PRODUCT MONOGRAPH

PEDIACEL®

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

Suspension for injection

(For active immunization against Diphtheria, Tetanus, Pertussis, Poliomyelitis and *Haemophilus influenzae* Type b Disease)

ATC Code: J07CA06

Sanofi Pasteur Limited
Toronto, Ontario, Canada
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intramuscular injection.

Dosage Form/Strength

Suspension for injection.

Each 0.5 mL 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 [type 1 (Mahoney), type 2 (MEF1), type 3 (Saukett)] and purified polyribosylribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to tetanus protein.

Clinically Relevant Nonmedicinal Ingredients

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

Manufacturing process residuals: bovine serum albumin, neomycin, polymyxin B and trace amounts of streptomycin, formaldehyde and glutaraldehyde.

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

PEDIACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] 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 (vero cell origin) types 1, 2 and 3 (IPV), and *H. influenzae* type b capsular polysaccharide (polyribosylribitol phosphate, PRP)

covalently bound to tetanus protein, 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

PEDIACEL® 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 (whooping cough), poliomyelitis and invasive *H. influenzae* type b disease. (See DOSAGE AND ADMINISTRATION.)

Currently, Haemophilus b conjugate vaccines are not recommended for infants younger than 2 months of age.

According to the National Advisory Committee on Immunization (NACI), children who have had pertussis, tetanus, diphtheria or *H. influenzae* type b (Hib) invasive disease should still be immunized since these clinical infections do not always confer immunity. (1) For persons who have been exposed to invasive Hib and who are incompletely immunized, refer to the guidelines in the Canadian Immunization Guide.

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

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

Pediatrics

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

Geriatrics

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

CONTRAINDICATIONS

Hypersensitivity

NACI recommends that known systemic hypersensitivity reaction to any component of PEDIACEL® 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.

Acute Neurological Disorders

According to the Advisory Committee on Immunization Practices (ACIP), the following events are contraindications to administration of any pertussis-containing vaccine, (2) including PEDIACEL®:

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 PEDIACEL®, health-care providers should inform the parent or guardian of the recipient to be immunized 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.)

NACI states that 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. (1) (3)

As with any vaccine, PEDIACEL® may not protect 100% of vaccinated individuals.

Vaccines that contain Hib antigen do not provide protection against infections with other types of *H. influenzae*, or against meningitis of other origin.

Under no circumstances can the tetanus protein contained in conjugate vaccines containing tetanus toxoid as protein carrier be used to replace the usual tetanus vaccination.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTaP vaccines. By chance alone, some cases of SIDS can be expected to follow receipt of PEDIACEL®. (4)

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

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

PEDIACEL® should not be administered into the buttocks.

Granuloma or sterile abscess at the injection site has been reported with a product containing the same antigens.

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.

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 PEDIACEL® 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 PEDIACEL® 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 PEDIACEL® 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. (5)

As recommended by NACI and as with all other products, 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,

vaccination of persons with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited. (1) (2)

Neurologic

A review by the IOM found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). (6) ACIP recommends that if GBS occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give PEDIACEL® or any vaccine containing tetanus toxoid should be based on careful consideration of potential benefits and possible risks. (2)

A few cases of demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies have been reported following vaccines containing tetanus and/or diphtheria toxoids, although the IOM concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccination. (6)

ACIP recommends for infants or children at higher risk for seizures than the general population, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including PEDIACEL®) 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. The 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.

ADVERSE REACTIONS

Clinical Trial Adverse 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 a randomized, controlled clinical trial conducted in Canada, 339 infants were immunized with PEDIACEL® at 2, 4 and 6 months of age. In addition, 301 of these children were immunized as toddlers at 18 months. (7) Injection site reactions were generally mild. Up to one third of children

receiving PEDIACEL® experienced some degree of redness, swelling or tenderness around the injection site. Solicited injection site reaction rates are shown in Table 1.

Table 1: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose with PEDIACEL® Administered at 2, 4, 6 and 18 Months of Age

Solicited Reactions	2 months (N = 336)	4 months (N = 331)	6 months (N = 330)	18 months (N = 300)
Injection Site Reactions				
Redness	6.8	12.7	9.7	19.7
Swelling	12.5	10.3	9.7	13.7
Tenderness	22.6	22.1	14.8	33.0
Systemic Reactions				
Fever ≥38.0°C	13.4	19.6	15.9	19.5
Crying	27.7	34.7	23.0	17.0
Eating Less	29.2	19.3	15.2	13.3
Diarrhea	9.2	4.8	7.0	7.0
Vomiting	6.8	5.7	3.3	4.0
Fussiness	42.3	46.8	38.2	27.7
Less Active	44.9	29.9	13.9	12.0

Data from Post-Marketing Experience

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

Immune System Disorders

Hypersensitivity, anaphylactic reaction (such as urticaria, angioedema).

Psychiatric Disorders

Screaming.

Nervous System Disorders

Convulsion (with or without fever), prolonged or unusual high-pitched crying, hypotonic hyporesponsive episode (infant appears pale, hypotonic [limp] and unresponsive to parents). To date, this condition has not been associated with any permanent sequelae.

Vascular Disorders

Edematous reactions affecting one or both lower limbs have occurred following vaccination with *H. influenza* type b containing vaccines. When this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolved spontaneously without sequelae within 24 hours.

Skin and Subcutaneous Tissue Disorders

Erythema, rash.

Musculoskeletal, Connective Tissue and Bone Disorders

Pain in vaccinated limb.

General Disorders and Administration Site Conditions

High fever (>40.5°C), injection site mass, pallor, somnolence, asthenia, irritability and listlessness.

Large injection site reactions (>50 mm) including extensive limb swelling which may extend from the injection site beyond one or both joints, have been reported in children following PEDIACEL® 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 to 5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine, with a greater risk following the 4^{th} and 5^{th} doses.

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and 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.)

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) NACI recommends that

vaccines administered simultaneously should be given using separate syringes at separate sites. (1) (2) Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination.

PEDIACEL® should not be mixed in the same syringe with other parenterals.

Vaccine-Laboratory Test Interactions

Antigenuria has been detected in some instances following administration of a vaccine containing Hib antigen. Therefore, urine antigen detection may not have definite diagnostic value in suspected *H. influenzae* type b disease within two weeks of immunization. (8)

DOSAGE AND ADMINISTRATION

Recommended Dose

For routine immunization, PEDIACEL® is recommended as a 4-dose series, with a single dose of 0.5 mL of PEDIACEL® 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 approximately 6 to 12 months after the third dose.

Whenever feasible, PEDIACEL® should be used for all 4 doses in the vaccination series as there are no clinical data to support the use of PEDIACEL® with any other licensed acellular pertussis combination vaccine in a mixed sequence. For situations where a different brand of DTaP or 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 0.5 mL dose of Sanofi Pasteur Limited's QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] 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 PEDIACEL® was administered after the child's fourth birthday. (1)

A subsequent booster should be administered 10 years later, during adolescence with ADACEL® or Td Adsorbed. Thereafter, routine booster immunizations should be with Td at intervals of 10 years.

PEDIACEL® 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.

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. ACIP states that a serum diphtheria antitoxin level of 0.01 IU/mL is considered 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. ACIP states that 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 PEDIACEL® 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 PEDIACEL®, 100% (N = 300) of immunized children achieved serum diphtheria and tetanus antitoxin levels of at least 0.01 IU/mL and 100% of these children achieved serum antitoxin levels of at least 0.1 IU/mL for diphtheria and tetanus.

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 PEDIACEL® (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. (9) (10) (11) (12) (13) (14) In a controlled clinical trial in Sweden (Sweden II Trial), the efficacy of a DTaP vaccine with the same formulation in pertussis antigens as PEDIACEL® was demonstrated to provide a two-fold to three-fold higher protection against pertussis with any cough compared to the three pertussis antigens vaccine. The observed difference supports the role of fimbriae types 2 and 3 in the protection against colonization of *B. pertussis* and mild disease.

PEDIACEL® is a fully liquid version of PENTACEL® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] with both vaccines containing similar antigens. PENTACEL® has been used in the prevention and control of pertussis in Canada since it was introduced in 1997 – 1998. Over 13 million doses of PENTACEL® have been administered to Canadian children (at 2, 4, 6 and 18 months of age) since 1997.

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. (15) Overall, the data show declining rates of pertussis during the years in which PENTACEL® 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, (16) Newfoundland and Labrador (17) and British Columbia (18) 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. (19) A clinical study of PEDIACEL® in 300 Canadian infants showed that, after 4 doses, more than 99.7% of vaccinated children achieved protective antibody levels (titres ≥1:8) to poliovirus types 1, 2 and 3 following the primary series. (7)

***Haemophilus influenzae* Type b:** The response to a Haemophilus b conjugate vaccine is typical of a T-dependent immune response with induction of immunological priming and memory. (3) Bactericidal activity against Hib is demonstrated in serum after immunization and correlates with the anti-PRP antibody response induced by Hib conjugate vaccine. In children aged ≥24 months, antibody titres to *H. influenzae* capsular polysaccharide (anti-PRP) of ≥0.15 µg/mL following vaccination with unconjugated PRP vaccine correlated with protection against invasive *H. influenzae* type b disease immediately after immunization, whereas titres ≥1.0 µg/mL correlated with protection for at least 1 year. (20) Although the relevance of the 0.15 µg/mL and 1.0 µg/mL thresholds to clinical protection after immunization with conjugate vaccines is not known, these levels have been used to gauge antibody response to vaccination. In a clinical study of PEDIACEL® in 300 infants in Canada after 4 doses, 100% of vaccinated children achieved protective antibody titres ≥0.15 µg/mL, and 99.0% achieved protective antibody levels ≥1.0 µg/mL. (7)

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.

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

PEDIACEL® is supplied as a sterile, uniform, cloudy, white to off-white suspension in a vial.

Composition

Each single dose (0.5 mL) contains:

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 (MEF1)	8 D-antigen units
Type 3 (Saukett)	32 D-antigen units
Purified Polyribosylribitol Phosphate Capsular Polysaccharide (PRP) of *Haemophilus influenzae* Type b covalently bound to 20 µg of Tetanus Protein	10 µg

Other Ingredients

Excipients	
Aluminum Phosphate (adjuvant)	1.5 mg
2-phenoxyethanol	0.6% v/v
Polysorbate 80	≤0.1% w/v (by calculation)

Manufacturing Process Residuals
Bovine serum albumin, neomycin, polymyxin B, streptomycin, formaldehyde and glutaraldehyde are present in trace amounts.

Packaging

PEDIACEL® is supplied in single dose vials.

The vials are made of Type 1 glass. The container closure system of PEDIACEL® does not contain latex (natural rubber).

PEDIACEL® is available in a package of:

1 single dose (0.5 mL) vial

5 single dose (0.5 mL) vials

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 January 2009.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R7-0109 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 and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

Product Characteristics

PEDIACEL® is a sterile, uniform, cloudy, white to off-white suspension of diphtheria and tetanus toxoids adsorbed on aluminum phosphate and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine (vero cell origin) types 1, 2 and 3 and *H. influenzae* type b capsular polysaccharide (polyribosylribitol phosphate, PRP) covalently bound to tetanus protein, 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. (21) 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. (22) 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 (23) 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 co-purified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde and FHA is treated with formaldehyde. The residual aldehydes are removed by diafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

The adsorbed diphtheria, tetanus and acellular pertussis components are combined into an intermediate concentrate.

Inactivated poliomyelitis vaccine (IPV) is a highly purified, inactivated poliovirus vaccine including three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1) and Type 3 (Saukett). Each of the three strains of poliovirus is individually grown in vero cells cultivated on microcarriers. The single virus harvest is concentrated and purified, then inactivated with formaldehyde to produce the type 1, 2 or 3 monovalent. Monovalents of each type are then combined in appropriate quantities to produce a trivalent concentrate.

The Haemophilus b conjugate (Hib) component of PEDIACEL® consists of the Haemophilus b capsular polysaccharide (polyribosylribitol phosphate, PRP), a high molecular weight polymer prepared from the *H. influenzae* type b strain 1482 grown in a semi-synthetic medium, covalently bound to tetanus protein. (24) The tetanus protein is prepared by ammonium sulphate purification, and formalin inactivation of the toxin from cultures of *C. tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (25) The protein is filter sterilized prior to the conjugation process.

The adsorbed diphtheria, tetanus and acellular pertussis components intermediate concentrate is combined with concentrates of PRP-T conjugate and IPV (vero types 1, 2 and 3). Water for injection containing polysorbate 80 and 2-phenoxyethanol are added to make the final formulation.

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. Potency of PRP-T is specified on each lot by limits on the content of PRP polysaccharide in each dose and the proportion of free polysaccharide.

CLINICAL TRIALS

Four pivotal clinical trials (Sweden Trial I, Sweden Trial II, PB9502 and PB9602) conducted in Sweden and in Canada provide the clinical basis for the licensure of PEDIACEL® in Canada. (See Table 2.)

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

Study	Study Design	Dosage and Route of Administration	Vaccination Schedule/ Study Population*	Gender
Sweden I (7)	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 (7) (26)	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 (7)	Randomized, controlled, single-blinded multicentre safety and immunogenicity comparative trial with PEDIACEL®, PENTACEL®†, PENTA™‡ and QUADRACEL®§, Act-HIB®**.	0.5 mL I.M.	2, 4, 6 and 18 months of age N = 339	Males N = 183 Females N = 156
PB9602 (7)	Randomized, controlled, single-blinded, multicentre safety and immunogenicity comparative trial with PEDIACEL® and PENTA™.	0.5 mL I.M.	2, 4, 6 and 18 months of age N = 112	Males N = 65 Females N = 47

* Number enrolled.

† PENTACEL® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine].

‡ PENTA™ is a whole-cell DPT-Polio (MRC-5) with lyophilized PRP-T vaccine.

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

** Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)].

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). (26) 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 present in PEDIACEL® (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). (26) 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). Protection against pertussis by TRIPACEL® was sustained for the 2-year follow-up period. (26) (See Table 3.)

Table 3: Vaccine Efficacy Against Pertussis Infection of Varying Clinical Severity (7) (26)

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 (7) (26) 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 (7) (26)

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. (7) (26)

A sub-study of this trial looked specifically at immunized children exposed to pertussis from other members of their households. (9) 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 PEDIACEL® (N = 20,747); or a European whole-cell DTP vaccine (N = 20,720). (27) 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).

(28) 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 fimbriae types 2 and 3 (FIM) in the protection against colonization by *B. pertussis* and mild disease. (27)

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

Pertussis Antigens	TRIPACEL® (N = 80) GMT (EU/mL)
PT	51.6
FHA	57.0
PRN	134.4
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. (7) (27)

Clinical Trial PB9502

In a randomized controlled clinical trial conducted in Canada between 1995 and 1997, 787 infants received PEDIACEL® (N = 339), PENTACEL® (N = 335), PENTA™ (N = 112), or QUADRACEL® and Act-HIB®, given concomitantly at separate sites (N = 113) at 2, 4, and 6 months of age. Of the 787 children enrolled, 708 received a fourth dose of the same vaccine at 18-20 months of age.

Immunogenicity

In study PB9502 the immunogenicity of PEDIACEL® was found to be similar to that for PENTACEL®. One month after the third and fourth doses, no clinically significant differences were observed between the antibody responses to each of the vaccine antigens in children receiving PEDIACEL® and those receiving PENTACEL®. (See Table 3 through Table 7.) After the third and fourth doses, at least 97.9% of the PEDIACEL® vaccinees achieved seroprotective levels against Hib disease (anti-PRP antibody ≥0.15 µg/mL), diphtheria (diphtheria antitoxin ≥0.01 IU/mL), tetanus (tetanus antitoxin ≥0.01 EU/mL) and poliomyelitis types 1, 2, and 3 (poliovirus neutralizing antibody titre ≥1:8). (See Table 6 and Table 7.) Seroconversion rates (% ≥4-fold rise) were high for each of the pertussis antibodies after the primary series. (See Table 8.) A robust booster response was observed after the fourth dose. (7) (See Table 7 and Table 9.)

Table 6: Antibody Responses to PRP-T, Diphtheria and Tetanus Toxoids and Poliovirus Types 1, 2 and 3 Measured One Month After the Third Dose of the Primary Series with PEDIACEL® or PENTACEL® in Clinical Trial PB9502 (7)

		Post 3rd Dose (7 months of age)	
Antibody	**Result**	**PEDIACEL® (N = 324)**	**PENTACEL® (N = 321)**
Anti-PRP	**GMC**	4.86	4.40
	(95% CI)	(4.21, 5.62)	(3.78, 5.13)
	% ≥0.15 µg/mL	97.9	98.5
	% ≥1.0 µg/mL	88.9	84.7
Diphtheria	**GMC**	0.29	0.28
	(95% CI)	(0.25, 0.33)	(0.24, 0.33)
	% ≥0.01 IU/mL	100.0	98.4
	% ≥0.10 IU/mL	78.7	76.7
Tetanus	**GMC**	1.09	0.88
	(95% CI)	(1.00, 1.20)	(0.80, 0.96)
	% ≥0.01 EU/mL	100.0	100.0
	% ≥0.10 EU/mL	99.7	99.1
Polio Type 1	**GMT**	616	723
	(95% CI)	(526, 723)	(593, 882)
	% ≥1:8	100.0	99.4
Polio Type 2	**GMT**	2,382	2,178
	(95% CI)	(2,026, 2,800)	(1,841, 2,578)
	% ≥1:8	99.7	100.0
Polio Type 3	**GMT**	1,266	1,942
	(95% CI)	(1,079, 1,485)	(1,642, 2,297)
	% ≥1:8	99.7	99.4

Table 7: Antibody Responses to PRP-T, Diphtheria and Tetanus Toxoids and Poliovirus Types 1, 2 and 3 Measured Immediately Before and One Month After a Fourth Dose at 18 to 19 Months of Age with PEDIACEL® or PENTACEL® in Clinical Trial PB9502 (7)

Antibody	Result	Pre 4th Dose		Post 4th Dose	
		PEDIACEL® (N = 300)	PENTACEL® (N = 294)	PEDIACEL® (N = 300)	PENTACEL® (N = 294)
Anti-PRP	GMC	0.55	0.42	32.3	30.1
	(95% CI)	(0.48, 0.64)	(0.35, 0.49)	(28.4, 36.8)	(26.4, 34.2)
	% ≥0.15 µg/mL	85.2	75.4	100.0	100.0
	% ≥1.0 µg/mL	24.8	25.3	99.0	99.0
Diphtheria	GMC	0.05	0.05	4.13	4.42
	(95% CI)	(0.04, 0.06)	(0.04, 0.06)	(3.58, 4.76)	(3.82, 5.11)
	% ≥0.01 IU/mL	92.0	89.5	100.0	100.0
	% ≥0.10 IU/mL	27.2	25.5	100.0	99.7
Tetanus	GMC	0.53	0.40	10.1	7.52
	(95% CI)	(0.48, 0.59)	(0.35, 0.45)	(9.33, 11.0)	(6.89, 8.21)
	% ≥0.01 EU/mL	99.3	99.3	100.0	100.0
	% ≥0.10 EU/mL	96.7	90.8	100.0	100.0
Polio Type 1	GMT	115	108	7,804	14,874
	(95% CI)	(96.7, 137)	(88.3, 133)	(6,649, 9,160)	(12,303, 17,983)
	% ≥1:8	92.7	90.8	99.7	99.7
Polio Type 2	GMT	310	303	17,560	21,690
	(95% CI)	(256, 377)	(253, 364)	(15,052, 20,486)	(18,711, 25,145)
	% ≥1:8	97.0	98.3	100.0	100.0
Polio Type 3	GMT	141	243	12,417	22,931
	(95% CI)	(115, 172)	(197, 300)	(10,305, 14,962)	(19,207, 27,376)
	% ≥1:8	91.7	94.9	100.0	100.0

Table 8: Pertussis Antibody Responses Measured One Month After the Third Dose of the Primary Series with PEDIACEL® or PENTACEL® in Clinical Trial PB9502 (7)

Antibody	Result	Post 3rd Dose (7 months of age)	
		PEDIACEL® N = 324	PENTACEL® N = 321
PT	GMC (EU/mL)	86.7	89.0
	(95% CI)	(80.8, 93.0)	(82.5, 96.0)
	% ≥4-fold rise*	92.5	92.2
FHA	GMC (EU/mL)	155.0	152.6
	(95% CI)	(146.5, 164.1)	(143.7, 162.2)
	% ≥4-fold rise*	86.0	87.1
PRN	GMC (EU/mL)	55.4	55.9
	(95% CI)	(48.8, 62.8)	(49.3, 63.3)
	% ≥4-fold rise*	85.5	85.2
FIM	GMC (EU/mL)	277.2	243.8
	(95% CI)	(242.7, 316.5)	(210.8, 282.1)
	% ≥4-fold rise*	85.4	84.7

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level at 2 months of age.

Table 9: Pertussis Antibody Responses Measured Immediately Before and One Month After a Fourth Dose with PEDIACEL® or PENTACEL® in Clinical Trial PB9502 (7)

Antibody	Result	4th Dose (18 to 19 months of age)			
		Pre-Immunization		Post-Immunization	
		PEDIACEL® (N = 324)	PENTACEL® (N = 321)	PEDIACEL® (N = 300)	PENTACEL® (N = 294)
PT	GMC (EU/mL)	11.9	11.4	222	182
	(95% CI)	(10.8, 13.0)	(10.3, 12.7)	(204, 241)	(166, 199)
	% ≥4-fold rise*	-	-	98.6	96.8
FHA	GMC (EU/mL)	19.9	20.9	266	245
	(95% CI)	(18.1, 21.9)	(18.7, 23.2)	(248, 285)	(228, 263)
	% ≥4-fold rise	-	-	93.8	91.0
PRN	GMC (EU/mL)	9.3	9.6	208	210
	(95% CI)	(8.2, 10.6)	(8.4, 10.9)	(184, 235)	(185, 239)
	% ≥4-fold rise	-	-	98.3	97.8
FIM	GMC (EU/mL)	38.4	37.9	842	855
	(95% CI)	(33.4, 44.3)	(32.7, 44.0)	(748, 948)	(753, 971)
	% ≥4-fold rise	-	-	94.1	95.7

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level at 18 to 19 months of age.

Safety

Solicited injection site reactions occurred in 6.8% (redness) to 33.0% (tenderness) of PEDIACEL® vaccinees. Severe injection site reactions were observed in only 0.6% (tenderness) to 5.0% (redness). (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. Systemic reactions occurred in 3.3% (vomiting) to 46.8% (fussiness). Except for fussiness after the fourth dose (2.0%), severe systemic reactions were uncommon. (See Table 8.) No child immunized with PEDIACEL® experienced a fever ≥40°C. The adverse event profile of PEDIACEL® was comparable to that observed with PENTACEL®. (See Table 11.)

Table 10: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose with PEDIACEL® Administered at 2, 4, 6 and 18 Months of Age in Clinical Trial PB9502 (7)

Solicited Reaction		2 months (N = 336)	4 months (N = 331)	6 months (N = 330)	18 months (N = 300)
Crying	**Any**	27.7	34.7	23.0	17.0
	Severe*	0	0	0.3	0
Less Active	**Any**	44.9	29.9	13.9	12.0
	Severe†	0.9	0	0	0
Eating Less	**Any**	29.2	19.3	15.2	13.3
	Severe‡	0	0	0	0.3
Diarrhea	**Any**	9.2	4.8	7.0	7.0
	Severe§	0.3	0	0	0
Fever	**Any**	13.4	19.6	15.9	19.5
	≥40°C	0	0	0	0
Fussiness	**Any**	42.3	46.8	38.2	27.7
	Severe**	0.9	0.6	0.3	1.7
Injection Site Redness	**Any**	6.8	12.7	9.7	19.7
	≥35 mm	1.2	0.9	1.2	5.3
Injection Site Swelling	**Any**	12.5	10.3	9.7	13.7
	≥35 mm	5.1	3.6	3.3	4.0
Injection Site Tenderness	**Any**	22.6	22.1	14.8	33.0
	Severe††	0.6	2.4	1.8	1.7
Vomiting	**Any**	6.8	5.7	3.3	4.0
	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.

Table 11: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following the Administration of PEDIACEL® or PENTACEL® at 2, 4, 6 and 18 Months of Age in Clinical Trial PB9502 (7)

Solicited Reaction	Vaccine	Age (months)			
		2	4	6	18
	PEDIACEL®	N = 336	N = 331	N = 330	N = 300
	PENTACEL®	N = 333	N = 327	N = 320	N = 295
Crying	PEDIACEL®	27.7	34.7	23.0	17.0
	PENTACEL®	30.6	41.5	27.6	18.6
Less Active	PEDIACEL®	44.9	29.9	13.9	12.0
	PENTACEL®	46.8	30.8	20.7	9.8
Eating Less	PEDIACEL®	29.2	19.3	15.2	13.3
	PENTACEL®	27.6	20.7	15.4	17.0
Diarrhea	PEDIACEL®	9.2	4.8	7.0	7.0
	PENTACEL®	10.2	7.6	6.6	5.4
Fever	PEDIACEL®	13.4	19.6	15.9	19.5
	PENTACEL®	18.6	19.5	15.0	21.5
Fussiness	PEDIACEL®	42.3	46.8	38.2	27.7
	PENTACEL®	43.5	53.4	37.0	30.2
Injection Site Redness	PEDIACEL®	6.8	12.7	9.7	19.7
	PENTACEL®	8.7	11.9	11.6	19.3
Injection Site Swelling	PEDIACEL®	12.5	10.3	9.7	13.7
	PENTACEL®	11.7	8.8	9.4	14.2
Injection Site Tenderness	PEDIACEL®	22.6	22.1	14.8	33.0
	PENTACEL®	26.4	27.1	19.7	28.1
Vomiting	PEDIACEL®	6.8	5.7	3.3	4.0
	PENTACEL®	8.7	5.2	4.7	4.4

Clinical Trial PB9602

Additional safety and immunogenicity data were obtained from a randomized controlled clinical trial conducted in Canada during 1996 - 1998. This study involved 566 infants who were enrolled to receive one lot of PEDIACEL® (N = 112), one lot of PENTA™ (N = 113) or one of three lots (N = 341) of a formulation of PEDIACEL® containing reduced amounts of PT (10 µg) and FHA (5 µg), at 2, 4, 6 and 18 months of age.

Immunogenicity

After the third and fourth doses, at least 97.2% of the PEDIACEL® vaccinees achieved seroprotective levels against Hib disease (anti-PRP antibody ≥0.15 µg/mL), diphtheria (diphtheria antitoxin ≥0.01 IU/mL), tetanus (tetanus antitoxin ≥0.01 EU/mL) and poliomyelitis types 1, 2 and 3 (poliovirus neutralizing antibody titre ≥1:8). (See Table 12.)

Table 12: Antibody Responses to PRP-T, Diphtheria and Tetanus Toxoids and Poliovirus Types 1, 2 and 3 Measured One Month After the Third Dose of the Primary Series and Immediately Before and One Month After a Fourth Dose with PEDIACEL® in Clinical Trial PB9602 (7)

Antibody	Result	Post 3rd Dose (7 months) N = 108	Pre 4th Dose (18 – 19 months) N = 98	Post 4th Dose (19 – 20 months) N = 98
Anti-PRP	**GMC**	6.18	0.64	42.89
	(95% CI)	(4.69, 8.15)	(0.48, 0.84)	(33.30, 55.25)
	% ≥0.15 µg/mL	97.2	84.4	100.0
	% ≥1.0 µg/mL	90.7	39.6	99.0
Diphtheria	**GMC**	0.38	0.07	4.50
	(95% CI)	(0.31, 0.46)	(0.05, 0.09)	(3.54, 5.73)
	% ≥0.01 IU/mL	100.0	98.0	100.0
	% ≥0.10 IU/mL	86.1	40.8	100.0
Tetanus	**GMC**	3.80	0.60	11.71
	(95% CI)	(3.20, 4.52)	(0.49, 0.73)	(9.76, 14.04)
	% ≥0.01 EU/mL	100.0	100.0	100.0
	% ≥0.10 EU/mL	100.0	95.8	100.0
Polio Type 1	**GMT**	1,290	170	7,852
	(95% CI)	(945, 1,762)	(125, 231)	(6,096, 10,112)
	% ≥1:4	100.0	-	-
	% ≥1:8	100.0	95.9	100.0
Polio Type 2	**GMT**	4,089	516	22,365
	(95% CI)	(3,008, 5,559)	(379, 702)	(18,227, 27,443)
	% ≥1:4	100.0	-	-
	% ≥1:8	100.0	100.0	100.0
Polio Type 3	**GMT**	2,255	314	22,208
	(95% CI)	(1,644, 3,093)	(227, 434)	(16,067, 30,695)
	% ≥1:4	100.0	-	-
	% ≥1:8	100.0	100.0	100.0

Seroconversion rates (% ≥4-fold rise) were high for each of the pertussis antibodies after the primary series. (See Table 13.) A robust booster response was observed after the fourth dose for all the vaccine antigens. (See Table 12 and Table 13.)

Table 13: Pertussis Antibody Responses Measured One Month After the Third Dose of the Primary Series and Immediately Before and One Month After a Fourth Dose with PEDIACEL® in Clinical Trial PB9602 (7)

Antibody	Result	Post 3rd Dose (7 months) N = 108	Pre 4th Dose (18 – 19 months) N = 98	Post 4th Dose (19 – 20 months) N = 98
PT	**GMC (EU/mL)**	103.8	12.0	259.5
	(95% CI)	(91.7, 117.5)	(10.22, 14.08)	(223.4, 301.6)
	% ≥4-fold rise*	91.3	-	99.0
FHA	**GMC (EU/mL)**	221.2	22.68	258.1
	(95% CI)	(198.9, 246.0)	(18.84, 27.30)	(227.6, 292.7)
	% ≥4-fold rise*	92.3	-	90.8
PRN	**GMC (EU/mL)**	86.3	8.09	215.0
	(95% CI)	(68.1, 109.3)	(6.11, 10.72)	(171.5, 269.4)
	% ≥4-fold rise*	83.0	-	96.9
FIM	**GMC (EU/mL)**	370.2	44.28	1,287
	(95% CI)	(297.9, 460.2)	(35.03, 55.96)	(1,073, 1,543)
	% ≥4-fold rise*	91.2	-	94.9

* Percentage of vaccinees attaining at least a 4-fold increase over their pre-immunization antibody level.

Safety

Solicited injection site reactions occurred in 14.6% (redness) to 32.3% (tenderness) of PEDIACEL® vaccinees. Severe injection site reactions were observed in only 1.8% (tenderness) to 15.2% (redness). (See Table 14.) As seen in study PB9502 the frequency of injection site reactions were generally higher after the fourth dose than in the previous three doses in infants, however severe tenderness did not increase with the fourth dose. Systemic adverse reactions occurred in 3.0% (vomiting) to 51.8% (fussiness). Except for fussiness (2.7%) and crying (1.9%) severe systemic reactions were uncommon and there were no reports of fever ≥40°C. (See Table 14.)

Table 14: Frequency (%) of Solicited Reactions Observed Within 24 Hours Following a Single Dose with PEDIACEL® Administered at 2, 4, 6 and 18 Months of Age in Clinical Trial PB9602 (7)

Solicited Reaction		2 months N = 110	4 months N = 110	6 months N = 108	18 months N = 98
Crying	**Any**	23.6	34.6	25.0	19.2
	Severe*	0	1.8	1.9	1.0
Less Active	**Any**	30.9	24.6	16.7	14.1
	Severe†	0	0	0	0
Eating Less	**Any**	20.9	20.0	18.5	18.2
	Severe‡	0	0	0	0
Diarrhea	**Any**	10.0	9.1	4.6	6.1
	Severe§	0	0	0	0
Fever	**Any**	12.7	20.9	15.7	22.4
	≥40°C	0	0	0	0
Fussiness	**Any**	45.5	51.8	41.7	33.3
	Severe**	0	2.7	1.9	1.0
Injection Site Redness	**Any**	14.6	25.5	28.7	34.3
	≥35 mm	4.5	5.5	4.6	15.2
Injection Site Swelling	**Any**	20.9	16.4	22.2	23.2
	≥35 mm	10.0	1.8	5.6	12.1
Injection Site Tenderness	**Any**	20.9	22.7	16.7	32.3
	Severe††	2.7	1.8	1.9	1.0
Vomiting	**Any**	3.6	3.6	5.6	3.0
	Severe‡‡	0	0	0	0

* Cried continuously for ≥3 hours.

† Sleeping most of the time.

‡ Refused most or all feeds.

§ Multiple liquid stools without any solid consistency.

** Continuously fussy for ≥3 hours.

†† Baby cried when leg is moved.

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

ADDITIONAL RELEVANT INFORMATION

Simultaneous vaccination with combination vaccines during early childhood has been the cornerstone of Canada's immunization program for many years. PEDIACEL® combines five childhood vaccines and offers protection against diphtheria, tetanus, pertussis, poliomyelitis and invasive Hib disease. Immunization with these antigens has been associated with a striking decrease in the incidence of morbidity and mortality caused by these infections. PEDIACEL® is a fully liquid version of PENTACEL® with both vaccines containing similar antigens. PENTACEL® has been licensed in Canada since 1997 with over 13 million doses administered to children in Canada. (7)

Diphtheria and Tetanus: The information provide below is consistent with NACI recommendations. (1)

Diphtheria is a serious communicable disease caused by exotoxin-producing strains of the bacterium *C. diphtheriae*. Symptoms result from local infection of the respiratory tract, which may lead to breathing difficulties, or infection of the skin or mucosal surfaces, or from dissemination of diphtheria toxin, which damages the heart and central nervous system. Routine immunization against diphtheria in infancy and childhood has been widely practised in Canada since 1930, resulting in a decline in morbidity and mortality. In Canada, there are 0 to 5 isolates reported each year. The case fatality rate remains at about 5 to 10%, with the highest death rates in the very young and elderly. The disease occurs most frequently in unimmunized or partially immunized persons. (1)

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C. tetani*. The organism is ubiquitous and its occurrence in nature cannot be controlled. Immunization is highly effective, provides long-lasting protection, and is recommended for the whole population. Between 1980 and 2004, the number of cases reported annually in Canada ranged from 1 to 10, with an average of 4 cases per year. (1)

Both diphtheria and tetanus toxoids are prepared by detoxification of the respective toxins with formaldehyde. Intramuscular injection of diphtheria and tetanus toxoids results in the production of protective antibodies against the toxins and their lethal effects, but it does not preclude local infections by the bacteria. (1) After completion of a primary series, circulating antibodies to tetanus and diphtheria toxoids gradually decline but are thought to persist at protective levels for up to 10 years. (1) The National Advisory Committee on Immunization (NACI) continues to recommend tetanus and diphtheria boosters every 10 years based on concern regarding the decline of antibody levels with age and potential failure of single booster doses to produce protective levels in older individuals. (1)

Pertussis: Pertussis (whooping cough) results from an acute infection of the respiratory tract caused by *B. pertussis*. Severity and mortality are greatest in infancy and even infants born to apparently immune mothers are highly susceptible to infection, particularly if maternal immunity was induced by whole-cell pertussis vaccine.

Whole-cell pertussis vaccine was first introduced in Canada in 1943. NACI states that over the past 64 years, pertussis incidence has declined by over 90%, although outbreaks of pertussis

continue to arise. Because of concerns about the frequency and severity of systemic and injection site adverse reactions with whole-cell pertussis vaccines, acellular pertussis vaccines have replaced whole-cell formulations in Canada. Acellular vaccines provoke significantly fewer injection site reactions, lower rates of fever and fewer episodes of unusual or persistent crying. (7) (26) (27) (29)

PEDIACEL® contains a five component acellular pertussis vaccine stimulating immune response to PT, FHA, PRN and FIM. In an efficacy trial, five-component acellular pertussis vaccines were significantly more efficacious than other acellular pertussis formulations containing fewer antigens. (7) (26) (30)

Poliomyelitis*:* Poliomyelitis is caused by infection with one of the three antigenic types of poliovirus. Following introduction of poliovirus vaccine in Canada in 1955, the indigenous disease has been virtually eliminated. However, the persistence of wild virus cases in polio endemic regions of Africa and Asia (31) necessitates that the highest possible level of vaccine-induced immunity be maintained in the Canadian population.

Inactivated Poliomyelitis Vaccine (Vero Cell Origin) and its combinations have been studied in more than 5,000 infants as a primary immunizing agent and in more than 1,000 children and adults as a booster vaccine. Seroconversion rates ranged from 74 to 100% for all 3 types after two doses and usually over 90% after three doses. (32) Since 1982, more than 90 million doses of Inactivated Poliomyelitis Vaccine (Vero Cell Origin) have been used, either alone or in combination with other vaccines.

***Haemophilus influenzae* type b:** Before the introduction of Haemophilus b conjugate vaccines in Canada, *H. influenzae* type b (Hib) was the most common cause of bacterial meningitis and a leading cause of other serious infections in young children. Four hundred and eighty-five cases were recorded in 1985 before the first vaccine was available. (33) After 1997 when routine infant immunization with PENTACEL® (same Hib conjugate as PEDIACEL®) began, only 8 - 10 cases a year were reported. Only a single case of Hib infection in a child fully vaccinated with PENTACEL® was reported to Canada's nationwide vaccine surveillance system in 1999. (34) In 2000, case reports of Haemophilus b meningitis reached an historical low with only 4 cases reported, a reduction of 99% from pre-vaccine levels. (33)

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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.

Product information as of January 2009.

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R7-0109 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PEDIACEL®

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

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

ABOUT THIS VACCINE

What the vaccine is used for:

PEDIACEL® is a vaccine that is used to help prevent diphtheria, tetanus (lock jaw), pertussis (whooping cough), polio and invasive *H. influenzae* type b (Hib) infections. 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 PEDIACEL® will produce enough antibodies to help protect them against these 5 diseases. However, as with all vaccines, 100% protection cannot be guaranteed.

What it does:

PEDIACEL® causes the body to produce its own natural protection against diphtheria, tetanus, pertussis (whooping cough), poliomyelitis and invasive Hib infections. 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 it should not be used:

- Do not give PEDIACEL® 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 PEDIACEL® 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 PEDIACEL® contains: diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine (pertussis toxoid, filamentous haemagglutinin, fimbriae types 2 and 3, pertactin), inactivated polio vaccine, Hib conjugate vaccine.

What the non-medicinal ingredients are:

Aluminum phosphate, 2-phenoxyethanol, polysorbate 80, bovine serum albumin, trace amounts of formaldehyde, glutaraldehyde, neomycin, streptomycin and polymyxin B.

What dosage forms it comes in:

PEDIACEL® 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 or pharmacist BEFORE the child receives PEDIACEL®:

- **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 who are 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 take 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 may be given to your child.

INTERACTIONS WITH THIS VACCINE

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

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

Not applicable to this vaccine.

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 PEDIACEL® 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 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 PEDIACEL®.

Serious side effects are extremely rare.

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

HOW TO STORE IT

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 information on serious and unexpected adverse events following vaccination.
If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:
toll-free telephone: 613-954-5590 (1-866-844-0018)
toll-free fax: 613-954-9874 (1-866-844-5931)
email: caefi@phac-aspc.gc.ca

regular mail:
Vaccine Safety Section
Centre for Immunization & Respiratory Infectious Diseases
Public Health Agency of Canada
100 Eglantine Driveway
A/L 0602C, Bldg. 6
Tunney's Pasture
Ottawa, Ontario K1A 0K9

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: 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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