NEW ZEALAND DATA SHEET

NAME OF THE MEDICINE

QUADRACEL®

Pertussis Vaccine-Acellular and Diphtheria and Tetanus Toxoids (Adsorbed) Combined with Inactivated Poliovirus Types 1, 2 and 3 (MRC-5 Cell)

DESCRIPTION

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

Each vial of QUADRACEL contains:

20 µg	pertussis toxoid
20 µg	pertussis filamentous haemagglutinin
5 µg	pertussis fimbriae Types 2+3
3 µg	pertussis pertactin
≥30 IU (15 LfU)	diphtheria toxoid
≥40 IU (5 LfU)	tetanus toxoid
40 DagU	poliovirus inactivated type 1, MRC-5 (Mahoney)
8 DagU	poliovirus inactivated type 2, MRC-5 (MEF1)
32 DagU	poliovirus inactivated type 3, MRC-5 (Saukett)
1.5 mg	aluminium phosphate
0.6% v/v	phenoxyethanol
≤0.02%	polysorbate 80
≤50 ng	albumin – bovine serum
<4 pg	polymyxin B sulfate
<4 pg	neomycin
≤0.02%	formaldehyde
≤0.1%	glutaraldehyde

Water for injections to 0.5 mL

This product does not contain thiomersal.

The manufacture of this product includes exposure to bovine 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.

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

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

Inactivated Poliovirus (Diploid Cell Origin) – IPV (sometimes referred to as e-IPV), is an enhanced formaldehyde-inactivated product, which has a higher potency than the original IPV. The three poliovirus types are propagated in MRC-5 cells.

The 5 component pertussis antigens, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae 2 + 3 (FIM), contained in QUADRACEL are the same as those in TRIPACEL, POLIACEL, 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 POLIACEL and QUADRACEL have pertussis formulations that are similar to PEDIACEL. QUADRACEL contains DTPa combined with inactivated poliovirus vaccine (IPV). POLIACEL consists of Act-HIB reconstituted with QUADRACEL resulting in a combination of vaccine antigens that are similar to the fully liquid PEDIACEL at the time of administration.

PHARMACOLOGY

CLINICAL TRIALS

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 1.

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 1: 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 2).

Table 2. 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

Antibody to		TRIPACEL Sweden Trial 1 (n = 178)	TRIPACEL * Sweden Trial 2 (n = 80)	QUADRACEL Canadian trial (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
FIM	GMT	351	352	332
	95% CI	301 – 408	273 – 454	265 - 417
Pertactin	GMT	116	134	40.5
	95% CI	103 – 132	111 –163	33.0 – 49.7

Note: * 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.

INDICATIONS

QUADRACEL is indicated for primary immunisation of children from the age of 2 months to 12 months against diphtheria, tetanus, whooping cough, 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.

CONTRAINDICATIONS

Allergy to any component of QUADRACEL (see components listed in DESCRIPTION) or an anaphylactic or other allergic reaction to a previous dose of DTP, TRIPACEL, IPV or to a previous dose of this vaccine are contraindications to vaccination.

Vaccination should be postponed in cases of acute or febrile disease.

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.

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.

PRECAUTIONS

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

- temperature of ≥40.5°C within 48 hours of a dose of QUADRACEL, 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 crying lasting ≥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.

When immunisation with pertussis vaccine is contraindicated, immunisation against diphtheria, tetanus, poliomyelitis and invasive Hib disease, may be continued with Adsorbed Diphtheria and Tetanus Vaccine and Inactivated Poliovirus Vaccine at separate sites and with separate syringes. 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.

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

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.

Parents of infants and children with a personal or family history 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 a child with a personal history of convulsions.

Before administration of QUADRACEL, health-care providers should inform the patient, parent or guardian of the benefits and risks of immunisation, inquire about the recent health status of the patient and comply with any local requirements regarding information to be provided to the patient before immunisation and the importance of completing the immunisation series.

It is extremely important when a child returns for the next dose in the series that the patient, parent or guardian should be questioned concerning any symptoms and/or signs of an adverse reaction after the previous dose of vaccine.

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

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

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

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.

Do not administer by intradermal or intravenous injection. Ensure that the needle does not enter a blood vessel.

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

Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of the risk of haemorrhage.

QUADRACEL should not be administered into the buttocks due to the varying amount of fatty tissue in this region, nor by the intradermal route, since these methods of administration may induce a weaker immune response.

Use a separate sterile needle and syringe, or a sterile disposable unit, for each individual patient to prevent disease transmission.

Effects on Fertility

QUADRACEL has not been evaluated for the effects on fertility.

Use in pregnancy (Category B2)

Not applicable. QUADRACEL should not be used in adults.

Use in lactation

Not applicable. QUADRACEL should not be used in adults.

Use in the elderly

QUADRACEL should not be used in adults.

Paediatric use

QUADRACEL should not be administered to children after their seventh birthday or to adults because the quantity of diphtheria toxoid and pertussis antigens may provoke enhanced local reactions, fever and malaise.

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.

Genotoxicity

QUADRACEL has not been evaluated for the genotoxic potential.

Carcinogenicity

QUADRACEL has not been evaluated for the carcinogenic potential.

Effects on Laboratory Tests

Interference of QUADRACEL with laboratory tests has not been studied.

INTERACTIONS WITH OTHER MEDICINES

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. A combination vaccine pack, POLIACEL is provided for this purpose. 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. MMR and hepatitis B vaccine may be administered simultaneously with QUADRACEL for children who are the recommended age to receive them.

Children receiving immunosuppressive therapy may have a reduced response to active immunisation procedures.

As with other intramuscular injections, QUADRACEL should be given with caution to children on anticoagulant therapy.

ADVERSE EFFECTS

Clinical Trials Experience

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 3.

Table 3. 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 multicentre 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 have been reported in post-marketing experience with component acellular pertussis combination vaccines and other tetanus toxoid-, diphtheria toxoid-, acellular pertussis-, and polio-containing vaccines.

Application Site Disorders:

Very Rare (<1/10,000)	the following have been reported following administration of tetanus and/or diphtheria toxoid and/or pertussis and/or Act-HIB-containing vaccines: granuloma or sterile abscess at vaccination site, painless circumferential limb swelling following booster doses which resolves spontaneously, oedema of the lower extremities with cyanosis or transient purpura.

Body as a Whole - General Disorders:

Rare (< 1/1,000 to ≥ 1/10,000)	hypotonic/hyporesponsive episodes*, unusual high-pitched or inconsolable crying
Very Rare (<1/10,000)	the following have been reported following administration of tetanus and/or diphtheria toxoid and/or pertussis and/or Act-HIB-containing vaccines: anaphylactic reaction

Central and Peripheral Nervous System Disorders:

Uncommon (< 1/100 to ≥ 1/1000)	febrile convulsions
Very Rare (<1/10,000)	the following have been reported following administration of tetanus and/or diphtheria toxoid and/or pertussis and/or Act-HIB® containing vaccines: peripheral neuropathies, demyelinating disease, encephalopathy with and without permanent intellectual and/or motor impairment, polyradiculopathies

* Hypotonic/hyporesponsive episodes (infant appears pale, hypotonic (limp) and unresponsive) have not to date been associated with any permanent sequellae

As with any vaccine, there is the possibility that broad use of the vaccine could reveal rare adverse reactions not observed in clinical trials.

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), edema.

Listlessness.

Large injection site reactions (> 50mm), 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 4^{th} and 5^{th} doses.

DOSAGE AND ADMINISTRATION

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 persons after their seventh birthday (see PRECAUTIONS).

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

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

SHAKE THE VIAL WELL to distribute uniformly the suspension before withdrawing each 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. 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). If any other vaccines are administered during the same visit, they must be given at separate sites and with separate syringes.

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

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

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

The parent or guardian of the child should be given a card recording the details of the immunisation. In addition, it is essential that the physician or nurse record the immunisation 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

There are no reports of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Presentation
QUADRACEL is supplied in packs containing 1 vial and in packs containing 5 vials.

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

NAME AND ADRESS OF THE SPONSOR

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MEDICINE CLASSIFICATION

Prescription Medicine

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