PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

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, Intramuscular

(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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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 4 DOSAGE AND ADMINISTRATION.)[1]

1.1 Pediatrics

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

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for adult and geriatric use.

2 CONTRAINDICATIONS

Hypersensitivity

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. (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING) 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

The following events are contraindications to administration of any pertussis-containing vaccine, 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.

[1] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

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.

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.[2]

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

The childhood 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.[3]

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.

4.4 Administration

FOR INTRAMUSCULAR ADMINISTRATION ONLY

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions

[2] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

[3] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

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.

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.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Suspension for injection (see strength and composition below)	Excipients: aluminum phosphate (adjuvant), 2-phenoxyethanol, polysorbate 80. Manufacturing process residuals: bovine serum albumin, neomycin, polymyxin B and trace amounts of streptomycin,

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
		formaldehyde and glutaraldehyde.

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 18-30 µg of Tetanus Protein	10 µg

* or the equivalent antigen quantity, determined by suitable immunochemical method

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. PEDIACEL® is available in a package of:

- 1 single-dose (0.5 mL) vial.
- 5 single-dose (0.5 mL) vials.

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

7 WARNINGS AND PRECAUTIONS

General

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.

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 2 CONTRAINDICATIONS and 8 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.[4]

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

[4] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

vaccines. By chance alone, some cases of SIDS can be expected to follow receipt of PEDIACEL®.

Febrile or Acute Disease: It is recommended that vaccination should be postponed in cases of acute or febrile disease. 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.

- 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.

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. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. For instructions on recognition and treatment of anaphylactic reactions see the current edition of the Canadian Immunization Guide or visit the Health Canada website.[5]

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. Nevertheless, vaccination of

[5] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

persons with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.[6]

Neurologic

A review by the IOM found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). It is recommended 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.

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.

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. A history of HHEs is not a contraindication to the use of acellular pertussis vaccines but recommends caution in these cases.[6]

Syncope related precautions

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

7.1 Special Populations

7.1.1 Pregnant Women

The vaccine should not be administered to pregnant women.

7.1.2 Breast-feeding

The vaccine should not be administered to nursing women.

7.1.3 Pediatrics

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

[6] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

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.

7.1.4 Geriatrics

The vaccine should not be administered to adult and elderly populations.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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. 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 2.

Table 2: 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

Solicited Reactions	2 months (N = 336)	4 months (N = 331)	6 months (N = 330)	18 months (N = 300)
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

8.5 Post-Market Adverse Reactions

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®.

General Disorders and Administration Site Conditions

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

Immune System Disorders

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

Musculoskeletal, Connective Tissue and Bone Disorders

Pain in vaccinated limb.

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. Somnolence.

Psychiatric Disorders

Irritability, screaming.

Respiratory, Thoracic and Mediastinal Disorders

Apnea.

Skin and Subcutaneous Tissue Disorders

Erythema, rash.

Vascular Disorders

Pallor.

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 4th and 5th doses.

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.

Healthcare professionals should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements. (See PATIENT MEDICATION INFORMATION, Reporting Side Effects for Vaccines).

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Use with Immunosuppressive Therapies

Immunosuppressive treatments may interfere with the development of the expected immune response. (See 7 WARNINGS AND PRECAUTIONS.)

Concomitant Vaccine Administration

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. Vaccines administered simultaneously should be given using separate syringes at separate sites. Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination.[7]

[7] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of action

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 considered the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. Levels of 1.0 IU/mL have been associated with long-term protection.

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. 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.

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.

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.

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. 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. 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.

10.2 Pharmacodynamics

Diphtheria and Tetanus: 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. Diphtheria and tetanus toxoids boosters are recommended every 10 years. [8]

Pertussis: 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. 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.

[8] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on diphtheria, tetanus, pertussis, poliomyelitis and Hepatitis.

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. 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, Newfoundland and Labrador and British Columbia support national and IMPACT data demonstrating a progressive decline of pertussis cases among infants and children through 9 years of age.

Poliomyelitis: 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.

10.3 Pharmacokinetics

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.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2° to 8°C (35° to 46°F). Do not freeze. Discard product if exposed to freezing (≤ 0°C). PEDIACEL® 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.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use after expiration date.

PART II: SCIENTIFIC INFORMATION

13 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. 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. 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 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. 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. 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 3).

Table 3: 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	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

Study	Study Design	Dosage and Route of Administration	Vaccination Schedule/ Study Population*	Gender
Sweden II	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	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	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
U01-A5I-302	Randomized, controlled, open, multicentre safety and immunogenicity trial of PEDIACEL® Compared to (Act-HIB /DTP and OPV), Each Co-Administered with NeisVac-C™ or Menjugate™	0.5 mL I.M.	2, 3, and 4 months of age N= 241	Males N = 128 Females N = 113

* Number enrolled, I.M - Intramuscular.

† 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)].

14.2 Study Results

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). 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). 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. (See Table 4.)

Table 4: Vaccine Efficacy Against Pertussis Infection of Varying Clinical Severity

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 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 5: Duration of Vaccine Efficacy for TRIPACEL® Compared to Placebo

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.

A sub-study of this trial looked specifically at immunized children exposed to pertussis from other members of their households. 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). 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). 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.

Table 6: 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.

14.4 Immunogenicity

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.

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 4 through Table 8.) 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 7 and Table 8) Seroconversion rates (% ≥4-fold rise) were high for each of the pertussis antibodies after the primary series. (See Table 9.) A robust booster response was observed after the fourth dose. (See Table 8 and Table 10.)

Table 7: 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

		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 8: 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

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 9: Pertussis Antibody Responses Measured One Month After the Third Dose of the Primary Series with PEDIACEL® or PENTACEL® in Clinical Trial PB9502

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 age.

Table 10: Pertussis Antibody Responses Measured Immediately Before and One Month After a Fourth Dose with PEDIACEL® or PENTACEL® in Clinical Trial PB9502

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)

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)
	% ≥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 9.) 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 9.) 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 12)

Table 11: 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

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

Solicited Reaction		2 months (N = 336)	4 months (N = 331)	6 months (N = 330)	18 months (N = 300)
	≥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 12: 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

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.

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 13)

Table 13: 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

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	-	-

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
	% ≥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 14.) A robust booster response was observed after the fourth dose for all the vaccine antigens. (See Table 13 and Table 14.)

Table 14: 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

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 15.) 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 15.)

Table 15: 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

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 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 U01-A5I-302

In a randomized, controlled clinical trial conducted in the United Kingdom (U01-A5I-302), 3 doses of PEDIACEL® were administered to infants concomitantly with 3 doses of either a meningococcal group C CRM_{197} conjugate vaccine (MCC-CRM; N=60) or a meningococcal group C tetanus toxoid conjugate vaccine (MCC-TT; N=61). The vaccines were administered according to the UK immunization schedule at 2, 3, and 4 months of age without a booster in the second year of life.

One month after the third dose, anti-PRP responses in infants who received MCC-CRM were lower in comparison to those who received MCC-TT: 88.0% (95%CI: 76.2, 94.4) vs 98.1% (95%CI: 90.1, 99.7) achieved an anti-PRP concentration of at least 0.15 µg/mL, with GMCs of 1.26 µg/mL (95%CI: 0.75, 2.13) and 3.67 µg/mL (95%CI: 2.56, 5.26). PEDIACEL® did not affect the proportions of infants with meningococcal group C serum bactericidal antibody (SBA) titres of at least 1:8 (measured with rabbit complement) when co-administered with MCC-CRM or MCC-TT; at least 98% of the infants attained seroprotective levels against meningococcal group C. The Men C SBA GMTs in infants who received concomitant MCC-TT were lower in comparison to those observed with MCC CRM-197: 690 (95%CI: 418, 1140) vs 2165 (95%CI: 1517, 3089), respectively. The clinical significance of these differences is unknown.

Safety

Following each vaccination, solicited injection site reactions within the first seven days of vaccination occurred in 13.2% (tenderness) to 38.0% (redness) of PEDIACEL® vaccinees. Severe injection site reactions were observed in 4.1% (tenderness) to 12.4% (redness). The frequency of reactions at the injection site was similar after each dose, although tenderness was lower at the second and third dose. Solicited systemic reactions within 7 days after vaccination occurred in 9.1% (fever ≥37.5°C) to 60.3% (irritability), and tended to decrease with each vaccination. Severe systemic reactions were observed in 0% (fever and diarrhea) to 14.9% (irritability). No child immunized with PEDIACEL® experienced a fever ≥39.5°C.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PEDIACEL®

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

Read this carefully before you start taking **PEDIACEL®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PEDIACEL®**.

What is PEDIACEL® 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.

How does PEDIACEL® work?

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

What are the ingredients in PEDIACEL®?

Medicinal ingredients: diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine (pertussis toxoid, filamentous haemagglutinin, fimbriae types 2 and 3, pertactin), inactivated polio vaccine, Hib conjugate vaccine.

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

PEDIACEL® comes in the following dosage forms:

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

Do not use PEDIACEL® if:

- a child has an allergy to any ingredient in the vaccine or has had an allergic reaction after receiving a vaccine that contained similar ingredients.
- a person 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child get PEDIACEL®. Talk about any health conditions or problems you or your child may have or have had, including:

- 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.
- Fainting can occur following, or even before, any needle injection. Therefore, tell your doctor or nurse if your child fainted with a previous injection

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take PEDIACEL®:

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:

If you think you, or a person you are caring for, have taken too much PEDIACEL®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to go back to the healthcare professional at the scheduled time, ask the healthcare professional for advice.

What are possible side effects from using PEDIACEL®?

These are not all the possible side effects you may have when taking PEDIACEL®. If you experience any side effects not listed here, tell your healthcare professional.

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.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi Pasteur Limited cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

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 and sight of children.

If you want more information about PEDIACEL®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofipasteur.ca, or by calling 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area).

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