

## TRIPACEL®

Pertussis Vaccine-Acellular, Combined With  
Diphtheria And Tetanus Toxoids (Adsorbed)

### Description

TRIPACEL® is a sterile, cloudy, uniform suspension of diphtheria and tetanus toxoids combined with purified pertussis antigens derived from pertussis fermentation.

Each 0.5 mL dose is formulated to contain:

Pertussis antigens:

Pertussis toxoid (PT)	10 mcg
Pertussis filamentous haemagglutinin (FHA)	5 mcg
Pertussis fimbriae 2 + 3	5 mcg
Pertussis 69 kDa outer membrane protein (Pertactin)	3 mcg
Diphtheria toxoid	LFL ≥30 IU
Tetanus toxoid	LFL ≥ 40 IU

Each injection also contains 1.5 mg aluminium phosphate as an adjuvant, and 3.4 mg phenoxyethanol as a preservative, in water for injections.

### Pharmacology

The acellular pertussis component of the vaccine contains five pertussis antigens which are thought to be related to protection against pertussis. The diphtheria and tetanus toxoids, as well as the acellular pertussis components, are adsorbed on to aluminium phosphate as an adjuvant.

The diphtheria and tetanus toxoids, which are obtained from cultures of *Corynebacterium diphtheria* and *Clostridium tetani*, are detoxified and purified. The acellular pertussis components PT, FHA, 69 kDa outer membrane protein and fimbriae 2 + 3 are manufactured by culturing *Bordetella pertussis*, from which the components are extracted and purified. The PT and FHA components are detoxified.

### Clinical Trial Data

This product has been shown to be less reactogenic than whole cell pertussis vaccines. Protective antibody levels against diphtheria and tetanus can be demonstrated one month following the third dose of a three dose primary series given at 2, 4, and 6 months of age. In a randomized controlled efficacy study conducted in Sweden where 2,551 infants received TRIPACEL® and 2,539 received a control vaccine containing diphtheria and tetanus toxoids at 2, 4, and 6 months of age, TRIPACEL® was shown to have an absolute vaccine efficacy of 85% (95% CI 81-89) against pertussis disease (defined as at least 21 days of paroxysmal cough with culture, serologic, or epidemiologic confirmation of infection with *Bordetella pertussis*). The incidence of local and systemic reactions after administration of TRIPACEL® was comparable to the Diphtheria Tetanus Vaccine (DT) control group.

TRIPACEL® has been administered to 92 children (see Table 1) in 3 different clinical trials as an 18-month booster following primary immunisation with a whole cell pertussis-containing vaccine. Control groups in two of these trials received 4 doses of whole cell DTP.

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**Table 1: Geometric Mean Titres Following 18 Month Dose**

Antigens	Trial A		Trial B		Trial C
	DTP (n=13)	TRIPACEL® (n=28)	TRIPACEL® (n=34)	DTP (n=30)	TRIPACEL® (n=30)
Diphtheria toxoid	8.7	9.8	15.6	10.0	7.8
Tetanus toxoid	3.8	6.4	5.2	3.6	4.9*
Pertussis toxoid (PT)	221.9	306.6	38.1	26.9	50.9*
Pertussis filamentous haemagglutinin (FHA)	30.1	29.9	91.6	22.0	55.1*
Pertussis fimbriae 2 + 3	314.7	1292.5	1968	795	1054
Pertussis 69 kDa outer membrane protein (Pertactin)	60.2	116.4	368	43.1	96.1

\* Significantly different from DTP ( $p \leq 0.05$ )

TRIPACEL® has also been administered to 324 children as an 18 month booster, following primary immunisation with TRIPACEL®. Strong booster responses for all antigens were achieved.

TRIPACEL® has been given as a booster at 4-6 years of age as follows:

- to 21 children following four doses (primary plus 18 month-booster) of whole cell pertussis-containing vaccine. Over 77% of children had a four-fold or greater rise in antibody titre for all pertussis components.
- to 11 children following a three dose primary immunisation with whole cell pertussis-containing vaccine and an 18-month booster of TRIPACEL®. Post fifth dose antibodies were substantially higher than pre-fifth dose levels.
- to 13 children following four doses (primary plus 18 month-booster) of TRIPACEL®. Antibody levels increased significantly after the fifth dose of TRIPACEL® when compared with pre-fifth dose levels.

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## Indications

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TRIPACEL® is indicated for primary immunisation against diphtheria, tetanus and pertussis when commenced between 2 months and 12 months of age;

TRIPACEL® is also indicated for the fourth and fifth dose for children from 15 months of age up to their eighth birthday who have been immunised previously with three or four doses of diphtheria, tetanus and pertussis (whole cell or acellular) vaccines.

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## Contraindications

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Known allergy to any component of TRIPACEL® or an immediate severe allergic or anaphylactic reaction to a previous dose of whole cell or acellular Diphtheria, Tetanus and Pertussis (DTP) vaccine is a contraindication to vaccination.

Encephalopathy not due to an identifiable cause, occurring within 7 days of a prior whole cell or acellular DTP immunisation and characterised by a severe acute neurological illness with prolonged seizures and/or unconsciousness and/or focal neurological signs, (but not a simple febrile convulsion) is a contraindication to vaccination.

## Precautions

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Immunisation with TRIPACEL® should be postponed in the presence of any major acute illness, including high fever. A minor febrile illness such as mild upper respiratory tract infection is not usually a reason to defer immunisation.

The vaccine should not be administered to persons after their eighth birthday because of the quantity of diphtheria toxoid and pertussis toxoid.

The following events require consideration of whether further doses of TRIPACEL® should be given:

- Fever  $\geq 40.5^{\circ}\text{C}$  within 48 hours of a dose of TRIPACEL®, not due to another identifiable cause;
- Hypotonic/hyporesponsive episodes within 48 hours. A hypotonic/hyporesponsive episode is one in which the child becomes pale, limp and unresponsive, lasting from 10 minutes to 36 hours. Shallow respiration and cyanosis are frequently observed. However, resuscitation is rarely required;
- Persistent inconsolable screaming > 3 hours, within 48 hours or
- Convulsions, with or without fever, within 3 days.

Clinical data in such patients are inadequate. The Australian National Health and Medical Research Council recommends completion of the primary course of vaccination as in its view there is no evidence that these reactions increase the risk of neurological sequelae.

TRIPACEL® should be deferred in children with a progressive, evolving, or unstable neurologic condition (including seizures) because administration of the pertussis component may coincide with the onset of overt manifestations of such disorders and result in confusion about causation. It is prudent to defer immunisation with pertussis vaccine until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. Vaccination with TRIPACEL® may thus be deferred in children who have had a convulsion in the past three weeks. Immunisation with TRIPACEL® should be undertaken when the condition has been controlled or stabilised or resolved.

When immunisation with pertussis vaccine is contraindicated, immunisation with diphtheria and tetanus toxoids, when necessary, may be continued using Adsorbed Diphtheria and Tetanus Vaccine (CDT™ Vaccine). The use of fractional doses in an attempt to reduce the severity of adverse reactions cannot be recommended because there is insufficient evidence on the safety or efficacy of such smaller doses.

When pertussis infections are occurring in the community the benefits of pertussis vaccine greatly outweigh any risk of vaccination.

There are currently no data to support the use of TRIPACEL® in persons with an immunodeficiency. However, it is generally advised that HIV-infected individuals, both asymptomatic and symptomatic, should be immunised against diphtheria, pertussis and tetanus according to standard schedules.

Elective immunisation of individuals over 6 months of age should be deferred during an outbreak of poliomyelitis because of the risk of provocation paralysis.

Before an injection of any vaccine, appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines, previous immunisation history, presence of any contraindications to immunisation, and current health status.

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As with other injectable vaccines, appropriate medical treatment and supervision should always be available in case of anaphylactic reactions. Adrenaline should always be readily available whenever the injection is given.

*Antipyretic Prophylaxis:* Based upon experience with whole cell pertussis vaccines, administration of paracetamol (15 mg/kg per dose) at the time of immunisation and at 3-4 hourly intervals afterwards up to a maximum of 4 doses, decreases the incidence of febrile and local reactions. Since convulsions after whole cell pertussis vaccine are almost always associated with fever, antipyretic prophylaxis may benefit children at increased risk of seizures. Caregivers should be aware that antipyretic therapy could also obscure fever caused by concomitant, unrelated infection.

Parents of infants and children with family histories of convulsions should be informed of their children's increased risk of seizures following administration of any vaccine causing a febrile reaction. A family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination. Paracetamol prophylaxis is particularly recommended for children with a personal or family history of convulsions.

The vaccine must be given intramuscularly as subcutaneous administration increases the chances of a severe local reaction.

Special care should be taken to ensure that the product is not injected into a blood vessel.

Intramuscular injections should be given with care in patients suffering from coagulation disorders because of the risk of haemorrhage.

If TRIPACEL® is used in persons with malignancies, receiving immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, who are otherwise immunocompromised or on corticosteroid therapy, the expected immune response may not be obtained.

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

The product must not be mixed with other vaccines in the same syringe.

Rarely, an anaphylactic reaction (ie. hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Arthus-type hypersensitivity reactions, characterised by severe local reactions (generally starting 2 to 8 hours after an injection), may follow receipt of tetanus and diphtheria toxoids. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.

Persistent nodules at the site of injection have occurred following the use of adsorbed vaccine, but this complication is unusual. Sterile abscess at the site of injection have been reported following use of adsorbed vaccines (6-10 per million doses).

Persistent, inconsolable crying lasting 3 or more hours (1%) and high-pitched, unusual screaming (0.1%) have been reported after whole cell DTP vaccination. Convulsions and hypotonic/hyporesponsive episodes have each been reported to occur at a frequency of about 1:1750 injections of whole cell DTP. Most convulsions are brief, generalised and self-limited, and are usually associated with fever. Neither febrile nor afebrile convulsions have shown to be associated with subsequent seizure disorder. Complete recovery, with no persistent sequelae, has been observed on follow-up of children with hypotonic/hyporesponsive episodes or convulsions.

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## ***Use In Pregnancy***

Not relevant.

## ***Use in Lactation***

Not relevant.

## ***Interactions with Other Drugs***

Administration of the vaccine during treatment with immunosuppressive drugs may cause a decreased response to the vaccine. While interactions with other vaccine antigens were not measured, the safety and efficacy of TRIPACEL® was demonstrated in 2,551 infants in Sweden in a randomized controlled trial where they also received simultaneous administration with Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) and Inactivated Poliomyelitis Vaccine at separate sites. In clinical trials conducted in Canada, TRIPACEL® was administered simultaneously with *Haemophilus influenzae* Type b (Hib) conjugate vaccine given at a separate site and Oral Poliomyelitis Vaccine (OPV). Although the interactions with the OPV and Hib vaccines were not studied, the safety and immunogenicity of the TRIPACEL® was shown to be satisfactory.

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## **Adverse Reactions**

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### ***Clinical Trial Data***

In a clinical study conducted in Canada, 324 children received TRIPACEL® and 108 children received whole cell DTP\* adsorbed at 2, 4, 6 and 18 months of age. The following rates of reactions were observed in this trial:

**Table 2: Percentage of Children with Reactions within 48 Hours of Vaccination**

REACTION (Any)	2 Months		4 Months		6 Months		18 Months	
	TRIPACEL®	DTP*	TRIPACEL®	DTP*	TRIPACEL®	DTP*	TRIPACEL®	DTP*
Redness > 0 cm	13	44	20	58	22	52	36	56
Swelling > 0 cm	4	23	4	32	5	24	18	29
Tenderness	10	37	7	52	9	48	23	86
Fever > 37°C	7	36	5	45	9	44	10	63
Irritability	37	63	39	69	36	67	35	78
Prolonged Crying	2	12	3	12	1	8	1	7
Drowsiness	42	52	21	33	14	33	13	30
Decreased Feeding	15	21	8	15	10	22	16	41
Listlessness	6	18	2	10	3	14	3	29
Pallor	5	11	2	9	2	7	2	11
Vomiting	7	12	6	9	5	10	5	7

\* Note: The whole cell DTP vaccine is licensed by the Canadian Bureau of Biologics and Radiopharmaceuticals and is not the DTP vaccine available in Australia.

Most reactions were described as mild and resolved spontaneously within 24-72 hours. Seizures and hypotonic/hyporesponsive episodes were not observed in this study. In a clinical trial in Sweden comparing 2 acellular pertussis vaccines, DT, and a whole cell DTP vaccine, 2587 infants received TRIPACEL® at 2, 4 and 6 months of age. Rates of reactions following TRIPACEL® administration were similar to those following DT and

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significantly lower than following whole cell DTP. There were 2 reports of fever > 40°C and 1 report of a hypotonic-hyporesponsive episode following TRIPACEL® administration. There were 7 reports of convulsions, but none were within 7 days of vaccination.

In another clinical trial conducted in Sweden comparing 3 acellular pertussis vaccines and 1 whole cell DTP vaccine, 20,745 infants received an acellular pertussis DTP vaccine similar to TRIPACEL® but containing twice the amount of PT and four times the amount of FHA per dose at 2, 4 and 6 or 3, 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. Rates of hypotonic/hyporesponsive episodes were comparable, with 29 reports following administration of TRIPACEL®-related vaccine. No deaths or cases of encephalitis/acute encephalopathy, invasive bacterial infection, infantile spasms or anaphylactic reactions were reported within 48 hours of vaccination.

In clinical studies conducted in Canada, children who had received 3 or 4 doses of a whole cell DTP vaccine received TRIPACEL®. Tables 3 and 4 below show adverse reactions reported in the above 3 studies.

**Table 3: Percentage of Children with Reactions within 48 Hours of Vaccination**

17 - 18 Months*		
Reaction (%)	DPT (n=30)	TRIPACEL® (n=30)
Redness (>0 cm)	77	53
Swelling (>0 cm)	57	33
Tenderness	80	33 <sup>†</sup>
Fever (>37°C)	47	3 <sup>†</sup>
Irritability	73	33 <sup>†</sup>
Prolonged Crying	10	0
Drowsiness	43	20 <sup>†</sup>
Decreased appetite	47	10 <sup>†</sup>
Listlessness	27	20
Pallor	10	3
Vomiting	10	3

\* Received 3 doses of whole cell DTP at 2, 4 and 6 months of age

† p < 0.05

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**Table 4: Percentage of Children with Reactions within 24 Hours of Vaccination**

4 - 6 Years <sup>‡</sup>	
% Any reported reactions within 24 hours	TRIPACEL® (n=21)
Redness (>0 cm)	10
Swelling (>0 cm)	5
Tenderness	71
Fever (>37°C)	10
Irritability	19
Prolonged Crying	N/A
Drowsiness	24
Decreased appetite	14
Listlessness	0
Pallor	0
Vomiting	0

‡ Received 4 doses of whole cell DTP at 2, 4, 6 and 18 months of age

Now that there has been significant experience with acellular pertussis-containing vaccines at the fourth and fifth doses, the occurrence of large local reactions, consisting of redness and/or swelling >50 mm, some circumferential swelling of the injected limb, has been identified. These local reactions are usually not associated with significant pain and resolve spontaneously.

In a study conducted by the U.S. National Institutes of Health (NIH) to evaluate safety and immunogenicity of six formulations of acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP), it was found that large injection site reactions occurred more frequently after the fifth dose of DTaP than after the previous fourth dose. This formulation of TRIPACEL® vaccine was not used in the NIH study.

In a review by NIH of 1015 children who received 4 consecutive doses of the same DTaP, circumferential thigh swelling was reported in 20 children (2%). No reports were received for circumferential swelling of the upper arm in 121 children who received a fifth dose of the same DTaP. In 146 recipients who received 5 doses of a mixed schedule of DTaP vaccines, 4 (2.7%) children were reported to have such swelling. There was a significant linear association between the rates of entire thigh swelling after dose 4 and diphtheria toxoid content in the DTaP products. In all reports the swelling subsided spontaneously and completely, without sequelae.

Other adverse reactions have been reported with diphtheria, tetanus and/or pertussis vaccines (see PRECAUTIONS).

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## ***Post-marketing Experience***

The following adverse reactions have been reported in the post-marketing experience to date:

Very common:  $\geq 1/10$  ( $\geq 10\%$ )

Common:  $\geq 1/100$  and  $< 1/10$  ( $\geq 1\%$  and  $< 10\%$ )

Uncommon:  $\geq 1/1000$  and  $< 1/100$  ( $\geq 0.1\%$  and  $< 1\%$ )

Rare:  $\geq 1/10000$  and  $< 1/1000$  ( $\geq 0.01\%$  and  $< 0.1\%$ )

Very rare:  $< 1/10000$  ( $< 0.01\%$ )

### **Application site disorders:**

Very rare: Injection site reaction  
Injection site inflammation

### **Body as a whole:**

Very rare: Fever  
Malaise  
Crying abnormal  
Oedema  
Hypnotic-hyporesponsive episode  
Pallor

### **Cardiovascular Disorders:**

Very rare: Cyanosis

### **Central and Peripheral Nervous System Disorders:**

Very rare: Fever convulsions  
Hypotonia

### **Gastrointestinal Disorders:**

Very rare: Faeces discoloured  
Tenesmus  
Vomiting  
Appetite decreased

### **Psychiatric Disorders:**

Very rare: Irritability  
Agitation  
Nervousness

### **Respiratory System Disorders:**

Very rare: Apnoea

### **Skin and Appendages Disorders:**

Very rare: Rash  
Urticaria  
Sweating increased  
Pigmentation abnormal

Because of variability of reporting rates and the threshold for reporting vaccine-associated adverse events, particularly those which are not serious or unexpected, spontaneous, passive surveillance systems may underestimate the occurrence of these events.

## Dosage and Administration

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For primary immunisation of infants the following routine TRIPACEL® immunisation schedule is recommended: one 0.5 mL dose administered at 2, 4 and 6 months of age.

A booster dose of 0.5 mL should be administered at 18 months of age. TRIPACEL® may be used irrespective of whether a whole cell DTP or TRIPACEL® was used for the primary immunisation.

A booster dose of 0.5 mL should be administered between four and six years of age (i.e., at the time of school entry). TRIPACEL® may be used irrespective of whether a whole cell DTP or TRIPACEL® was used for the primary immunisation and 18-month booster dose.

The vaccine should not be administered to persons after their eighth birthday.

Infants born prematurely whose clinical condition is satisfactory should be vaccinated according to their chronological age from birth.

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discolouration prior to administration. If these conditions exist, the product should not be administered.

Shake the vial or ampoule well to distribute uniformly the suspension before withdrawing dose. Before withdrawing a dose from an ampoule, tap the container first to ensure that any vaccine in the ampoule neck falls to the lower portion of the ampoule. When administering a dose from a rubber-stoppered vial, do not remove either the rubber stopper or the metal seal holding it in place. Once the ampoule or vial has been opened, any of its contents not used immediately should be discarded. Aseptic technique must be used for withdrawal of the dose. Before injection, the skin over the site should be cleansed with a suitable germicide.

Administer the vaccine **intramuscularly**. The anterolateral thigh is the preferred site for vaccination in infants and children under 12 months of age. The deltoid region is an alternative site for vaccination in older children (those who have commenced walking). Alternate limbs should be used for multiple injections, given at the same visit.

After insertion of the needle, ensure that the needle has not entered a blood vessel.

The vaccine may be administered concurrently with *Haemophilus influenzae* Type b (Hib) conjugate vaccine, and oral polio vaccine. When the vaccine is administered at the same time as Hib, separate syringes and different injection sites must be used. A record should be kept of which vaccine was injected at which site.

The parent or guardian of the child should be given a card recording the details of the immunisation.

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## Overdose

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No information is available.

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## Presentation

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TRIPACEL® is available as single dose vials containing 0.5 mL of vaccine.

## Medicine Classification

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Prescription Medicine

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## Storage

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TRIPACEL® should be stored at 2°C to 8°C. **DO NOT FREEZE.** Vaccine that has been frozen must not be used. Do not use after expiry date.

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## Manufacturer

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**Sanofi Pasteur Limited**  
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## Date of Preparation

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1 November 2007

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