AUSTRALIAN PRODUCT INFORMATION – QUADRACEL (PERTUSSIS VACCINE - ACELLULAR AND DIPHTHERIA AND TETANUS TOXOIDS (ADSORBED) COMBINED WITH INACTIVATED POLIOVIRUS TYPES 1, 2 AND 3 (VERO CELL))

1 NAME OF THE MEDICINE

Pertussis Vaccine-Acellular and Diphtheria and Tetanus Toxoids (Adsorbed) Combined with Inactivated Poliovirus Types 1, 2 and 3 (Vero Cell).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5mL dose of Quadracel contains:

Diphtheria toxoid	≥ 30 IU (15 Lf)
Tetanus toxoid	≥ 40 IU (5 Lf)
Pertussis toxoid (PT)	20 microgram
Pertussis filamentous haemagglutinin (FHA)	20 microgram
Pertactin (PRN)	3 microgram
Pertussis fimbriae 2 + 3 (FIM)	5 microgram
Poliovirus inactivated type 1, Vero (Mahoney)	29 D-antigen Units
Poliovirus inactivated type 2, Vero (MEF-1)	7 D-antigen Units
Poliovirus inactivated type 3, Vero (Saukett)	26 D-antigen Units

Absorbed on 1.5 mg Aluminium phosphate (0.33 mg aluminium)

This product does not contain thiomersal.

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

Diphtheria toxoid is a cell-free preparation of diphtheria toxin detoxified with formaldehyde.

Tetanus toxoid is prepared by detoxification of tetanus toxin with formaldehyde.

Each of the three strains of poliovirus is individually grown in Vero cells cultivated on microcarriers. The single virus harvest is concentrated and purified, then inactivated with formaldehyde to produce the type 1, 2 or 3 monovalent. Monovalents of each type are then combined in appropriate quantities to produce a trivalent concentrate.

The 5 component pertussis antigens, pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA), pertactin (PRN) and pertussis fimbriae types 2 + 3 (FIM), contained in Quadracel are the same as those in TRIPACEL or PEDIACEL. TRIPACEL consists of an acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTPa), and has lesser amounts of PT and FHA, while Quadracel has pertussis formulations that are similar to PEDIACEL. Quadracel contains DTPa combined with inactivated poliovirus vaccine (IPV).

This product contains residual streptomycin sulfate, neomycin and polymyxin B sulfate.

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

3 PHARMACEUTICAL FORM

Quadracel is a sterile, uniform, cloudy white to off-white suspension for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Quadracel is indicated for primary immunisation of children from the age of 2 months to 12 months against diphtheria, tetanus, pertussis, and poliomyelitis.

Quadracel is also indicated for the fourth dose for children from 15 months to six years of age who have been immunised previously with three doses of diphtheria, tetanus, pertussis and polio vaccines.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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

A fourth dose of Quadracel may be administered as a booster dose for children from 15 months to 6 years of age who have been immunised previously with up to three doses of diphtheria, tetanus, pertussis and polio vaccines.

The vaccine should not be administered to individuals after their seventh birthday (see Section 4.4 Special warnings and precautions for use).

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

Administration

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.

SHAKE THE SYRINGE WELL to distribute uniformly the suspension.

Administer the vaccine **intramuscularly**. The anterolateral thigh is the preferred site for vaccination in infants and children under 12 months of age. In older children, the deltoid muscle is usually large enough for injection. Separate syringes, separate injection sites and preferably separate limbs must be used in case of concomitant administration.

Do not administer the product intravascularly or subcutaneously.

Needles should not be recapped and should be disposed of properly.

Product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Hypersensitivity

Quadracel should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine (see components listed in in Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients) or after previous administration of the vaccine or a vaccine containing the same components or constituents.

Febrile or acute disease

Vaccination should be postponed in cases of moderate or severe febrile and/or acute disease. Low-grade fever does not constitute a contraindication.

Neurological disorders

The following events are contraindications to administration of any pertussis-containing vaccine, including Quadracel:

- 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 neurological disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilised.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prior history of severe adverse events following pertussis 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 Quadracel should be based on careful consideration of potential benefits and possible risks. The following events require consideration of whether further doses of Quadracel should be given:

- temperature of ≥ 40.5°C within 48 hours, not attributable to another identifiable cause;
- collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- persistent crying lasting ≥ 3 hours within 48 hours,

- convulsions with or without fever within 3 days

Hypersensitivity

Bovine serum albumin, formaldehyde and glutaral have been used in the manufacturing process of this product and residual trace amounts may be present in the final product. Therefore, a hypersensitivity reaction may occur.

Neomycin, polymyxin B sulfate and streptomycin sulfate have been used in the manufacturing process of this product. As each dose may contain residual trace amounts of neomycin, polymyxin B sulfate and streptomycin sulfate, caution must be exercised when the vaccine is administered to individuals with hypersensitivity to these antibiotics (and other antibiotics of the same class).

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.

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

Protection

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

Neurological adverse events

A review by the US Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). If GBS occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Quadracel 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 (including Quadracel) and for the following 24 hours, to reduce the possibility of post-vaccination fever.

Hypotonic-hyporesponsive episodes (HHEs) rarely follow vaccination with whole-cell pertussis- containing DTP vaccines and occur even less commonly after acellular pertussis-containing DTP vaccines and DT vaccines. A history of HHEs is not a contraindication to the use of acellular pertussis vaccines but caution should be exercised in these cases.

Administration route-related precautions

Do not administer by intravascular route.

As with all parenterals, this vaccine must be administered with caution to individuals with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular injection.

Serious and severe adverse events-related precautions

In persons who have a history of serious or severe reactions following a previous injection with the same vaccine or a vaccine containing similar components, the risks and benefits of vaccination must be carefully considered.

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

Altered immune status

The immunogenicity of Quadracel could be reduced by immunosuppressive treatment. In such cases it is recommended to postpone the vaccination until the end of the immunosuppression. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.

Syncope related precautions

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

Use in the elderly

Quadracel 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 Quadracel with laboratory tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When both vaccines are indicated, Quadracel may be used to reconstitute Act-HIB® (Haemophilus influenzae Type b Polysaccharide Conjugated to Tetanus Protein) for simultaneous administration of all 5 antigens in a single injection. Quadracel must not be mixed in the same syringe with any other vaccines.

There are currently no data regarding the concomitant administration of Quadracel with MMR or hepatitis B vaccine. The Australian Immunisation Handbook accepts that inactivated vaccines can be given during the same visit at separate sites with separate syringes.

Immunosuppressive treatments may interfere with the development of the expected immune response.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Quadracel has not been evaluated for the effects on fertility.

Use in pregnancy

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

Use in lactation.

Not applicable. 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 Trials Experience

Safety information described below are based upon studies with Quadracel formulated with MRC-5 cell-derived IPV.

The most frequent reactions observed with Quadracel include redness and tenderness at the injection site, irritability and slight fever. These symptoms usually occur within the first 24 hours after vaccination and may continue for 24 - 48 hours. The rates of adverse events observed in children who received Quadracel at 2, 4, 6 and 18 months of age during a clinical trial with the vaccine in Canada are shown in Table 1.

Table 1 - Adverse event rates (%) observed within 24 and 24 to 72 hours of vaccination with Quadracel according to age and number of doses

		1st Dose 2 months (n = 113)		2nd Dose 4 months (n = 111)		3rd Dose 6 months (n – 111)		4th Dose 18 months (n = 104)	
Reaction	**Severity**	**0-24***	**24-72***	**0-24***	**24-72***	**0-24***	**24-72***	**0-24***	**24-72***
Redness	severe¥	0	0	0	0	0	0	1.9	10.6
	any	0.9	0	8.1	1.8	12.6	4.5	18.3	19.2
Swelling	severe¥	2.7	0	0.9	0	0.9	0	4.8	6.7
	any	5.3	4.5	3.6	1.8	7.2	3.6	13.5	14.4
Tenderness	severe	1.8	0	3.6	0	0	0	0	0
	any	18.6	1.8	18.0	1.8	9.0	0	28.9	6.7
Fever	severe§	0	0	0	0	0	0.9	0	0
	any	22.1	2.7	21.1	9.4	18.0	4.6	24.0	10.8
Fussiness	severe	2.7	0.9	0	0	0	0	1.0	0
	any	46.0	29.5	45.0	20.0	35.1	27.0	33.7	16.4
Crying	severe	1.8	0	0	0	0	0	0	0
	any	31.0	6.3	28.8	18.2	23.4	17.1	19.2	10.6
Decreased activity	severe	0.9	0	0.9	0	0	0	0	0
	any	51.3	20.5	27.9	16.4	21.6	9.0	16.4	4.8
Decreased eating	severe	0	0	0	0	0	0	0	0
	any	34.5	17.0	20.7	18.2	16.2	19.8	20.2	15.4
Vomiting	severe	0	0	0	0	0	0	0	0
	any	8.0	6.3	2.7	0.9	6.3	5.4	6.7	3.9
Diarrhoea	severe	0	0	0	0.9	0	0	0	0.96
	any	6.2	9.8	7.2	7.3	9.9	9.0	2.88	7.69

Note: * interval of time in hours following vaccination
¥ redness or swelling ≥ 35 mm
§ fever ≥ 40.0°C

In a clinical trial conducted in Sweden comparing three acellular pertussis vaccines and one whole-cell DTP vaccine, 20,745 infants received a "hybrid" formulation of TRIPACEL which contained the same amounts of pertussis antigens as in Quadracel 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. No deaths or cases of encephalitis/acute encephalopathy, invasive bacterial infection, infantile spasms or anaphylactic reactions were reported within 48 hours of vaccination.

There are currently no clinical data to support administration of a fifth dose with Quadracel. In a study conducted by the U.S. National Institutes of Health (NIH), thirteen different

formulations of acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTPa), including TRIPACEL (containing less PT and FHA than Quadracel), were evaluated for safety and immunogenicity when administered at 2, 4, 6 and 18 months, and 4 – 6 years of age. In an analysis of fourth and fifth dose follow-up studies from this multicenter trial, entire limb swelling was reported in 20 children (2%) of 1,015 children who received four consecutive doses of the same DTPa. It was found that large injection site reactions occurred more frequently after the fifth dose of DTPa than after the previous fourth dose. No reports were received of entire limb swelling in 121 children who received a fifth dose of the same DTPa. In 146 recipients who received 5 doses with different DTPa vaccines, 4 (2.7%) children were reported to have such swelling. In all reports the swelling subsided spontaneously and completely, without sequelae.

Data from Post-Marketing Experience

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

Immune System Disorders

Anaphylactic reaction, hypersensitivity and allergic reactions (such as rash, urticaria, dyspnoea)

Psychiatric Disorders

Screaming

Nervous System Disorders

Somnolence, convulsion, febrile convulsion, hypotonic-hyporesponsive episode, hypotonia

Cardiac Disorders

Cyanosis

Vascular Disorders

Pallor

General Disorders and Administration Site Conditions

Injection site reactions (including inflammation, mass, abscess and sterile abscess), oedema, injection site vesicles.

Listlessness

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

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

There are no reports of overdosage.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Bacterial and Viral Vaccines, Combined, ATC code: J07CA02

Clinical trials

Clinical trial results described below are based upon studies with Quadracel formulated with MRC-5 cell-derived IPV.

Studies of protective efficacy of TRIPACEL against pertussis

A randomised controlled double-blind efficacy study was conducted in Sweden (Trial 1) where 2,551 infants received the regular formulation of TRIPACEL (containing lower concentrations of PT and FHA than Quadracel) 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.

A second randomised, double-blind controlled efficacy trial (Trial 2) was carried out in Sweden with 82,892 infants comparing 3 acellular pertussis and one European whole-cell DTP vaccines where 20,746 infants received a “hybrid” formulation of TRIPACEL (DTPa) which contained the same concentration of pertussis antigens as Quadracel, at 2, 4 and 6 (n = 2,552) or 3, 5 and 12 (n = 18,194) months of age. The “hybrid” TRIPACEL and the European whole-cell DTP vaccine had similar and high efficacy against culture-confirmed pertussis irrespective of duration. The other acellular pertussis combination vaccines were less

effective. Rates of adverse events were less than or comparable to the rates observed in the other acellular pertussis and European whole-cell DTP groups in this study.

Immunogenicity of Quadracel

In a clinical trial conducted in Canada, infants received either PEDIACEL (n=339), PENTA [Act-HIB reconstituted with a whole cell pertussis DTP-IPV vaccine] (n=112), POLIACEL [Quadracel used to reconstitute Act-HIB] (n=335), or Quadracel and Act-HIB, given at separate sites at the same visit (n=113) at 2, 4 and 6 months of age. Of the 899 children enrolled, 798 received a fourth dose of the same vaccine at 18-20 months of age. Serologic responses are shown in Table 2.

The following antibody levels are considered to be protective: diphtheria, diphtheria antitoxin levels ≥ 0.01 IU/mL; tetanus, tetanus antitoxin levels ≥ 0.01 IU/mL; and, poliomyelitis, neutralising poliovirus antibody titre levels ≥ 1:8.

Table 2 - Antibody responses observed one month after a third and fourth dose with Quadracel

Antibody Response	1 month Post-Dose 3 (7 months of age) (n = 108)	1 month Post-Dose 4 (17 - 19 months of age) (n = 103)
% diphtheria antitoxin ≥ 0.01 IU/mL	99.1	100
% tetanus antitoxin ≥ 0.01 EU/mL	100	100
% polio ≥1:8:		
Type 1	98.1	100
Type 2	100	100
Type 3	99.1	100
GMT:		
PT	103	223
FHA	165	252
FIM	332	1079
Pertactin	40.5	160

The pertussis antibody responses observed with Quadracel were comparable to those observed following administration of the two different formulations of TRIPACEL (Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed), given at 2, 4 and 6 months, in the two Swedish pertussis efficacy trials (Table 3).

Table 3 - Comparison of pertussis antibody GMTs obtained one month after a 3-dose primary series given at 2, 4 and 6 months of age with TRIPACEL in the two Swedish efficacy trials with those reported in a Canadian trial with Quadracel

		TRIPACEL Sweden Trial 1	TRIPACEL * Sweden Trial 2	Quadracel Canadian trial
Antibody to		(n = 178)	(n = 80)	(n = 108)
PT	GMT	49.4	51.6	103
	95% CI	44.8 - 54.4	44.8 - 59.5	90.5– 116
FHA	GMT	34.1	57.0	165
	95% CI	30.8 - 37.8	49.1 - 66.2	148 – 184
Pertactin	GMT	116	134	40.5
	95% CI	103 – 132	111 - 163	33.0 – 49.7
FIM	GMT	351	352	332
	95% CI	301 – 408	273 - 454	265 – 417

*The TRIPACEL used in Sweden Trial 2 was a “hybrid” formulation of the currently licensed TRIPACEL which had higher amounts of PT and FHA and contained pertussis antigen concentrations that were similar to those for Quadracel.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Quadracel has not been evaluated for the genotoxic potential.

Carcinogenicity

Quadracel has not been evaluated for the carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Aluminium phosphate
Phenoxyethanol
Polysorbate 80

Manufacturing process residuals include bovine serum albumin, formaldehyde, glutaral, streptomycin sulfate, neomycin and polymyxin B sulfate.

6.2 INCOMPATIBILITIES

Clinical studies have demonstrated that Quadracel may be used to reconstitute freeze-dried Act-HIB.

The vaccine must not be mixed with other vaccines or medicinal products (see Section 4.5 Interactions with other medicines and other forms of interactions).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2° to 8°C. REFRIGERATE. DO NOT FREEZE. Do not use after expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

Single dose pre-filled syringe containing 0.5 mL of vaccine. Pack of 10 syringes.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

20 October 2002

10 DATE OF REVISION

08 July 2026

Summary table of changes

Section Changed	Summary of new information
8	Sponsor address updated