Quadracel

MIMS Abbreviated Prescribing Information
Diphtheria toxoid; pertussis vaccine; poliomyelitis vaccine; tetanus toxoid
Sanofi Pasteur
Section: **10(a)** Vaccines - Immunology
Use in pregnancy: B2
Permitted in sport

Use: Primary immunisation against diphtheria, tetanus, pertussis, polio (children 2-12 mnths); booster (4th dose) (children 15 mnths-6 yrs)
Contraindications: Previous vaccine assoc encephalopathy (see full PI)
Precautions: Febrile illness; previous vaccine assoc hypotonia/ hyporesponsiveness, screaming, fits; coagulopathy; immunodeficiency; neurological conditions (incl fits (recent, family history)); malignancy; current polio outbreak (children > 6 mnths)
Adverse Reactions: Local reactions; fits; fever; others, see full PI
Interactions: Imunosupressants incl steroids, irradiation, alkylating agents, cytotoxics, antimetabolites; anticoagulants

Quadracel (Injection) **Rx** (S4) **CMI**
Acellular pertussis vaccine, adsorbed diphtheria, tetanus toxoids, inactivated poliovirus types 1, 2 and 3 (MRC-5 cell); sterile cloudy susp; vials
Dose: Admin IM, pref anterolateral thigh, deltoid (not IV, intradermal, SC, buttocks); do not mix with other vaccines; Primary immunisation: 0.5 mL at 2, 4 and 6 mnths; booster: 0.5 mL
Pack 0.5 mL [1] : $117.19
Pack 0.5 mL [5]

MIMS Full Prescribing Information
MIMS revision date: 01 Apr 2005
Name of the medicine Pertussis vaccine - acellular, diphtheria and tetanus toxoids (adsorbed), inactivated poliovirus types 1, 2 and 3 (MRC-5 cell).
Description Each vial of Quadracel contains: 20 microgram pertussis toxoid;
20 microgram pertussis filamentous haemagglutinin; 5 microgram pertussis fimbriae 2+3; 3 microgram pertussis 69kDa outer membrane protein; ≥ 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 aluminum phosphate; 0.6% v/v phenoxyethanol; ≤ 0.02% polysorbate 80; ≤ 50 nanogram albumin - bovine serum; < 4 picogram polymyxin B sulfate; < 4 picogram neomycin; ≤ 0.02% formaldehyde; ≤ 0.1% glutaraldehyde; water for injections to 0.5 mL.
This product does not contain thimerosal.
The manufacture of this product includes exposure to bovine materials. No evidence exists that any case of vCJD (variant Creutzfeld-Jakob disease) (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 five component pertussis antigens, pertussis toxoid (PT), filamentous haemagglutinin (FHA), 69 kDa membrane protein (pertactin or PRN) and fimbriae 2 and 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 (DTaP), and has lesser amounts of PT and FHA, while Poliacel and Quadracel have pertussis formulations that are similar to Pediacel. Quadracel contains DTaP 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.
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 to 89%) against pertussis disease (defined as at least 21 days of paroxysmal cough with culture, serological or epidemiological 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 three acellular pertussis and one European whole cell DTP (diphtheria pertussis tetanus) vaccine where 20,746 infants received a hybrid formulation of Tripacel (DTaP) 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 (diphtheria tetanus pertussis)-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 to 20 months of age. Serological 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.

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Quadracel **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).

Quadracel **Table 2**

Comparison of pertussis antibody GMTs obtained one month after a three 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
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

Indications Primary immunisation of children from the age of 2 months to 12 months against diphtheria, tetanus, whooping cough, 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 Composition) 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.
Encephalopathy not due to an identifiable cause, occurring within seven 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 The following events require consideration of whether further doses of Quadracel should be given: fever ≥ 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, inconsolable screaming > three hours, within 48 hours;
convulsions, with or without fever, within three 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. Quadracel should be deferred in children with a progressive, evolving or unstable neurological 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 neurological status. In addition, the effect of treatment, if any, can be assessed.
Vaccination with Quadracel may be deferred in children who have had a convulsion in the past three weeks. Immunisation with

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Quadracel should be undertaken when the condition has been controlled or stabilised or resolved.
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.
Do not administer by intradermal or intravenous injection. Ensure that the needle does not enter a blood vessel.
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.
Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of the risk of haemorrhage.
Vaccination should be delayed in the presence of any acute disease.
Vaccination should be postponed in the event of febrile illness. The presence of a minor infection is not a contraindication.
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.
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.
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.
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.
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.
The vaccine must be given intramuscularly, as subcutaneous administration increases the chances of a local reaction.
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.
Elective immunisation of persons over six months of age should be deferred during an outbreak of poliomyelitis because of the risk of provocation paralysis.
Use in the elderly. Quadracel should not be used in adults.
Carcinogenesis, mutagenesis, impairment of fertility. Quadracel has not been evaluated for carcinogenicity, mutagenicity or impairment of fertility.
Use in pregnancy. (Category B2)
Quadracel should not be used in adults.
Use in lactation. Quadracel should not be used in adults.
Use in children. See Dosage and Administration.
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 five 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 (measles mumps rubella) or hepatitis B vaccine. The Australian Immunisation Handbook 2000 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 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 to 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.

Quadracel **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[Ψ]	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[Ψ]	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	0.0	0	0

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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

* interval of time in hours following vaccination
Ψ redness or swelling ≥ 35 mm
§ fever ≥ 40.0

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 US National Institutes of Health (NIH), thirteen different formulations of acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP), 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 to 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 DTaP. It was found that large injection site reactions occurred more frequently after the fifth dose of DTaP 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 DTaP. In 146 recipients who received five doses with different DTaP vaccines, four (2.7%) children were reported to have such swelling. In all reports the swelling subsided spontaneously and completely, without sequelae.

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.

Quadracel **Table 4**

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 sequelae

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

Dosage and administration For primary immunisation of infants the following routine Quadracel immunisation schedule is

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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.
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 doctor 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.
Do not inject intravenously.

Overdosage There are no reports of overdosage.

Presentation Injection, 5 mL (sterile, cloudy, uniform suspension): 1's; 5's (vials).

Storage Store at 2° to 8°C. Refrigerate. Do not freeze. Do not use after expiry date.

Poison Schedule S4.

Source Reference Date of TGA approved information: 20/04/2004

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