QUADRACEL®

Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine

For Active Immunization against Diphtheria, Tetanus, Whooping Cough and Poliomyelitis

DESCRIPTION

QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine], as supplied by Aventis Pasteur Limited, is a sterile, uniform, cloudy, white to off-white (yellow tinge) suspension.

Each dose (0.5 mL) contains:

pertussis toxoid (PT)	20 µg
filamentous haemagglutinin (FHA)	20 µg
fimbrial agglutinogens 2 + 3 (FIM)	5 µg
pertactin (PRN)	3 µg
diphtheria toxoid	15 Lf
tetanus toxoid	5 Lf
poliovirus type 1 (Mahoney)	40 D-antigen units
poliovirus type 2 (MEF1)	8 D-antigen units
poliovirus type 3 (Saukett)	32 D-antigen units
aluminum phosphate	1.5 mg
2-phenoxyethanol (not as a preservative)	0.6% v/v
polysorbate 80	10 ppm (by calculation)
bovine serum albumin	≤50 ng

trace amounts of formaldehyde

trace amounts of polymyxin B and neomycin may be present from the cell growth medium

INDICATIONS

QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] is indicated for the primary immunization of infants, at or above the age of two months and as a booster in children up to their 7th birthdays against diphtheria, tetanus, whooping cough and poliomyelitis.

When both vaccines are indicated, QUADRACEL® may be used to reconstitute Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)] for simultaneous administration of all 5 antigens in a single injection. QUADRACEL® must **not** be mixed in the same syringe with any vaccines other than Act-HIB®.

Children who have had tetanus, diphtheria or pertussis should still be immunized since these clinical infections do not always confer immunity.[1]

Premature infants whose clinical condition is satisfactory should be immunized with full doses of vaccine at the same chronological age and according to the same schedule as full-term infants, regardless of birth weight.[1,2]

Human Immunodeficiency Virus (HIV) Infected Persons

HIV-infected persons, both asymptomatic and symptomatic, should be immunized against diphtheria, pertussis, tetanus and poliomyelitis according to standard schedules.[1]

CONTRAINDICATIONS

Immunization with QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] should be deferred in the presence of any acute illness, including febrile illness to avoid superimposing potential adverse effects from the vaccine on the underlying illness or mistakenly identifying a manifestation of the underlying illness as a complication of vaccine use. A minor illness such as mild upper respiratory infection is not reason to defer immunization.[1]

Allergy to any component of QUADRACEL®, or its container, or an anaphylactic or other allergic reaction to a previous dose of QUADRACEL® is a contraindication to vaccination with QUADRACEL®. QUADRACEL® may contain trace amounts of antibiotics (polymyxin B and neomycin) to which vaccinees may be hypersensitive. (See components listed in DESCRIPTION, and HOW SUPPLIED.)

QUADRACEL® should not be administered to children after their 7th birthdays or to adults because the quantity of diphtheria toxoid and pertussis antigens may provoke enhanced local reactions, fever and malaise.

Hypotonic-hyporesponsive episodes rarely follow vaccination with whole-cell pertussis-containing DTP vaccines and occur even less commonly after acellular pertussis-containing DTP and DT vaccines. The National Advisory Committee on Immunization (NACI) states that a history of hypotonic-hyporesponsive episodes is not a contraindication to the use of acellular pertussis vaccines, but recommends precaution in these cases.[1]

WARNINGS

Intramuscular injections should be given with care in patients suffering from coagulation disorders or on anticoagulant therapy because of the risk of hemorrhage.[1]

QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] should not be administered into the buttocks due to the varying amount of fatty tissue in this region or by the intradermal route, since these methods of administration may induce a weaker immune response.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response.[1] If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment.[1]

Whole-cell pertussis DTP vaccine has been associated with acute encephalopathy.[3] A 10-year follow-up to the UK National Childhood Encephalopathy Study (NCES) of children who experienced acute neurologic disorders in infancy concluded that serious acute neurologic illness increased the risk of chronic neurologic disease or death.[4]

A committee of the US Institute of Medicine (IOM) has concluded that the evidence is consistent with a causal relationship between whole-cell pertussis DTP vaccine and acute neurologic illness[4] and that, because whole-cell pertussis DTP vaccine may cause acute neurologic illness, whole-cell pertussis DTP vaccine may also cause chronic neurologic disease in the context of the NCES report (that is, in children whose chronic nervous system dysfunctions followed a serious acute neurologic illness that occurred within 7 days after receiving DTP vaccine).[5] However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell pertussis DTP vaccine increased the overall risk of chronic neurological disease.[5] (See ADVERSE REACTIONS.)

Infants and children with demonstrated or possible underlying neurologic conditions seem to be at enhanced risk of manifesting of the underlying neurologic disorder within 2 or 3 days following whole-cell pertussis DTP vaccine immunization. Whether vaccination merely 'unmasks' such underlying neurologic conditions, or whether there is a true cause-and-effect relationship between vaccination and such neurological conditions is unknown. Whether to administer QUADRACEL® to children with proven or suspected underlying neurological disorders must be decided on an individual basis after consideration of the risks and benefits. An important consideration is the current local incidence of pertussis.[6] NACI states that deferral of pertussis immunization for children with evolving neurologic conditions is no longer necessary because of the availability of acellular pertussis vaccines such as that contained in QUADRACEL®.[1]

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

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

PRECAUTIONS

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.[1] Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings including proper airway management.[1,2]

For instructions on recognition and treatment of anaphylactic reactions see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Before administration, take all appropriate precautions to prevent adverse reactions. This includes a review of the patient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization, and current health status.

Before administration of QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine], health-care providers should inform the parent or guardian of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements regarding information to be provided to the patient before immunization and the importance of completing the immunization series.

It is extremely important that, before immunizing a child, the parent or guardian be questioned concerning any symptoms and/or signs of an adverse reaction after a previous dose of vaccine. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

High fever within 48 hours of a previous dose of vaccine, attributed to immunization and not to intercurrent illness, indicates the likelihood of recurrence of fever with subsequent doses. Febrile convulsions may be more likely in a susceptible child who develops high fever.[1] Parents of children who may be at increased risk of a seizure after pertussis vaccination, such as from a personal or family history of seizures, should be informed of the risks and benefits of pertussis immunization in these circumstances. For infants or children at higher risk of seizures than the general population, an antipyretic (i.e., acetaminophen) in the dosage recommended in its prescribing information, may be administered at the time of vaccination with QUADRACEL® and for 24 hours thereafter, to reduce the possibility of post-vaccination fever. Caregivers should be aware that antipyretic therapy may also obscure fever caused by concomitant, unrelated infection.[2]

Do not inject into a blood vessel.

Aseptic technique must be used. Use a separate sterile needle and syringe or a sterile disposable unit, for each individual dose to prevent disease transmission.

Frequent booster doses of tetanus or diphtheria toxoids in the presence of adequate or excessive serum levels of tetanus or diphtheria antitoxins have been associated with increased incidence and severity of reactions including Arthus-type reactions and should be avoided.

Drug Interactions

Administering the most widely used live and inactivated vaccines during the same patient visit has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately.[1,7] Simultaneous administration using separate syringes at separate sites is suggested, particularly when there is concern that an individual may not return for subsequent vaccination. Clinical trials have shown that QUADRACEL® is safe and immunogenic if administered at the same time as other vaccines (including meningococcal C conjugate vaccine[8] and hepatitis B vaccine[9]) provided separate syringes are used for each vaccine and each vaccine is administered at separate sites. When both vaccines are indicated, QUADRACEL® may be used to reconstitute Act-HIB® for administration of both vaccines in a single injection.

Topical use of lidocaine-prilocaine to reduce injection site pain has no adverse effect on antibody response to QUADRACEL®.[9]

ADVERSE REACTIONS

In clinical trials conducted in Canada, more than 3,000 children have received QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] alone or used to reconstitute Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)]. Adverse reactions are generally mild and self-limiting. Serious adverse events are rare.

Local Reactions

In a randomized, controlled clinical trial conducted in Canada, 113 infants were immunized with QUADRACEL® at 2, 4 and 6 months of age.[10] In addition, 104 of these children were immunized as toddlers at 18 months.[10] In another randomized, controlled Canadian trial, 163 children 4 to 6 years of age, previously immunized with a whole-cell DTP vaccine, were immunized with QUADRACEL®.[10] Local reactions from these trials are shown in Table 1. Local reactions were generally mild and occurred in approximately a quarter of infants receiving QUADRACEL®. The size and frequency of the injection site reactions was higher after the 4th and 5th doses, however severe tenderness did not increase. Similar observations have been made with other acellular pertussis combination (DTaP) vaccines.[11] In a recent study involving 800 children 4 to 6 years old immunized at public health units in British Columbia, the extent of local reactions 48 to 96 hours after immunization was evaluated by means of a cross-sectional telephone survey. Among the 398 children who had previously received PENTACEL® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Reconstituted with Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] at 2, 4, 6 and 18 months of age, 24% experienced moderate to severe redness (≥46 mm), 16% reported moderate to severe swelling (≥46 mm), and only 7% had severe tenderness or marked limitation of movement.[12]

TABLE 1: FREQUENCY OF LOCAL REACTIONS 24 HOURS AFTER VACCINATION WITH QUADRACEL® [10]

Reaction	2 Months* (n = 113)	4 Months* (n = 111)	6 Months* (n = 111)	18 Months* (n = 104)	4-6 Years** (n = 130)
Redness					
Any	0.9	8.1	12.6	18.3	18.5
≥35 mm	0	0	0	1.9	13.8
Swelling					
Any	5.3	3.6	7.2	13.5	18.5
≥35 mm	2.7	0.9	0.9	4.8	16.2
Tenderness					
Any	18.6	18	9	28.9	74.6
Severe	1.8	3.6	0	0	0.8
Any Local	20.4	26.1	19.8	40.4	76.9
Severe Local	4.4	4.5	0.9	5.8	20.8

* Act-HIB®was administered concurrently at a separate site.

** Previously immunized with a whole-cell DTP vaccine.

Systemic Reactions

In the same clinical trials as indicated in Table 1, the rate of systemic adverse events seen in infants and toddlers receiving QUADRACEL® was substantially lower than observed in those receiving whole-cell pertussis vaccines. Rates of any systemic reactions for children receiving QUADRACEL® are listed in Table 2.

TABLE 2: FREQUENCY OF ANY SYSTEMIC REACTION 24 HOURS AFTER VACCINATION WITH QUADRACEL® * [10]

Reaction	2 Months n = 113	4 Months n = 111	6 Months n = 111	18 Months n = 106	4-6 Years** n = 130
Fever >38.0°C	22.1	21.1	18	24	17.3
Fussiness	46	45	35.1	33.7	20
Crying	31	28.8	23.4	19.2	-
Less Active	51.3	27.9	21.6	16.4	23.1
Eating Less	34.5	20.7	16.2	20.2	23.1
Vomiting	8	2.7	6.3	6.7	4.6
Diarrhea	6.2	7.2	9.9	2.9	2.3
Any	77.9	66.7	54.1	55.8	38.5

* Act-HIB® was administered concurrently at a separate site.

** Previously immunized with a whole-cell DTP vaccine.

TABLE 3: ADVERSE EVENTS REPORTED DURING CLINICAL TRIALS AND POST-MARKET SURVEILLANCE OF VACCINES CONTAINING THE ANTIGENS FOUND IN QUADRACEL® [10]

Common (>1/100) (Symptoms usually occur in the first 24 hours and may persist for 24 - 48 hours.)	
Gastrointestinal Disorders	Vomiting, diarrhea
Metabolic and Nutrition Disorders	Decreased feeding
General Disorders and Administration Site Conditions	Fever, redness, tenderness, swelling at the vaccination site
Nervous System Disorders	Irritability, crying, drowsiness
Uncommon (<1/100)	
General Disorders and Administration Site Conditions:	Pallor, listlessness
Rare (<1/1,000)	
Nervous System Disorders	Febrile convulsions,* prolonged or unusual high-pitched crying,* hypotonic-hyporesponsive episodes* (Infant appears pale, hypotonic [limp] and unresponsive to parents. To date, this condition has not been associated with any permanent sequelae.[6,13])
General Disorders and Administration Site Conditions	High fever (>40.5°C)*
Very Rare (<1/10,000)	
General Disorders and Administration Site Conditions	Anaphylactic reaction,† granuloma or sterile abscess at the vaccination site[6]
Nervous System Disorders	Neurological disorders‡ including peripheral neuropathies;[14,15,16] demyelinating diseases (including Guillain-Barré Syndrome);[6,14] encephalopathy, with and without permanent intellectual and/or motor impairment;[4,6] and polyradiculopathies[17] have been reported.

* There are fewer reports of these conditions since the introduction of acellular pertussis vaccines and vaccine combinations.[1,18,19]

† Death following vaccine-caused anaphylaxis has been reported.[14]

‡ The occurrence and background rate of most of these conditions is so low that it may never be possible to accept or reject a causal relationship between these events and immunization. The US IOM has concluded that the evidence favours acceptance of a causal relationship between tetanus toxoid and both brachial neuritis and Guillain-Barré Syndrome.[14]

Sudden infant death syndrome (SIDS) has been reported in temporal relationship to the administration of vaccines containing diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP). Review of the evidence does not indicate a causal relationship between whole-cell DTP vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DTP immunization usually occurs.[4,20] There are limited data relating to SIDS and vaccines containing diphtheria and tetanus toxoids and acellular pertussis vaccines. A committee of the US IOM found no reason to suspect that a causal relationship might exist between DTaP and SIDS when the evidence indicates that none exists with DTwP.[21]

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

Following booster doses, local erythema and swelling are not uncommon and Arthus-type sensitivity may occur. (See PRECAUTIONS.)

Physicians, nurses, and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and report to the Global Pharmacovigilance Department, Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DOSAGE AND ADMINISTRATION

For the routine immunization of infants a single dose of approximately 0.5 mL of QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] is recommended at 2, 4, 6 and 18 months of age.

If for any reason this schedule is delayed, it is recommended that three doses be administered with an interval of two months between doses, followed by a fourth dose administered approximately 6 - 12 months following the third dose.

A booster dose of 0.5 mL should be administered between 4 and 6 years of age (i.e., at the time of school entry). This booster dose is unnecessary if the fourth primary immunizing dose has been administered after the fourth birthday.

A subsequent booster should be administered 10 years later, during adolescence, with Td Adsorbed or with ADACEL® [Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis Vaccine]. Thereafter, routine booster immunizations should be with Td at intervals of 10 years.

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH QUADRACEL®.[1] (See CONTRAINDICATIONS.)

Whenever feasible, QUADRACEL® should be used for all doses in the vaccination series as there are no clinical data to support the use of QUADRACEL® with any other licensed acellular pertussis combination vaccine in a mixed sequence. For situations where a different brand of DTaP or DTaP-IPV vaccine was originally used, or where the brand is unknown, please refer to the latest edition of Health Canada's Canadian Immunization Guide for guidance.

Inspect the vials of vaccine 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 the suspension uniformly. Before withdrawing a dose from a vial, apply a sterile piece of cotton moistened with a suitable antiseptic to the surface of the stopper. Do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit, to administer each individual dose to prevent disease transmission. (See PRECAUTIONS.)

Administer the vaccine **intramuscularly**. The preferred site is into the anterolateral aspect of the mid-thigh (vastus lateralis muscle) or into the deltoid muscle. In children >1 year of age, the deltoid is the preferred site since use of the anterolateral thigh results in frequent reports of limping due to muscle pain.[1]

Do not inject intravenously.

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

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization 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.

STORAGE

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard product if exposed to freezing.

Do not use vaccine after expiration date.

HOW SUPPLIED

Vial 5 x 0.5 mL (Single Dose)

QUADRACEL® is also supplied in packages containing five single-dose vials of Act-HIB® and five x 0.5 mL (single-dose) vials of QUADRACEL® to be used for reconstitution in place of the diluent and sold under the tradename PENTACEL®.

The stoppers of the vials for QUADRACEL® may contain dry natural latex rubber.

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779.

Visit us at www.aventispasteur.com

Full product monograph available on request.

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