AUSTRALIAN PRODUCT INFORMATION – TRIPACEL® (PERTUSSIS VACCINE ACELLULAR, COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ADSORBED))

1 NAME OF THE MEDICINE

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tripacel is a sterile, isotonic suspension of purified acellular pertussis antigens and diphtheria and tetanus toxoids adsorbed on aluminium phosphate.

Each 0.5 mL dose is formulated to contain:

Diphtheria toxoid (*Corynebacterium diphtheriae*)	≥ 30 IU (15 Lf)
Tetanus toxoid (*Clostridium tetani*)	≥ 40 IU (5 Lf)
Pertussis toxoid (PT)	10 micrograms
Pertussis Filamentous Haemagglutinin (FHA)	5 micrograms
Pertussis Fimbriae 2 + 3 (FIM)	5 micrograms
Pertactin (PRN)	3 micrograms
Adsorbed on aluminium phosphate	1.5 milligrams (0.33 milligrams aluminium)

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Suspension for injection.

After shaking, Tripacel is a white to off-white cloudy suspension for intramuscular administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

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 well to distribute uniformly the suspension before withdrawing dose. When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Once the vial has been opened, any of its contents not used immediately should be discarded. Aseptic technique must be used for withdrawal of the dose.

Administer the vaccine intramuscularly. The preferred site is into the anterolateral aspect of the mid thigh in infants younger than 1 year or into the deltoid muscle in children over 1 year of age.

Do not administer the product intravascularly or subcutaneously.

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

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

Product is for single use only and must not be used in more than one individual. Discard any remaining unused contents.

4.3 CONTRAINDICATIONS

Hypersensitivity
Known systemic hypersensitivity reaction or life-threatening reaction to any component of Tripacel after previous administration of the vaccine or a vaccine containing the same components.

Febrile or Acute Disease
Vaccination should be postponed in case of an acute or febrile disease; however a disease with low-grade fever should not usually be a reason to postpone vaccination.

Acute Neurological Disorders
The following events are contraindications to administration of any pertussis-containing vaccine, 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 individuals with such conditions until a treatment regime has been established and the condition has stabilised.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

As a precautionary measure adrenaline (epinephrine) injection must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

Syncope (fainting) has been reported following vaccination with Tripacel. Vaccinees should be observed for 15 minutes after vaccine administration, and procedures should be in place to prevent and manage syncopal reactions.

Hypersensitivity

Anaphylaxis has been reported after receiving preparations containing diphtheria toxoids, tetanus toxoids, and/or pertussis antigens.

Serious and severe adverse event-related precautions

A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although a causal relationship has not been established.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to administer Tripacel should be based on careful consideration of potential benefits and possible risks. When a decision is made to withhold any recommended dose of pertussis vaccine, immunisation with DT (For Paediatric Use) vaccine should be continued.

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

Bleeding disorders

Because any intramuscular injection can cause an injection site haematoma in persons with any bleeding disorders, such as haemophilia 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 haematoma formation following injection.

Altered immune status

Immunocompromised persons (whether due to a medical condition or immunosuppressive therapy) may not obtain 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 Human Immunodeficiency Virus infection is recommended even if the antibody response might be limited.

Neurological disorders

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. If Guillain-Barré syndrome occurred within 6 weeks of receipt of a 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.

For infants or children at higher risk for seizures than the general population, 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 (such as Tripacel) and for 24 hours following immunisation, to reduce the possibility of post-vaccination fever. Caregivers should be aware that antipyretic therapy could also obscure fever caused by concomitant, unrelated infection.

Protection

As with many vaccines, immunisation with Tripacel may not protect 100% of vaccinated individuals.

Use in the elderly

Tripacel should not be used in adults.

Paediatric use

The potential risk of apnoea and the need for respiratory monitoring for 48 – 72 hours should be considered when administering the primary immunisation 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.

Effects on laboratory tests

Interference of Tripacel with laboratory and/or diagnostic tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 randomised 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.

In cases where Tripacel and Menactra are to be administered at 4 to 6 years of age, preference should be given to simultaneous administration of the two vaccines, or administration of Menactra prior to Tripacel.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Tripacel has not been evaluated for the effects on fertility.

Use in pregnancy

This vaccine is not intended for administration to women of child-bearing age.

Use in lactation.

This vaccine is not intended for administration to women of child-bearing age.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable – for paediatric use only.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data Section

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:

Table1 - 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 two 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 significantly lower than following whole-cell DTP. There were two reports of fever > 40°C and one report of a hypotonic-hyporesponsive episode following Tripacel administration. There were seven reports of convulsions, but none were within 7 days of vaccination.

In another clinical trial conducted in Sweden comparing three acellular pertussis vaccines and one 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. Table 2 and Table 3 below show adverse reactions reported in the above 3 studies.

Table 2 - Percentage of Children with Reactions within 48 Hours of Vaccination (17 - 18 Months*)

Reaction (%)	DTP (n=30)	TRIPACEL (n=30)
Redness (>0 cm)	77	53
Swelling (>0 cm)	57	33
Tenderness	80	33†
Fever (>37°C)	47	3†
Irritability	73	33†
Prolonged Crying	10	0
Drowsiness	43	20†
Decreased appetite	47	10†
Listlessness	27	20
Pallor	10	3
Vomiting	10	3

* Received 3 doses of whole-cell DTP at 2, 4 and 6 months of age
† $p < 0.05$

Table 3 - Percentage of Children with Reactions within 24 Hours of Vaccination (4 - 6 Years‡)

% Any reported reactions within 24 hours	TRIPACEL (n=21)
Redness (>0 cm)	10
Swelling (>0 cm)	5
Tenderness	71
Fever (>37°C)	10
Irritability/Fussiness	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 Section 4.4 Special warnings and precautions for use).

Post-marketing Experience

The following adverse events have been spontaneously reported during the post-marketing use of Tripacel. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Tripacel.

Blood and lymphatic disorders

Lymphadenopathy

Cardiac disorders

Cyanosis

Gastro-intestinal disorders

Nausea, diarrhoea

General disorders and administration site conditions

Injection site reactions: injection site pain, injection site rash, injection site nodule, injection site mass

Large injection site reactions (> 50 mm), including extensive limb swelling that 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.

Immune system disorders

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

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

Infections and infestations

Injection site cellulitis, cellulitis, injection site abscess

Nervous system disorders

Convulsions: febrile convulsion, grand mal convulsion, partial seizures

Hypotonic-hyporesponsive episode, hypotonia, somnolence, syncope

Psychiatric disorders

Screaming

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Pertussis, purified antigens, combinations with toxoids

ATC code: J07AJ52

Mechanism of action

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 *C. diphtheriae and C. tetani*, are detoxified and purified. The acellular pertussis components PT, FHA, PRN and FIM are manufactured by culturing *B. pertussis*, from which the components are extracted and purified. The PT and FHA components are detoxified.

Clinical trials

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 4) 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.

Table 4 - 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 (FIM)	314.7	1292.5	1968	795	1054
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.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tripacel has not been tested for genotoxic potential.

Carcinogenicity

Tripacel has not been tested for carcinogenetic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tripacel contains the excipients:
Aluminium phosphate
Phenoxyethanol
Water for injections
Other ingredients per dose include ≤ 5 micrograms residual formaldehyde and < 50 ng residual glutaral.

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other medicinal products except those mentioned above.

6.3 SHELF LIFE

36 months at 2ºC to 8ºC

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC to 8ºC. Refrigerate. **DO NOT FREEZE**. Vaccine that has been frozen must not be used. Do not use after expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

Tripacel is available as single dose vials containing 0.5 mL of vaccine. The vial stopper for this product does not contain latex (natural rubber).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely according to locally agreed procedures.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not relevant to vaccines

CAS number

Not relevant to vaccines

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
12 – 24 Talavera Road
Macquarie Park NSW 2113
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

23 April 1998

10 DATE OF REVISION

3 April 2024

Summary table of changes

Section changed	Summary of new information
Heading	Correction of active
4.8, 4.9, 8	Removal of New Zealand details

Section changed	Summary of new information
8	Minor update of Australian details