PRODUCT MONOGRAPH

TRIPACEL®

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

Suspension for injection

(For active immunization against Diphtheria, Tetanus and Pertussis)

ATC Code: J07AJ52

Sanofi Pasteur Limited
Toronto, Ontario, Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intramuscular injection.

Dosage Form/Strength

Suspension for injection.

Each 0.5 mL is formulated to contain:

Active Ingredients

Diphtheria toxoid, tetanus toxoid and acellular pertussis [pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)]

Clinically Relevant Non-medicinal Ingredients

Excipients: aluminum phosphate (adjuvant), 2-phenoxyethanol

Manufacturing process residuals: formaldehyde and glutaraldehyde are present in trace amounts.

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed] is a sterile, uniform, cloudy, white to off-white suspension of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed separately on aluminum phosphate and suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified pertussis antigens (PT, FHA, PRN and FIM).

INDICATIONS AND CLINICAL USE

TRIPACEL® is indicated for the primary immunization of infants from the age of 2 months and in children up to 6 years of age (prior to their 7th birthday) against diphtheria, tetanus and pertussis (whooping cough). (See DOSAGE AND ADMINISTRATION.)

According to the National Advisory Committee on Immunization (NACI), children who have had diphtheria, tetanus or pertussis should still be immunized since these clinical infections do not always confer immunity. (1)

NACI recommends that Human Immunodeficiency Virus (HIV)-infected persons, both asymptomatic and symptomatic, should be immunized against diphtheria, tetanus and pertussis according to standard schedules. (1)

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

Pediatrics

TRIPACEL® is not indicated for persons less than 2 months of age or persons 7 years of age or older.

Geriatrics

TRIPACEL® is not indicated for use in adult and elderly populations.

CONTRAINDICATIONS

Hypersensitivity

NACI recommends that known systemic hypersensitivity reaction or a life threatening reaction to any component of TRIPACEL® after previous administration of the vaccine or a vaccine containing one or more of the same components are contraindications to vaccination. (1) (2) (3) (See SUMMARY PRODUCT INFORMATION.) Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such persons may be referred to an allergist for evaluation if further immunizations are considered.

Neurological Disorders

According to the US Advisory Committee on Immunization Practices (ACIP), the following events are contraindications to administration of any pertussis-containing vaccine, (2) including TRIPACEL®:

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause.

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to persons with such conditions until a treatment regimen has been established and the condition has stabilized.

WARNINGS AND PRECAUTIONS

General

Before administration of TRIPACEL® health-care providers should inform the parent or guardian of the recipient to be immunized 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 contraindication to immunization and comply with any local requirements with respect to information to be provided to the parent or guardian before immunization and the importance of completing the immunization series.

It is extremely important that the parent or guardian be questioned concerning any symptoms and/or signs of an adverse reaction after a previous dose of vaccine. (See CONTRAINDICATIONS and 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. (3)

Syncope (fainting) has been reported following vaccination with TRIPACEL®. Procedures should be in place to prevent falling injury and manage syncopal reactions.

As with any vaccine, TRIPACEL® may not protect 100% of vaccinated individuals.

Administration Route Related Precautions: Do not administer TRIPACEL® by intravascular injection: ensure that the needle does not penetrate a blood vessel.

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

TRIPACEL® should not be administered into the buttocks.

Febrile and Acute Disease: ACIP recommends that vaccination should be postponed in cases of an acute or febrile disease. (2) (3) However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

If any of the following events occur within the specified period after administration of a whole-cell pertussis vaccine or a vaccine containing an acellular pertussis component, the decision to administer TRIPACEL® should be based on careful consideration of potential benefits and possible risks. (2)

- Temperature of ≥40.5°C (105°F) within 48 hours, not attributable to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode - HHE) within 48 hours;
- Persistent crying lasting ≥3 hours within 48 hours;
- Convulsions with or without fever within 3 days.

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 TRIPACEL® 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 TRIPACEL® even in persons with no prior history of hypersensitivity to the product components. Cases of allergic or anaphylactic reactions have been reported after receiving some preparations containing diphtheria and tetanus toxoids and/or pertussis antigens. (4)

As recommended by NACI, 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. (1) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. (1) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

According to NACI, immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. (1) Nevertheless, vaccination of persons with chronic immunodeficiency such as HIV infection is recommended even if the immune response might be limited. (1) (2)

Neurologic

A review by the US Institute of Medicine (IOM) found evidence for a causal relationship between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). (5) ACIP recommends that if GBS occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give TRIPACEL® or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (2)

ACIP recommends that for infants or children at higher risk for seizures than the general population that an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including TRIPACEL®) and for the following 24 hours, to reduce the possibility of post-vaccination fever. (2)

Hypotonic-hyporesponsive episodes (HHEs) rarely follow vaccination with whole-cell pertussis-containing DTP vaccines and occur even less commonly after acellular pertussis-containing DTP and DT vaccines. NACI states that a history of HHE is not a contraindication to the use of acellular pertussis vaccines, but recommends precaution in these cases. (1)

Pregnant Women

The vaccine should not be administered to pregnant women.

Nursing Women

The vaccine should not be administered to nursing women.

Pediatrics

The potential risk of apnea and the need for respiratory monitoring for 48 – 72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

ADVERSE REACTIONS

Clinical Trial Adverse Reactions

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 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.

TRIPACEL® has been safely administered to over 4,000 children in clinical trials. (6) (7) (8) (9) (10) (11) (12) In these trials, recipients of TRIPACEL® consistently experienced lower rates of injection site and systemic solicited reactions than those receiving whole-cell pertussis vaccines. The size and frequency of injection site reactions increase with the number of doses administered. Although these injection site reactions may produce large injection site swelling, pain is generally limited. (1)

In a clinical study conducted in Canada, 324 children received TRIPACEL® at 2, 4, 6 and 18 months of age. (9) (10) In another Canadian study, 21 children received TRIPACEL® at 4-6 years of age. (13) (14) The following rates of reactions were observed:

Table 1: Frequency (%) of Selected Solicited Reactions Observed in Children After Vaccination with TRIPACEL® Within 48 Hours at 2, 4, 6 and 18 Months of Age and Within 28 Days at 4-6 Years of Age (9) (10) (13) (14)

Solicited Reactions	2 Months N = 324	4 Months N = 322	6 Months N = 319	18 Months N = 301	4-6 Years N = 21
Injection Site Reactions					
Redness	13.0	20.0	22.0	35.9	9.5
Swelling	4.3	4.1	4.7	18.3	4.8
Tenderness	9.8	7.1	8.6	23.3	71.4
Systemic Reactions					
Fever ≥38°C	6.5	4.7	8.1	10.0	9.5
Irritability	37.0	39.0	36.0	34.6	19.0
Crying	2.2	3.1	1.2	0.7	NS*
Drowsiness	42.0	21.0	14.0	12.6	23.8
Decreased Feeding	15.0	8.1	9.7	15..6	14.3

* Not solicited.

In the 2-18 month study, there was a trend towards increased rates of redness, swelling and mild tenderness after administration of the 4th dose, but no increase in severe tenderness or limitation of movement was observed. (9) (10) Other less frequent solicited reactions noted included vomiting, listlessness and pallor. Most reactions were described as mild and resolved spontaneously within 24 - 72 hours. Seizures or HHE were not observed in either study.

In a clinical trial in Sweden comparing 2 acellular pertussis vaccines, DT and a whole-cell DTP vaccine, 2,587 infants received TRIPACEL® at 2, 4 and 6 months of age. Rates of adverse events following TRIPACEL® administration were similar to those following DT and significantly lower than following whole-cell DTP. There were 2 reports of fever >40°C and 1 report of an HHE following TRIPACEL® administration. There were 7 reports of convulsions, but none were within 7 days of vaccination. (6)

In another clinical trial conducted in Sweden comparing 3 acellular pertussis vaccines and 1 whole-cell DTP vaccine, 20,745 infants received a different formulation (20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM) of TRIPACEL® at 2, 4 and 6 or 2, 5 and 12 months of age. Rates of adverse events were less than or comparable to the rates in the other acellular pertussis vaccine and whole-cell DTP groups in this study. The rates of reports of fever >40.5°C and seizures or suspected seizures were significantly higher following whole-cell DTP than following acellular pertussis vaccines. (15) Rates of HHE were comparable, with 29 reports following administration of TRIPACEL®. No deaths or cases of encephalitis or acute encephalopathy, invasive bacterial infection, infantile spasms or anaphylactic reactions were reported within 48 hours of vaccination. (15) (16)

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of TRIPACEL® worldwide. 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 TRIPACEL®.

Blood and Lymphatic Disorders

Lymphadenopathy

Cardiac Disorders

Cyanosis

Gastro-intestinal Disorders

Nausea, diarrhea

General Disorders and Administration Site Conditions

Injection site reactions: pain, rash, nodule, mass

Large injection site reactions (>50 mm), including extensive limb swelling which may extend from the injection site beyond one or both joints have been reported in children following TRIPACEL® administration. 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, with a greater risk following the 4th and 5th doses.

Infections and Infestations

Injection site cellulitis, cellulitis, injection site abscess

Immune System Disorders

Hypersensitivity, allergic reaction, anaphylactic reaction (edema, face edema)

Pruritus, generalized rash and other types of rash (erythematous, macular, maculo-papular)

Nervous System Disorders

Convulsions: febrile convulsion, grand mal convulsion, partial seizures

Hypotonic-hyporesponsive episode, hypotonia, somnolence, syncope

Psychiatric Disorders

Screaming

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and report to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

Vaccine-Drug Interactions

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

Concomitant Vaccine Administration

NACI states that administering the most widely used live and inactivated vaccines during the same patient visit has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately. (1) NACI recommends that vaccines administered simultaneously should be given using separate syringes at separate sites. (1) (2) Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination. Simultaneous administration of childhood vaccines such as TRIPACEL®, MMR, varicella, pneumococcal conjugate and hepatitis B vaccines, is encouraged for children who are at the recommended age to receive these vaccines and for whom no contraindications exist.

TRIPACEL® may be used to reconstitute Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein-Conjugate)] permitting the administration of these vaccines in a single dose. (17)

DOSAGE AND ADMINISTRATION

Recommended Dose

For routine immunization, TRIPACEL® is recommend as a 4-dose series, with a single dose of 0.5 mL of TRIPACEL® at 2, 4, 6 and 18 months of age.

If for any reason this schedule is delayed, it is recommended that 3 doses be administered with an interval of 2 months between each dose, followed by a fourth dose approximately 6 to 12 months after the third dose.

Whenever feasible, TRIPACEL® should be used for all 4 doses in the vaccination series as there are no clinical data to support the use of TRIPACEL® with any other licensed acellular pertussis combination vaccine in a mixed sequence. For situations where a different brand of DTaP, DTaP-IPV or DTaP-IPV/Hib vaccine was originally used, or where the brand is unknown, please refer to the latest edition of the Canadian Immunization Guide.

NACI recommends that premature infants whose clinical condition is satisfactory should be immunized with full doses of vaccine at the same chronological age and according to the same schedule as full-term infants, regardless of birth weight. (1)

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

In compliance with NACI's recommended schedule the childhood immunization series should be completed with a single 0.5 mL dose of DTaP such as TRIPACEL® between 4 and 6 years of age. A dose of IPV vaccine should be administered concomitantly at a separate site. Alternatively, Sanofi Pasteur Limited's QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] or ADACEL® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed] accompanied with IPV, may be used for this booster dose. This booster dose is unnecessary if the fourth dose of TRIPACEL® was administered after the child's fourth birthday. (1)

TRIPACEL® should not be administered to persons less than 2 months or to persons 7 years of age or older. (See INDICATIONS AND CLINICAL USE.)

Administration

Inspect for extraneous particulate matter and/or discolouration before use. 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 syringe and needle or a sterile disposable unit, for each individual patient to prevent disease transmission. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

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.). In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children the deltoid muscle is usually large enough for injection.

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.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Diphtheria and Tetanus: 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. A serum diphtheria antitoxin level of 0.01 IU/mL is considered the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (2) (3) Levels of 1.0 IU/mL have been associated with long-term protection. (3)

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. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. (2) (3) Levels of 1.0 IU/mL have been associated with long-term protection.

In a clinical trial in Canada (N = 324), protective levels of diphtheria and tetanus antitoxin antibodies were present in all but one participant after 3 doses of TRIPACEL® and in 100% after four doses. (9) (10)

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. However, in a clinical trial in Sweden (Sweden I Efficacy Trial), the same pertussis components as in TRIPACEL® (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%.

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. (18) (19) (20) (21) (22) (23) In a controlled clinical trial in Sweden (Sweden II Trial), the efficacy of a DTaP vaccine with a different formulation in pertussis antigens as TRIPACEL® was demonstrated to provide a two-fold to three-fold higher protection against pertussis with any cough compared to the three pertussis antigens vaccine. The observed difference supports the role of fimbriae types 2 and 3 in the protection against colonization of *B. pertussis* and mild disease. (24)

Duration of Effect

To ensure optimal protection during childhood, 4 consecutive doses should be given at 2, 4, 6 and 18 months of age. A booster with a vaccine containing diphtheria, tetanus, acellular pertussis with or without IPV is required at 4 to 6 years.

STORAGE AND STABILITY

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

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

TRIPACEL® is supplied as a sterile, uniform, cloudy, white to off-white suspension in a monodose vial.

Composition

Each 0.5 mL dose is formulated to contain:

Active Ingredients

Diphtheria Toxoid	15 Lf
Tetanus Toxoid	5 Lf
Acellular Pertussis	
Pertussis Toxoid (PT)	10 µg
Filamentous Haemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg

Other Ingredients

Excipients:

Aluminum Phosphate (adjuvant) (aluminum 0.33 mg)	1.5 mg
2-phenoxyethanol	0.6% v/v

Manufacturing Process Residuals: formaldehyde and glutaraldehyde are present in trace amounts.

Packaging

TRIPACEL® is supplied in single dose vials.

The vials are made of Type 1 glass. The vial stopper for this product does not contain latex (natural rubber).

TRIPACEL® is available in a package of

1 x 0.5 mL (single dose) vial

5 x 0.5 mL (single dose) vials

TRIPACEL® is also supplied in a package (marketed as ACTacel®) of:

1 x 0.5 mL (single dose) vial of TRIPACEL® for reconstituting 1 x 1 dose of Act-HIB®

5 x 0.5 mL (single dose) vials of TRIPACEL® for reconstituting 5 x 1 dose of Act-HIB®

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of April 2013.

Manufactured by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

R11-0413 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

Product Characteristics

TRIPACEL® is a sterile, uniform, cloudy, white to off-white suspension of diphtheria and tetanus toxoids adsorbed on aluminum phosphate and acellular pertussis vaccine and suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified pertussis antigens (PT, FHA, PRN and FIM).

C. diphtheriae is grown in modified Mueller's growth medium. (25) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered. *C. tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (26) 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 produced from *B. pertussis* cultures grown in Stainer-Scholte medium (27) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. The FIM components are extracted and co-purified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde and FHA is treated with formaldehyde. 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 into an intermediate concentrate.

Both diphtheria and tetanus induce at least 2 neutralizing units/mL in the guinea pig potency test. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized guinea pigs to PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA).

CLINICAL TRIALS

Three pivotal clinical trials (Sweden Trial I, Sweden Trial II and Canada Phase II) conducted in Sweden and in Canada provide the clinical basis for the licensure of TRIPACEL® in Canada. (See Table 2.)

Table 2: Summary of Demographics and Study Design of the Trials with TRIPACEL®

Study	Study Design	Dosage and Route of Administration	Vaccination Schedule/ Study Population	Gender
Sweden I (6) (7)	Randomized, placebo-controlled, double-blind, efficacy and safety trial with one whole-cell DTP, two DTaP vaccines (2 and 5-component).	0.5 mL I.M.	2, 4, 6 months of age N = 2,587	Males N = 1,330 Females N = 1,257
Sweden II (24) (28)	Randomized, controlled, double-blind, multicentre efficacy trial with one whole-cell DTP and three DTaP vaccines (2, 3 and 5-component).	0.5 mL I.M.	2, 4, 6 months of age N = 2,551 and 3, 5, 12 months of age N = 18,196	Males N = 10,590 Females N = 10,157
Canada Phase II (9) (10)	Randomized, double-blind controlled, multicentre efficacy and safety trial with one DTaP and one whole-cell DTP vaccines. (5-component).	0.5 mL I.M.	2, 4, 6, 18 months of age N = 432	Males N = 214 Females N = 218
Canada Phase IIC PB9301 (17)	Randomized, partially blinded, controlled, multicentre safety and efficacy when DTaP is combined with *Haemophilus influenzae* B conjugate vaccine.	0.5 mL I.M.	17-19 months of age N = 545	Males N = 306 Females N = 239
Canada Phase 1C (13) (14)	Safety and efficacy trial with DTaP in children previously immunized with DTP at 2, 4, 6 and 18 months of age.	0.5 mL I.M.	4-6 years of age N = 21	Males N = 11 Females N = 10
Canadian Study PB9503 (29)	Randomized, controlled, double-blinded multicentre safety and immunogenicity trial with QUADRACEL®	0.5 mL I.M.	4-6 years of age N = 131	Males N = 71 Females N = 60

Sweden I Efficacy Trial

A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in Sweden from 1992 - 1995 (Sweden I Efficacy Trial) under the sponsorship of the National Institute of Allergy and Infectious Diseases (NIAID). (6) A total of 9,829 infants received 1 of 4 vaccines: TRIPACEL® (N = 2,587); a two-component DTaP vaccine (N = 2,566); a whole-cell pertussis DTP vaccine from the US (N = 2,102); or DT vaccine (Swedish National Bacteriological Laboratory) as placebo (N = 2,574). Infants were immunized at 2, 4 and 6 months of age. The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of TRIPACEL® against pertussis after 3 doses of vaccine using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 85.2% (95% confidence interval [CI] 80.6 to 88.8). (6) The protective efficacy of TRIPACEL® against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by TRIPACEL® was sustained for the 2-year follow-up period. (6) (See Table 3.)

Table 3: Vaccine Efficacy Against Pertussis Infection of Varying Clinical Severity (6) (7)

Clinical Severity of Pertussis	Vaccine Efficacy (%) of TRIPACEL® (N = 2,551) Compared to DT Control (N = 2,539)
cough ≥1 day	77.9
cough >7 days	78.4
cough ≥21 days	81.4
cough ≥30 days	87.3
paroxysmal cough ≥14 days	82.3
paroxysmal cough ≥21 days	85.1

Another arm of the trial (6) (7) looked at the persistence of the protection provided by TRIPACEL® compared to a placebo. High levels of protection were sustained for TRIPACEL® over the entire 2-year follow-up period.

Table 4: Duration of Vaccine Efficacy for TRIPACEL® Compared to Placebo (6) (7)

Vaccine Efficacy (%) Compared to DT (Placebo N = 2,068)	
Interval Since Third Dose (in days)	**TRIPACEL® (N = 2,069)**
0 - 89	95
90 - 179	83.6
180 - 269	86.7
270 - 359	84.4
360 - 449	92.1
450 - 539	78.3
540-629	86.4
630-719	81.3

The incidence of injection site and systemic reactions after administration of TRIPACEL® was comparable to the DT control group. (6) (7)

A sub-study of this trial looked specifically at immunized children exposed to pertussis from other members of their household. (18) TRIPACEL® was more efficacious than the DT, other acellular pertussis and whole-cell pertussis vaccines studied. There was a correlation between clinical protection and the presence of anti-PRN, anti-FIM and anti-PT antibodies respectively in the serum of immunized children. (18)

Serology was done in a subset of children with the following responses following the third dose. (See Table 5.)

Table 5: Summary of Antibody Response (GMT) Following 3 Doses of TRIPACEL® in Sweden I Efficacy Trial (7)

Vaccine	N	Pertussis Toxoid (PT) (EU/mL)	Filamentous Haemagglutinin (FHA) (EU/mL)	Fimbriae Types 2 and 3 (FIM) (EU/mL)	Pertactin (PRN) (EU/mL)	Diphtheria Toxoid (IU/mL)	Tetanus Toxoid (EU/mL)
TRIPACEL®	178	49.43	34.12	350.75	116.41	0.83	3.75
DT	181	0.98	0.81	0.91	0.62	0.97	4.07
DPT	144	1.88	8.73	15.0	12.62	0.62	4.39

Canada Phase II Clinical Trial

In a clinical trial conducted in Canada, 324 infants received TRIPACEL® at 2, 4, 6 and 18 months of age. (9) (10)

Antibody titres are shown in Table 6. Protective levels of diphtheria and tetanus antitoxin antibodies were present in all but one participant after 3 doses and in 100% after four doses. (9) (10)

Table 6: Geometric Mean Titres After 3 and 4 Doses of TRIPACEL® (9) (10)

Antibody	7 Months (Post 3rd Dose)	19 Months (Post 4th Dose)
Pertussis Toxoid (PT) (EU/mL)	87.1	137.7
Filamentous Haemagglutinin (FHA) (EU/mL)	50.2	102.9
Fimbriae Types 2 and 3 (FIM) (EU/mL)	239.8	758.8
Pertactin (PRN) (EU/mL)	29.9	234.4
Diphtheria Toxoid (IU/mL)	0.3	5.98
Tetanus Toxoid (EU/mL)	1.5	3.57

Safety

The frequency of selected solicited adverse reactions observed in children within 48 hours of vaccination with TRIPACEL® at 2, 4, 6 and 18 months is shown in Table 1.

Canada Phase IC Clinical Trial

In another Canadian study, 21 children previously immunized with DTP at 2, 4, 6 and 18 months of age received TRIPACEL® at 4-6 years of age. (13) (14)

Table 7: Geometric Mean Antibody Rise After Immunization with TRIPACEL® at 4-6 Years of Age (13) (14)

Antibody	GMT (Post 5th Dose)
Pertussis Toxoid (PT) (EU/mL)	171.0
Filamentous Haemagglutinin (FHA) (EU/mL)	125.0
Fimbriae Types 2 and 3 (FIM) (EU/mL)	1337.0
Pertactin (PRN) (EU/mL)	161.0
Diphtheria Toxoid (IU/mL)	39.4
Tetanus Toxoid (EU/mL)	5.0

Safety

The frequency of selected solicited adverse reactions observed in children between 2 hours and 28 days of vaccination with TRIPACEL® at 4-6 years of age is shown in Table 1. (13) (14)

Clinical Trial PB9503

In a randomized controlled clinical trial conducted in Canada in 1995, 131 infants received Sanofi Pasteur Limited's QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] at 4 to 6 years of age. QUADRACEL® is a five-component DTaP vaccine that contains the same antigens (but with a higher content of PT and FHA per dose) than TRIPACEL® and includes IPV. The results of this trial have been included in support of the booster dose recommended by NACI at 4 to 6 years of age. (29)

In study PB9503, a single dose of QUADRACEL® produced a strong booster immune response for diphtheria, tetanus, pertussis and poliovirus antigens in 4 to 6 year-old children. Protective levels of serum antibodies were achieved by 100% of children for diphtheria and tetanus (0.01 IU/mL and 0.1 IU/mL), and for all 3 types of poliovirus (1:8). At least 81% of children achieved a 4-fold increase in anti-pertussis serum antibody levels. Table 8 details the immune response observed in children after one dose of QUADRACEL® at 4 to 6 years of age. (29)

Table 8: Antibody Responses to Diphtheria and Tetanus Toxoids, Poliovirus Types 1, 2 and 3 and Pertussis Antigens Measured One Month After the Fifth Dose of QUADRACEL® in Clinical Trial PB9503 (29)

Antibody	Result	Post 5th Dose (N = 125)
Diphtheria	**GMT (IU/mL) (95% CI)**	15.1 (12.1, 18.9)
	% ≥0.01 IU/mL	100
	% ≥0.10 IU/mL	100
Tetanus	**GMT (EU/mL) (95% CI)**	5.1 (4.6,5.7)
	% ≥0.01 EU/mL	100
	% ≥0.10 EU/mL	100
Polio Type 1	**GMT (95% CI)**	10903.3 (8718.9, 13635.0)
	% ≥1:8	100
Polio Type 2	**GMT (95% CI)**	27337.4 (23198.0, 32215.3)
	% ≥1:8	100
Polio Type 3	**GMT (95% CI)**	9165.1 (7125.5, 11788.6)
	% ≥1:8	100
PT	**GMT (EU/mL) (95% CI)**	123.2 (103.7, 146.4)
	% ≥4-fold rise *	97.6
FHA	**GMT (EU/mL) (95% CI)**	176.2 (149.2, 208.1)
	% ≥4-fold rise*	81.3
PRN	**GMT (EU/mL) (95% CI)**	64.2 (51.8, 79.5)
	% ≥4-fold rise*	98.4
FIM	**GMT (EU/mL) (95% CI)**	737.9 (625.6, 870.3)
	% ≥4-fold rise*	95.2

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level at 2 months of age for post-3rd dose and 18 months of age for post-4th dose.

Safety

Solicited injection site reactions occurred in 18.5% (redness) to 74.6% (tenderness) of QUADRACEL® vaccinees. Severe injection site reactions were observed in up to 16.2% (swelling) of QUADRACEL® vaccinees. (See Table 9.) Solicited systemic reactions occurred in 2.3% (diarrhea) to 23.1% (less active, eating less). Except for fussiness (4.6%) severe systemic reactions were uncommon. (See Table 9.)

Table 9: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose of QUADRACEL® Administered at 4 to 6 Years of Age in Clinical Trial PB9503 (29)

Solicited Reactions		Post 5th Dose (N = 130)
Less Active	**Any**	23.1
	Severe *	0.8
Eating Less	**Any**	23.1
	Severe †	0.8
Diarrhea	**Any**	2.3
	Severe ‡	0.8
Fever	**Any**	17.3
	≥40°C	0
Fussiness	**Any**	20.0
	Severe §	4.6
Injection Site Redness	**Any**	18.5
	≥35 mm	13.8
Injection Site Swelling	**Any**	18.5
	≥35 mm	16.2
Injection Site Tenderness	**Any**	74.6
	Severe **	0.8
Vomiting	**Any**	4.6
	Severe ††	0.8

* Sleeping most of the time.
† Refused most or all feeds.
‡ Multiple liquid stools without any solid consistency.
§ Continuously fussy for ≥3 hrs.
** Baby cries when leg is moved.
†† Frequent vomiting and inability to have any oral intake.

ADDITIONAL RELEVANT INFORMATION

Immunization against diphtheria, tetanus and pertussis has been associated with a striking decrease in the incidence of morbidity and mortality from these diseases. Simultaneous vaccination with combination vaccines containing diphtheria and tetanus toxoids and pertussis vaccine has been a cornerstone of the Canadian immunization programme.

Diphtheria and Tetanus: The information provided below is consistent with NACI recommendations. (1)

Diphtheria is an acute communicable disease caused by exotoxin-producing strains of the bacterium *C. diphtheriae*. Symptoms result from local infection of the respiratory tract, which may lead to breathing difficulties, or infection of the skin or mucosal surfaces, or from dissemination of diphtheria toxin, which damages the heart and central nervous system. Routine immunization against diphtheria in infancy and childhood has been widely practised in Canada since 1930, resulting in a decline in morbidity and mortality. In Canada, there are 0 to 5 isolates reported each year. The case-fatality rate remains at about 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. (1)

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. (1)

Both diphtheria and tetanus toxoids are prepared by detoxification of the respective toxins with formaldehyde. Intramuscular injection of diphtheria and tetanus toxoids results in the production of protective antibodies against the toxins and their lethal effects, but it does not preclude local infections with the bacteria. (1) After completion of a primary series, circulating antibodies to tetanus and diphtheria toxoids gradually decline but are thought to persist at protective levels for up to 10 years. NACI continues to recommend tetanus and diphtheria boosters every 10 years based on concern regarding the decline of antibody levels with age and potential failure of single booster doses to produce protective levels in older individuals.

Pertussis: Pertussis (whooping cough) results from an acute infection of the respiratory tract caused by *B. pertussis*. Severity and mortality are greatest in infancy and even infants born to apparently immune mothers are highly susceptible to infection, particularly if maternal immunity was induced by whole-cell pertussis vaccine.

Whole-cell pertussis vaccine was first introduced in Canada in 1943. NACI states that over the past 64 years, pertussis incidence has declined by over 90%, although outbreaks of pertussis continue to arise. Because of concerns about the frequency and severity of systemic and injection site adverse reactions with whole-cell pertussis vaccines, acellular pertussis vaccines have replaced whole-cell formulations in Canada. Acellular vaccines provoke significantly fewer injection site reactions, lower rates of fever and fewer episodes of unusual or persistent crying. (6) (7) (8) (24) (28)

TRIPACEL® contains a five-component acellular vaccine stimulating immune response to PT, FHA, FIM and PRN. In an efficacy trial, five-component acellular pertussis vaccines were proven significantly more efficacious than other acellular pertussis formulations containing fewer antigens. (6) (7) (19)

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of April 2013.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R11-0413 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

TRIPACEL®

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

This leaflet is part III of a three-part "Product Monograph" published when TRIPACEL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRIPACEL®. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

TRIPACEL® is a vaccine that is used to help prevent diphtheria, tetanus (lock jaw) and pertussis (whooping cough) infections. This vaccine may be given to children aged 2 months or older. It may also be given as a booster to children up to age 7.

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

What the vaccine does:

TRIPACEL® causes the body to produce its own natural protection against diphtheria, tetanus and pertussis (whooping cough). After your child receives the vaccine, the body begins to make substances called antibodies. Antibodies help the 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.

When it should not be used:

- Do not give TRIPACEL® to a child who has an allergy to any ingredient in the vaccine, or has had an allergic reaction after receiving a vaccine that contained similar ingredients.
- Do not give TRIPACEL® to a person who has had a serious nervous system disorder within 7 days after a previous pertussis vaccine. In case of progressive nervous system disorder or uncontrolled epilepsy, vaccination may be considered only after a treatment has been established and the condition is stabilized.

What the medicinal ingredient is:

Each 0.5 mL dose of TRIPACEL® contains: diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine (pertussis toxoid, filamentous haemagglutinin, pertactin and fimbriae types 2 and 3).

What the non-medicinal ingredients are:

Aluminum phosphate and 2-phenoxyethanol. Formaldehyde and glutaraldehyde are present in trace amounts.

What dosage forms the vaccine comes in:

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

WARNINGS AND PRECAUTIONS

If your child has any of the following conditions, talk to your doctor or pharmacist BEFORE the child receives TRIPACEL®:

- **A high fever or serious illness.** Wait until the child is better to give the vaccination.
- **An allergy to any component of the vaccine.**
- **A serious nervous system adverse event following a previous pertussis vaccination.**
- **Diseases of the immune system or taking a medical treatment that affects the immune system.** The vaccine may provide your child with a lower level of protection than it does for people with healthy immune systems. If possible, try to postpone the vaccination until after your child has completed the treatment.
- **A bleeding disorder or taking blood-thinning medications.** Tell the person giving the injection about your child's condition. The injection must be done carefully to prevent excessive bleeding.
- **A higher risk of seizure than the general population.** A fever-reducing medication may be given to your child.
- **Fainted with a previous injection.** Fainting can occur following vaccination. Appropriate measures should be taken to prevent falling injury.

INTERACTIONS WITH THIS VACCINE

TRIPACEL® may be mixed with Act-HIB®. Do not mix TRIPACEL® with other vaccines or medicinal products in the same syringe.

PROPER USE OF THIS VACCINE

Usual Dose

A single dose of 0.5 mL is recommended for routine immunization of infants at 2, 4, 6 and 18 months of age and in children up to their 7th birthday.

The vaccination should be given in the muscle, preferably in the thigh for children up to 1 year-old. In children >1 year of age, the shoulder is the preferred site since use of the thigh results in limping due to muscle pain.

Overdose

In case of drug overdose, contact a health-care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If immunization is delayed for any reason – the recommended schedule is:

- 3 single doses of 0.5 mL with 2 months between doses
- A 4th dose given 6 to 12 months after the 3rd dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause side-effects. Common reactions include redness, swelling or pain at the site of injection. They may also have vomiting, listlessness and pallor.

Tell your doctor, nurse or pharmacist as soon as possible if your child is not feeling well after receiving TRIPACEL®.

Serious side effects are extremely rare.

This is not a complete list of side effects. For any unexpected effects while taking TRIPACEL®, contact your doctor, nurse or pharmacist.

HOW TO STORE THE VACCINE

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 of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected case reports on adverse events following immunization.

For Health Care Professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should your child experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: (1-866-844-0018)

By toll-free fax: (1-866-844-5931)

By email: caefi@phac-aspc.gc.ca

Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9
A/L 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information. Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area). Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

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