines or medicinal products in the same syringe.

ADACEL® may be given at the same time but at separate sites with:

- inactivated influenza vaccine
- hepatitis B vaccine

How to take ADACEL®:

Usual dose:

For persons aged 4 years of age and older – recommended dose is 0.5 mL.

The vaccination should be given in the muscle, preferably in the deltoid (shoulder) region.

Overdose:

If you think you, or a person you are caring for, have taken too much ADACEL®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable to this vaccine.

What are possible side effects from using ADACEL®?

These are not all the possible side effects you may have when taking ADACEL®. If you experience any side effects not listed here, tell your healthcare professional.

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of ADACEL® causing serious harm is extremely small. The small risks associated with ADACEL® are much less than the risks associated with getting the diseases.

Serious side effects are extremely rare.

Some people who receive ADACEL® may have mild side effects such as redness, swelling or pain at the site of the injection. They may also feel tired, or have a headache, generalized body ache and sore or swollen joints. These side effects usually go away within a few days.

Uncommonly, a small lump in the area where the vaccine was injected may develop.

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
Anaphylaxis and Hypersensitivity: severe allergic reaction with symptoms that can include: angioedema, edema, rash, hypotension		✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi Pasteur cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze**. Throw the product away if it has been exposed to freezing.

Do not use after the expiration date.

Keep out of reach and sight of children.

If you want more information about ADACEL®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the Sanofi Canada website (www.sanofi.ca) or by contacting the vaccine producer, Sanofi Pasteur Limited, at 1-888-621-1146 (no charge).

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