PRODUCT MONOGRAPH

QUADRACEL®

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

Suspension for injection

(For active immunization against
Diphtheria, Tetanus, Pertussis and Poliomyelitis)

ATC Code: J07CA02

Sanofi Pasteur Limited
Toronto, Ontario, Canada

Control No.: 14690 **Date of Approval:** August 2011

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intramuscular injection

Dosage Form / Strength

Suspension for injection

Each dose is formulated to contain:

Active Ingredients:

Diphtheria toxoid, tetanus toxoid, acellular pertussis [pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)], inactivated poliomyelitis vaccine (IPV) type 1 (Mahoney), type 2 (MEF-1) and type 3 (Saukett)].

Clinically Relevant Non-medicinal Ingredients

Excipients: Aluminum phosphate (adjuvant), 2-phenoxyethanol, polysorbate 80

Manufacturing process residuals: Bovine serum albumin (BSA), formaldehyde, glutaraldehyde, neomycin and polymyxin B may be present in trace amounts.

For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.

DESCRIPTION

QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] is a sterile, uniform, cloudy, white to off-white suspension of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed separately on aluminum phosphate combined with inactivated poliomyelitis vaccine types 1, 2 and 3 and suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified pertussis antigens (PT, FHA, PRN and FIM).

INDICATIONS AND CLINICAL USE

QUADRACEL® is indicated for primary immunization of infants, from the age of 2 months and in children up to 6 years of age (prior to their 7th birthday), against diphtheria, tetanus, pertussis and poliomyelitis. (See DOSAGE AND ADMINISTRATION.)

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.

According to the National Advisory Committee on Immunization (NACI) children who have had diphtheria, tetanus, or pertussis, should still be immunized since these clinical infections do not always confer immunity. (1)

NACI recommends that Human Immunodeficiency Virus (HIV)-infected persons, both asymptomatic and symptomatic, should be immunized against diphtheria, pertussis, tetanus and poliomyelitis according to standard schedules. (1)

QUADRACEL® is not to be used for the treatment of diseases caused by *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis* or poliovirus infections.

Pediatrics

QUADRACEL® is not indicated for persons less than 2 months of age or persons 7 years of age or older.

Geriatrics

QUADRACEL® is not indicated for use in adult and elderly populations.

CONTRAINDICATIONS

Hypersensitivity

NACI recommends that known systemic hypersensitivity reaction to any component of QUADRACEL® or a life-threatening reaction after previous administration of the vaccine or a vaccine containing one or more of the same components are contraindications to vaccination. (1) (2) (3) (See SUMMARY PRODUCT INFORMATION.) Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such persons may be referred to an allergist for evaluation if further immunizations are considered.

Neurological Disorders

According to the US Advisory Committee on Immunization Practices (ACIP), the following events are contraindications to administration of any pertussis-containing vaccine, (2) 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 neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to persons with such conditions until a treatment regimen has been established and the condition has stabilized.

WARNINGS AND PRECAUTIONS

General

Before administration of QUADRACEL®, health-care providers should inform the parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements with respect to information to be provided to the parent or guardian before immunization and the importance of completing the immunization series.

It is extremely important that 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.)

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. (3)

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

Administration Route-Related Precautions: Do not administer QUADRACEL® by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Intradermal or subcutaneous routes of administration are not to be utilized.

QUADRACEL® should not be administered into the buttocks.

Febrile or Acute Disease: ACIP recommends that vaccination should be postponed in cases of acute or febrile disease. (2) (3) However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

ACIP recommends that 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. (2)

- Temperature of ≥40.5°C (105°F) 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.

Hematologic

Because any intramuscular injection can cause an injection site hematoma in persons with any bleeding disorders, such as hemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with QUADRACEL® should not be administered to such persons unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection.

Immune

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Hypersensitivity reactions may occur following the use of QUADRACEL® even in persons with no prior history of hypersensitivity to the product components. Cases of allergic or anaphylactic reaction have been reported after receiving some preparations containing diphtheria and tetanus toxoids and/or pertussis antigens. (4)

As recommended by NACI 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) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

According to NACI immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. (1) Nevertheless, ACIP advises that vaccination of persons with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited. (2)

Neurologic

A review by the US Institute of Medicine (IOM) found evidence for a causal relationship between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). (5) ACIP recommends that 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 potential benefits and possible risks. (2)

ACIP recommends that for infants or children at higher risk for seizures than the general population that 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. (2)

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. NACI states that a history of HHEs is not a contraindication to the use of acellular pertussis vaccines but recommends caution in these cases. (1)

Pregnant Women:

The vaccine should not be administered to pregnant women.

Nursing Women:

The vaccine should not be administered to nursing women.

Pediatrics

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

In clinical trials conducted in Canada, more than 3,000 children have received QUADRACEL® alone or used to reconstitute Act-HIB®. Adverse reactions are generally mild and self-limiting. Serious adverse events are rare.

In a randomized, controlled clinical trial conducted in Canada, 113 infants were immunized with QUADRACEL® at 2, 4 and 6 months of age. In addition, 104 of these children were immunized as toddlers at 18 months. (6) (7) (8) In another randomized, controlled Canadian trial, 130 children 4 to 6 years of age, previously immunized with a whole-cell DTP vaccine, were immunized with QUADRACEL®. (9) Table 1 below provides a summary of the frequency of solicited reactions observed within 24 hours following each dose of QUADRACEL®. Injection site 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. (10)

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 Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine 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. (11)

Table 1: Frequency (%) of Solicited Reactions Following a Single Dose of QUADRACEL® Administered at 2, 4, 6, 18 Months and 4-6 Years of Age (6) (7) (8) (9)

Solicited Reactions	**2 Months*** (6) **(N = 113)** (8)	**4 Months*** (6) **(N = 111)** (8)	**6 Months*** (6) **(N = 111)** (8)	**18 Months*** (7) **(N = 104)**	**4-6 Years†** (9) **(N = 130)**
Injection Site Reactions					
Redness/Erythema	0.9	8.1	12.6	18.3	18.5
Swelling	5.3	3.6	7.2	13.5	18.5
Tenderness	18.6	18.0	9.0	28.8	74.6
Systemic Reactions					
Fever >38.0°C	22.1	21.1	18.0	24.0	17.3
Less Active	51.3	27.9	21.6	16.3	23.1
Eating Less	34.5	20.7	16.2	20.2	23.1
Fussiness	46.0	45.0	35.1	33.7	20.0
Crying	31.0	28.8	23.4	19.2	N.S.‡
Diarrhea	6.2	7.2	9.9	2.9	2.3
Vomiting	8.0	2.7	6.3	6.7	4.6

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

† Previously immunized with a whole-cell DTP vaccine.

‡ N.S.: not solicited

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. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to QUADRACEL®.

Immune system disorders

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

Psychiatric disorders

Screaming

Nervous system disorders

Somnolence, convulsion, febrile convulsion, HHE, hypotonia

Cardiac disorders

Cyanosis

Vascular disorders

Pallor

General disorders and administration site conditions

Injection site reactions (including inflammation, mass, abscess and sterile abscess), edema.

Very rarely, 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/DTaP vaccine, with a greater risk following the 4^{th} and 5^{th} doses.

Listlessness

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, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

Vaccine-Drug Interactions

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

Topical use of lidocaine-prilocaine patches to reduce injection site pain has no adverse effect on antibody response to QUADRACEL®. (12)

Concomitant Vaccine Administration

NACI states that 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) (2) Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination. Simultaneous administration of childhood vaccines such as QUADRACEL®, Hib, MMR, varicella, pneumococcal conjugate and hepatitis B vaccines, is encouraged for children who are at the recommended age to receive these vaccines and for whom no contraindications exist.

Clinical trials have shown that QUADRACEL® is safe and immunogenic if administered at the same time as other vaccines (including meningococcal C conjugate vaccine (13) and hepatitis B vaccine). When both vaccines are indicated, QUADRACEL® may be used to reconstitute Act-HIB® for administration of both vaccines in a single injection.

NACI recommends that unless otherwise indicated, vaccines administered simultaneously should be given using separate syringes at separate sites.

QUADRACEL® should not be mixed in the same syringe with other parenterals, with the exception of Act-HIB® when both vaccines are indicated.

DOSAGE AND ADMINISTRATION

Recommended Dose

For routine immunization, QUADRACEL® is recommended as a 4-dose series, with a single dose of 0.5 mL of QUADRACEL® at 2, 4, 6 and 18 months of age.

If for any reason this schedule is delayed, it is recommended that 3 doses be administered with an interval of 2 months between each dose, followed by a fourth dose administered approximately 6 to 12 months after the third dose.

Whenever feasible, QUADRACEL® should be used for all 4 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, DTaP-IPV or DTaP-IPV/Hib vaccine was originally used, or where the brand is unknown, please refer to the latest edition of the Canadian Immunization Guide.

NACI recommends that 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)

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

In compliance with NACI's recommended immunization schedule, the childhood immunization series should be completed with a single booster dose of 0.5 mL of QUADRACEL® administered between 4 and 6 years of age (i.e., at the time of school entry). Alternatively, ADACEL® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed] and IPV may be administered at separate sites for this booster at 4 to 6 years of age. This booster dose is unnecessary if the fourth dose of QUADRACEL® was administered after the child's fourth birthday. (1)

QUADRACEL® should not be administered to persons less than 2 months or to persons 7 years of age or older. (See INDICATIONS AND CLINICAL USE.)

Administration

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

Shake the vial well until a uniform, cloudy, suspension results. Cleanse the vial stopper with a suitable germicide prior to withdrawing the dose. Do not remove either the stopper or the metal seal holding it in place.

Aseptic technique must be used. Use a separate, sterile syringe and needle, or a sterile disposable unit, for each individual patient to prevent disease transmission. Needles should not be recapped but should be disposed of according to biohazard waste guidelines.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. Administer the total volume of 0.5 mL **intramuscularly** (I.M.). In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for injection.

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.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Diphtheria and Tetanus: Strains of *C. diphtheriae* that produce diphtheria toxin can cause severe or fatal illness characterized by membranous inflammation of the upper respiratory tract and toxin-induced damage to the myocardium and nervous system. Protection against disease attributable to *C. diphtheriae* is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (2) (3) Levels of 1.0 IU/mL have been associated with long-term protection. (3)

Tetanus is an acute and often-fatal disease caused by an extremely potent neurotoxin produced by *C. tetani*. The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. Protection against disease attributable to *C. tetani* is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. (2) (3) A tetanus antitoxin level of at least 0.1 IU/mL as measured by the ELISA used in clinical studies of QUADRACEL® is considered protective for tetanus. Levels of 1.0 IU/mL have been associated with long-term protection.

In a clinical trial in Canada, after 4 doses of QUADRACEL®, 100% (N = 104) of immunized children achieved serum diphtheria and tetanus antitoxin levels of at least 0.01 IU/mL. 99.0% and 100% of these children achieved serum antitoxin levels of at least 0.1 IU/mL for diphtheria and tetanus, respectively. (6) (7) (8) After a booster dose of QUADRACEL® at 4 to 6 years of age, in a clinical trial in Canada, 100% (N = 125) of children achieved serum diphtheria and tetanus antitoxin levels of at least 0.1 IU/mL. (9)

After completion of the childhood immunization series, circulating antibodies to diphtheria and tetanus toxoids gradually decline but are thought to persist at protective levels for up to 10 years. NACI recommends diphtheria and tetanus toxoids boosters every 10 years. (1)

Pertussis: Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined. The mechanism of protection from *B. pertussis* disease is not well understood. However, in a clinical trial in Sweden (Sweden I Efficacy Trial), pertussis components in QUADRACEL® (i.e., PT, FHA, PRN and FIM) have been shown to prevent pertussis in infants with a protective efficacy of 85.2% using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiological link to a confirmed case). In the same study, the protective efficacy against mild disease was 77.9%.

Minimum serum antibody levels to specific pertussis vaccine components that confer protection against the development of clinical pertussis have not been identified. Nevertheless, a number of studies have demonstrated a correlation between the presence of serum antibody responses to pertussis vaccine components and protection against clinical disease. (14) (15) (16) (17) (18) (19) In a controlled clinical trial in Sweden (Sweden II Trial), the efficacy of a DTaP vaccine with the same formulation of five pertussis antigens as QUADRACEL® was demonstrated to provide a two-fold to three-fold higher protection against pertussis with any cough compared to the vaccine containing three pertussis antigens. The observed difference supports the role of FIM in the protection against colonization of *B. pertussis* and mild disease. (20)

In a recent publication, Bettinger *et al* reviewed pertussis cases during 1991-2004 using surveillance data from the Canadian Immunization Monitoring Program, Active (IMPACT), an active surveillance network based in 12 pediatric tertiary-care hospitals across Canada. (21) Overall, the data show declining rates of pertussis during the years in which PENTACEL® (QUADRACEL® in combination with Act-HIB®) has been used (1999-2004) compared to the period when whole-cell pertussis vaccine was used (1991-1996). Among children 1-4 years of age, incidence of pertussis declined 85%. Data from the Northwest Territories, (22) Newfoundland and Labrador (23) and British Columbia (24) support national and IMPACT data demonstrating a progressive decline of pertussis cases among infants and children through 9 years of age.

Poliomyelitis: Inactivated poliomyelitis vaccine induces the production of detectable levels of neutralizing antibodies against each type of poliovirus. The detection of type-specific neutralizing antibodies has been correlated with protection. (25) A clinical study of QUADRACEL® in 104 Canadian infants showed that, after 4 doses, 100% of vaccinated children achieved protective antibody levels (titres ≥1:8) to poliovirus types 1, 2, and 3 following the primary series. (6) (7) (8) In a clinical study in Canada, 100% (N = 125) of children immunized with QUADRACEL® at 4 to 6 years of age achieved protective antibody levels (titres ≥1:8) to poliovirus types 1, 2, and 3. (9)

Duration of Effect

To ensure optimal protection during childhood, 4 consecutive doses should be given at 2, 4, 6 and 18 months of age. A booster with a vaccine containing diphtheria, tetanus, acellular pertussis with or without IPV is required at 4 to 6 years.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do not freeze**. Discard product if exposed to freezing (≤ 0°C). QUADRACEL® has been shown to remain stable at temperatures above 8°C and up to 25°C, for a maximum of 3 days (72 hours). These data are not recommendations for shipping or storage, but may guide decision for use in case of temporary temperature excursions.

Do not use vaccine after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The stopper of the vial for QUADRACEL® does not contain latex (natural rubber).

1 dose package (1 x 0.5 mL vial)

5 dose package (5 x 0.5 mL vials)

QUADRACEL® is also supplied in 5 dose package containing QUADRACEL® (5 x 0.5 mL vials) for reconstitution of Act-HIB® (5 x 1 dose vials) and sold under the tradename PENTACEL®.

COMPOSITION

QUADRACEL® is a sterile, uniform, cloudy, white to off-white suspension.

Each 0.5 mL dose is formulated to contain:

Active Ingredients

Diphtheria Toxoid	15 Lf
Tetanus Toxoid	5 Lf
Acellular Pertussis	
Pertussis Toxoid (PT)	20 µg
Filamentous Haemagglutinin (FHA)	20 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Inactivated Poliomyelitis Vaccine	
Type 1 (Mahoney)	40 D-antigen units
Type 2 (MEF-1)	8 D-antigen units
Type 3 (Saukett)	32 D-antigen units

Other Ingredients

Excipients:

Aluminum Phosphate (adjuvant) (aluminum 0.33 mg)	1.5 mg
2-phenoxyethanol	0.6% v/v
Polysorbate 80	10 ppm (by calculation)

Manufacturing Process Residuals:

BSA, formaldehyde, glutaraldehyde, neomycin and polymyxin B may be present in trace amounts.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of August 2011.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R12-0811 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine

Product Characteristics

QUADRACEL® is a sterile, uniform, cloudy, white to off-white suspension of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed on aluminum phosphate combined with inactivated poliomyelitis vaccine types 1, 2 and 3 and suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified pertussis antigens (PT, FHA, PRN and FIM).

C. diphtheriae is grown in modified Mueller's growth medium. (26) After purification by ammonium sulphate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered. *C. tetani* is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (27) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulphate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The 5 acellular pertussis vaccine components are produced from *B. pertussis* cultures grown in Stainer-Scholte medium (28) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. The FIM components are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde. The residual aldehydes are removed by diafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

Inactivated poliomyelitis vaccine is a highly purified, inactivated poliovirus vaccine grown in cultures of MRC-5 cells, a line of normal human diploid cells, by the microcarrier technique. (29) (30) The cells are grown in CMRL 1969 medium, supplemented with calf serum. For viral growth, the culture medium is replaced by Medium 199, without calf serum.

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by two liquid chromatography steps. The monovalent viral suspensions are then inactivated with formaldehyde. After inactivation has been confirmed, one or more lots of inactivated monovalent virus are pooled, concentrated and equilibrated with phosphate buffered saline to produce an inactivated monovalent concentrate. The monovalent concentrates of each type are then combined to produce a trivalent concentrate.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined into an intermediate concentrate. IPV is added and the vaccine is diluted to a final concentration of 2 doses/mL.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig potency test. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized guinea pigs to PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). The antigenicity of the IPV is evaluated by the antibody response in rats measured by virus neutralization.

CLINICAL TRIALS

Four pivotal clinical trials (Sweden Trial I, Sweden Trial II, PB9502 and PB9503) conducted in Sweden and in Canada, provide the clinical basis for the licensure of QUADRACEL® in Canada. (See Table 2.)

Table 2: Summary of Demographics and Study Design of the Trials with QUADRACEL®

Study	Study Design	Dosage and Route of Administration	Vaccination Schedule/ Study Population*	Gender
Sweden I (31) (32)	Randomized, placebo-controlled, double-blind, efficacy and safety trial with one whole cell DTP, two DTaP vaccines (2 and 5-component)	0.5 mL I.M.	2, 4, 6 months of age N = 2,587	Males N = 1,330 Females N = 1,257
Sweden II (20)	Randomized, controlled, double-blind, multicentre efficacy trial with one whole cell DTP and three DTaP vaccines (2, 3 and 5-component)	0.5 mL I.M.	2, 4, 6 months of age N = 2,551 and 3, 5, 12 months of age N = 18,196	Males N = 10,590 Females N = 10,157
PB9502 (6) (7) (8)	Randomized, controlled, single-blinded multicentre safety and immunogenicity comparative trial with QUADRACEL® + Act-HIB®†.	0.5 mL I.M.	2, 4, 6 and 18 months of age N = 113	Males N = 63 Females N = 50
PB9503 (9)	Randomized, controlled, double-blinded multicentre safety and immunogenicity trial with QUADRACEL®	0.5 mL I.M.	4 to 6 years of age N = 131	Males N = 71 Females N = 60

* Number enrolled.

† Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)], given at separate site

Sweden I Efficacy Trial

A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in Sweden from 1992 - 1995 (Sweden I Efficacy Trial) under the sponsorship of the National Institute of Allergy and Infectious Diseases (NIAID). (31) (32) A total of 9,829 infants received 1 of 4 vaccines: TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed], the five-component DTaP vaccine that contains the same antigens (but with a lower content of PT and FHA per dose) present in QUADRACEL® (N = 2,587); a two-component DTaP vaccine (N = 2,566); a whole-cell pertussis DTP vaccine from the U.S. (N = 2,102); or DT vaccine (Swedish National Bacteriological Laboratory) as placebo (N = 2,574). Infants were immunized at 2, 4 and 6 months of age. The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of TRIPACEL® against pertussis after 3 doses of vaccine using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 85.2% (95% confidence interval [CI] 80.6 to 88.8). (32) The protective efficacy of TRIPACEL® against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2). (See Table 3.) Protection against pertussis by TRIPACEL® was sustained for the 2-year follow-up period. (31) (32) (See Table 3.)

Table 3: Vaccine Efficacy Against Pertussis Infection of Varying Clinical Severity (32)

Clinical Severity of Pertussis	Vaccine Efficacy (%) of TRIPACEL® (n = 2,551) Compared to DT Control (n = 2,539)
cough ≥1 day	77.9
cough >7 days	78.4
cough ≥21 days	81.4
cough ≥30 days	87.3
paroxysmal cough ≥14 days	82.3
paroxysmal cough ≥21 days	85.1

Another arm of the trial (32) looked at the persistence of the protection provided by this TRIPACEL® formulation compared to a placebo. High levels of protection were sustained for TRIPACEL® over the entire 2-year follow-up period.

Table 4: Duration of Vaccine Efficacy for TRIPACEL® Compared to Placebo (32)

Vaccine Efficacy (%) Compared to DT (Placebo n = 2,068)	
Interval Since Third Dose (in days)	**TRIPACEL® (n = 2,069)**
0-89	95
90-179	83.6
180-269	86.7
270-359	84.4
360-449	92.1
450-539	78.3
540-629	86.4
630-719	81.3

The incidence of injection site and systemic reactions after administration of TRIPACEL® was comparable to the DT control group. (32)

A sub-study of this trial looked specifically at immunized children exposed to pertussis from other members of their households. (14) This formulation of TRIPACEL® was more efficacious than any of the other acellular and whole-cell vaccines studied. There was a correlation between clinical protection and the presence of anti-PRN, anti-FIM and anti-PT antibodies respectively in the serum of immunized children.

Sweden II Efficacy Trial

A second NIAID-sponsored, prospective, randomized, double-blinded efficacy trial was conducted in Sweden (Sweden II Efficacy Trial) from 1993 to 1996. Infants (N = 82,892) were randomized to receive one of four vaccines: a two-component acellular DTaP vaccine (N = 20,697); a three-component acellular DTaP vaccine (n = 20,728); the same formulation of the five-component acellular DTaP vaccine that is contained in QUADRACEL® (N = 20,747); or a European whole-cell DTP vaccine (N = 20,720). (20) Vaccination occurred at 3, 5 and 12 months of age (88% of participants) or at 2, 4 and 6 months of age (12% of participants). The relative risk of typical pertussis (culture-confirmed *B. pertussis* infection with at least 21 days of paroxysmal cough) was 0.85 and 1.38 among children given the five-component and three-component vaccines, respectively, as compared with those given the whole-cell vaccine. The relative risk of typical pertussis was 0.62 among children given the five-component vaccine as compared with the three-component vaccine. The absolute efficacy of the three-component vaccine, when tested in an earlier double-blinded randomized placebo-controlled trial in Italy was

84% (95% CI, 76-89). (33) Although the absolute efficacy of the five-component vaccine could not be determined in the Sweden II Efficacy Trial because of the lack of a DT control group, based on the relative risk data, it appears that the five-component vaccine demonstrated improved efficacy compared with the 84% absolute efficacy associated with the three-component vaccine. The observed difference supports the role of FIM in the protection against colonization by *B. pertussis* and mild disease. (See Table 5.) (20)

Table 5: Geometric Mean Titres (GMTs) to Pertussis Antigens Following the Third Dose of TRIPACEL® (Vaccine Administered at 2, 4 and 6 Months) (20)

Pertussis Antigens	TRIPACEL® (n = 80) GMTs (EU/mL)
PT	51.6
FHA	57
PRN	134.3
FIM	351.9

Rates of serious adverse events were less than or comparable to the rates in the other acellular pertussis and European whole-cell DTP groups in this study. (20)

Clinical Trial PB9502

In a randomized controlled clinical trial conducted in Canada between 1995 and 1997, 113 infants received QUADRACEL® and Act-HIB®, given concomitantly at separate sites at 2, 4, and 6 months of age. Of the 113 children enrolled, 104 received a fourth dose of the same vaccine at 18-20 months of age. (6) (7) (8)

Immunogenicity

In study PB9502, immunization with QUADRACEL®, concomitantly administered with Act-HIB® at a separate site, produced strong immune responses against diphtheria, tetanus, pertussis and poliovirus antigens. Immunogenicity results after 3 and 4 doses of QUADRACEL® are presented in Table 6 and

Table 7 respectively. After 4 doses, 100% of infants had achieved the minimal protective serum level (≥0.01 IU/mL) of tetanus and diphtheria antibody, and at least 99% of infants achieved diphtheria and tetanus antibody levels of at least 0.1 IU/mL. Pertussis antibody levels achieved after 4 doses of QUADRACEL® were at least as high as levels demonstrated to be efficacious in studies in Sweden. After 4 doses of QUADRACEL®, 100% of infants achieved poliovirus antibody titres thought to be protective (≥1:8).

Table 6: Antibody Responses to Diphtheria and Tetanus Toxoids and Poliovirus Types 1, 2 and 3 Measured One Month After the Third and Fourth Doses of the Primary Series with QUADRACEL® in Clinical Trial PB9502 (6) (7) (8)

Antibody	Result	Post 3rd Dose (7 months of age) (N = 108) (6) (8)	Post 4th Dose (19 months of age) (N = 103-104) (7)
Diphtheria	**GMT (IU/mL) (95% CI)**	0.36 (0.28, 0.46)	4.39 (3.43, 5.62)
	% ≥0.01 IU/mL	99.1	100.0
	% ≥0.10 IU/mL	84.3	99.0
Tetanus	**GMT (EU/mL) (95% CI)**	1.61 1.40, 1.86)	13.4 (11.5, 15.7)
	% ≥0.01 EU/mL	100	100.0
	% ≥0.10 EU/mL	100	100.0
Polio Type 1	**GMT (95% CI)**	702 (513, 960)	15,113 (11,493, 19,872)
	% ≥1:8	98.1	100.0
Polio Type 2	**GMT (95% CI)**	2595 (2005, 3360)	20,735 (16,392, 26,230)
	% ≥1:8	100	100.0
Polio Type 3	**GMT (95% CI)**	1837 (1362, 2477)	20,596 (15,265, 27,790)
	% ≥1:8	99.1	100.0

Table 7: Pertussis Antibody Responses Measured One Month After the Third and Fourth Doses of the Primary Series with QUADRACEL® in Clinical Trial PB9502 (6) (7) (8)

Antibody	Result	Post 3rd Dose (7 months of age) (N = 107-108) (6) (8)	Post 4th Dose (19 months of age) (N = 103) (7)
PT	**GMT (EU/mL) (95% CI)**	102.6 (90.5, 116.4)	222.9 (196, 253)
	% ≥4-fold rise*	92.2	97.0
FHA	**GMT (EU/mL) (95% CI)**	165.3 (148.4, 184.3)	251.9 (224, 284)
	% ≥4-fold rise*	86.5	91.1
PRN	**GMT (EU/mL) (95% CI)**	40.5 (33.0, 49.7)	160.0 (132, 195)
	% ≥4-fold rise*	75.7	100
FIM	**GMT (EU/mL) (95% CI)**	332.3 (264.6, 417.3)	1079 (879, 1324)
	% ≥4-fold rise*	83.5	93.1

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level at 2 months of age for post-3rd dose, and 18 months of age for post-4th dose.

Safety

Solicited injection site reactions occurred in 0.9% (redness) to 28.9% (tenderness) of QUADRACEL® vaccinees. Severe injection site reactions were observed in only up to 4.8% (swelling) of QUADRACEL® vaccinees. (See Table 8.) The frequency of reactions at the injection site was generally higher after the fourth dose than in the previous three doses in infants, however, severe tenderness did not increase with the fourth dose. Solicited systemic reactions occurred in 2.3% (diarrhea) to 51.3% (less activity). Except for crying (1.8%) and fussiness (2.7%) after the first dose, severe systemic reactions were uncommon. (See Table 8.) No HHE was observed in this study.

Table 8: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose of QUADRACEL® Administered at 2, 4, 6 and 18 Months of Age in Clinical Trial PB9502 (6) (7) (8)

Solicited Reactions		2 months (6) (N = 113) (8)	4 months (6) (N = 111) (8)	6 months (6) (N = 111) (8)	18 months (7) (N = 104)
Crying	**Any**	31.0	28.8	23.4	19.2
	Severe*	1.8	0	0	0
Less Active	**Any**	51.3	27.9	21.6	16.3
	Severe†	0.9	0.9	0	0
Eating Less	**Any**	34.5	20.7	16.2	20.2
	Severe‡	0	0	0	0
Diarrhea	**Any**	6.2	7.2	9.9	2.9
	Severe§	0	0	0	0
Fever	**Any**	22.1	21.1	18.0	24.0
	≥40°C	0	0	0	0
Fussiness	**Any**	46.0	45.0	35.1	33.7
	Severe**	2.7	0	0.9	1.0
Injection Site Redness	**Any**	0.9	8.1	12.6	18.3
	≥35 mm	0	0	0	1.9
Injection Site Swelling	**Any**	5.3	3.6	7.2	13.5
	≥35 mm	2.7	0.9	0.9	4.8
Injection Site Tenderness	**Any**	18.6	18.0	9.0	28.8
	Severe††	1.8	3.6	0	0
Vomiting	**Any**	8.0	2.7	6.3	6.7
	Severe‡‡	0	0	0	0

* Cried continuously for ≥3 hrs.

† Sleeping most of the time.

‡ Refused most or all feeds.

§ Multiple liquid stools without any solid consistency.

** Continuously fussy for ≥3 hrs.

†† Baby cries when leg is moved.

‡‡ Frequent vomiting and inability to have any oral intake.

Clinical Trial PB9503

In a randomized controlled clinical trial conducted in Canada in 1995, 131 infants received QUADRACEL® at 4 to 6 years of age. (9)

Immunogenicity

In study PB9503, a single dose of QUADRACEL® produced a strong booster immune response for diphtheria, tetanus, pertussis and poliovirus antigens in 4 to 6 year-old children. Protective levels of serum antibodies were achieved by 100% of children for diphtheria and tetanus (0.01 IU/mL and 0.1 IU/mL), and for all 3 types of poliovirus (1:8). At least 81% of children achieved a 4-fold increase in anti-pertussis serum antibody levels. Table 9 details the immune response observed in children after one dose of QUADRACEL® at 4 to 6 years of age.

Table 9: Antibody Responses to Diphtheria and Tetanus Toxoids, Poliovirus Types 1, 2 and 3 and Pertussis Antigens Measured One Month After the Fifth Dose of QUADRACEL® in Clinical Trial PB9503 (9)

Antibody	Result	Post 5th Dose (N = 125)
Diphtheria	**GMT (IU/mL) (95% CI)**	15.1 (12.1, 18.9)
	% ≥0.01 IU/mL	100
	% ≥0.10 IU/mL	100
Tetanus	**GMT (EU/mL) (95% CI)**	5.1 (4.6,5.7)
	% ≥0.01 EU/mL	100
	% ≥0.10 EU/mL	100
Polio Type 1	**GMT (95% CI)**	10903.3 (8718.9, 13635.0)
	% ≥1:8	100
Polio Type 2	**GMT (95% CI)**	27337.4 (23198.0, 32215.3)
	% ≥1:8	100
Polio Type 3	**GMT (95% CI)**	9165.1 (7125.5, 11788.6)
	% ≥1:8	100
PT	**GMT (EU/mL) (95% CI)**	123.2 (103.7, 146.4)
	% ≥4-fold rise *	97.6
FHA	**GMT (EU/mL) (95% CI)**	176.2 (149.2, 208.1)
	% ≥4-fold rise*	81.3
PRN	**GMT (EU/mL) (95% CI)**	64.2 (51.8, 79.5)
	% ≥4-fold rise*	98.4
FIM	**GMT (EU/mL) (95% CI)**	737.9 (625.6, 870.3)
	% ≥4-fold rise*	95.2

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level at 2 months of age for post-3rd dose, and 18 months of age for post-4th dose.

Safety

Solicited injection site reactions occurred in 18.5% (redness) to 74.9% (swelling) of QUADRACEL® vaccinees. Severe injection site reactions were observed in up to 16.2% (swelling) of QUADRACEL® vaccinees. (See Table 10.) Solicited systemic reactions occurred in 2.3% (diarrhea) to 23.1% (less active, eating less). Except for fussiness (4.6%) severe systemic reactions were uncommon. (See Table 10.)

Table 10: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose of QUADRACEL® Administered at 4 to 6 Years of Age in Clinical Trial PB9503 (9)

Solicited Reactions		Post 5th Dose (N = 130)
Less Active	**Any**	23.1
	Severe *	0.8
Eating Less	**Any**	23.1
	Severe †	0.8
Diarrhea	**Any**	2.3
	Severe ‡	0.8
Fever	**Any**	17.3
	≥40°C	0
Fussiness	**Any**	20.0
	Severe §	4.6
Injection Site Redness	**Any**	18.5
	≥35 mm	13.8
Injection Site Swelling	**Any**	18.5
	≥35 mm	16.2
Injection Site Tenderness	**Any**	74.6
	Severe **	0.8
Vomiting	**Any**	4.6
	Severe ††	0.8

* Sleeping most of the time.

† Refused most or all feeds.

‡ Multiple liquid stools without any solid consistency.

§ Continuously fussy for ≥3 hrs.

** Baby cries when leg is moved.

†† Frequent vomiting and inability to have any oral intake.

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business Hours 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of August 2011.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R11-0811 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

QUADRACEL®

[Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine]

This leaflet is part III of a three-part "Product Monograph" published when QUADRACEL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about QUADRACEL®. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

QUADRACEL® is a vaccine that is used to help prevent against diphtheria, tetanus (lock jaw), pertussis (whooping cough) and polio. This vaccine may be given to children aged 2 months or older. It may also be given as a booster to children up to age 7.

The majority of children who are vaccinated with QUADRACEL® will produce enough antibodies to help protect them against these 4 diseases. However, as with all vaccines, 100% protection cannot be guaranteed.

What the vaccine does:

QUADRACEL® causes the body to produce its own natural protection against diphtheria, tetanus, pertussis (whooping cough) and poliomyelitis. After your child receives the vaccine, the body begins to make substances called antibodies. Antibodies help the body to fight disease. If a vaccinated person comes into contact with one of the germs that cause these diseases, the body is usually ready to destroy it.

When the vaccine should not be used:

- Do not give QUADRACEL® to a child who has an allergy to any ingredient in the vaccine or has had an allergic reaction after receiving a vaccine that contained similar ingredients.
- Do not give QUADRACEL® to a person who has had a serious nervous system disorder within 7 days after a previous pertussis vaccine. In case of progressive nervous system disorder or uncontrolled epilepsy, vaccination may be considered only after a treatment has been established and the condition is stabilized.

What the medicinal ingredient is:

Each 0.5 mL dose of QUADRACEL® contains: diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine (pertussis toxoid, filamentous haemagglutinin, pertactin, fimbriae types 2 and 3) and inactivated polio vaccine.

What the important nonmedicinal ingredients are:

Aluminum phosphate (adjuvant), 2-phenoxyethanol, polysorbate 80. Residual formaldehyde, glutaraldehyde, bovine serum albumin, neomycin, and polymyxin B may be present in trace amounts.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms the vaccine comes in:

QUADRACEL® is a liquid vaccine that is injected into a muscle. A single dose is 0.5 mL.

WARNINGS AND PRECAUTIONS

If your child has any of the following conditions, talk to your doctor, nurse or pharmacist BEFORE the child receives QUADRACEL®:

- **A high fever or serious illness.** Wait until the child is better to give the vaccination.
- **An allergy to any component of the vaccine or the container.**
- **A serious nervous system adverse event following a previous pertussis vaccination.**
- **Diseases of the immune system or taking a medical treatment that affects the immune system.** The vaccine may provide your child with a lower level of protection than it does for people with healthy immune systems. If possible, try to postpone the vaccination until after your child has completed the treatment.
- **A bleeding disorder or taking blood-thinning medications.** Tell the person giving the injection about your child's condition. The injection must be done carefully to prevent excessive bleeding.
- **A higher risk of seizure than the general population.** A fever-reducing medication (AW) may be given to your child.

INTERACTIONS WITH THIS VACCINE

DO NOT mix QUADRACEL® with other vaccines or medicinal products in the same syringe.

QUADRACEL® may be given at the same time but at separate sites with Hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and Varicella vaccines.

PROPER USE OF THIS VACCINE

Usual Dose:

A single dose of 0.5 mL is recommended for routine immunization of infants at 2, 4, 6 and 18 months of age and in children up to their 7th birthday.

The vaccination should be given in the muscle, preferably in the thigh for children up to 1 year-old. In children >1 year of age, the shoulder is the preferred site since use of the thigh results in limping due to muscle pain.

Overdose:

In case of drug overdose, contact a health-care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If immunization is delayed for any reason, the recommended schedule is:

- 3 single doses of 0.5 mL with 2 months between doses
- a 4th dose given 6 to 12 months after the 3rd dose

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause side effects. Up to one third of children who receive QUADRACEL® may have mild side effects such as redness, swelling or tenderness around the injection site. Other common reactions include fever, increased crying, fussiness, being less active and have decreased eating. These side effects are usually mild and last no more than 3 to 4 days. Severe reactions, such as high fever, swelling and redness of the entire arm or leg, or a serious allergic reaction are very rare.

Tell your doctor, nurse or pharmacist as soon as possible if your child is not feeling well after receiving QUADRACEL®.

Serious side effects are extremely rare.

This is not a complete list of side effects. For any unexpected effects while taking QUADRACEL®, contact your doctor, nurse or pharmacist.

HOW TO STORE THIS VACCINE

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze**. Throw the product away if it has been exposed to freezing.

Do not use after the expiration date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For Health Care Professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory**.

For the General Public:
Should your child experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: (1-866-844-0018)
By toll-free fax: (1-866-844-5931)
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php
Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9
A/L 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.sanofipasteur.ca
You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information. Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area). Business hours: 8 a.m. to 5 p.m. Eastern Time Monday to Friday.

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