PRODUCT MONOGRAPH

ACTacel®

Act-HIB® Reconstituted with TRIPACEL®

Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

Reconstituted product for injection

(For active immunization against *Haemophilus Influenzae* type b Disease, Diphtheria, Tetanus and Pertussis)

ATC Code: J07AG52

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

Reconstituted product for injection

Each single dose (0.5 mL) after reconstitution contains:

Active Ingredients

Purified polyribosylribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to tetanus protein, diphtheria toxoid, tetanus toxoid and acellular pertussis [pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)]

Clinically Relevant Non-medicinal Ingredients

Excipients: Aluminum phosphate (adjuvant), 2-phenoxyethanol, sucrose, Tris (hydroxymethyl aminomethane)

Manufacturing process residuals: formaldehyde, glutaraldehyde, are present in trace amounts.

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

DESCRIPTION

ACTacel® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed] is supplied in two vials: one vial containing lyophilized Haemophilus b conjugate vaccine consisting of the *Haemophilus influenzae* type b capsular polysaccharide PRP covalently bound to tetanus protein, and one vial containing a suspension of diphtheria and tetanus toxoids adsorbed onto aluminum phosphate and acellular pertussis vaccine suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified antigens (PT, FHA, PRN and FIM).

INDICATIONS AND CLINICAL USE

ACTacel® is indicated for the 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 invasive *Haemophilus influenzae*

type b disease, diphtheria, tetanus and pertussis (whooping cough). (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 invasive *H. influenzae* type b (Hib) infection diphtheria, tetanus or pertussis 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 *H. influenza* type b, diphtheria, tetanus and pertussis according to standard schedules. (1)

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

Pediatrics

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

Geriatrics

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

CONTRAINDICATIONS

Hypersensitivity

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

Neurological Disorders

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

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 ACTacel®, health-care providers should inform the parent or guardian 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 signs or symptoms of an adverse reaction after a previous dose of vaccine. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

The rates and severity of adverse events in recipients of tetanus toxoid are influenced by the number of prior doses and the level of pre-existing antitoxins. (3)

As with any vaccine, ACTacel® 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.

Edematous reaction affecting one or both lower limbs has occurred following vaccination with *Haemophilus influenzae* 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. In reported cases, all events resolved spontaneously without sequelae within 24 hours.

Inflammatory cellulitis without bacterial infection, drowsiness and high fever (>40.5º) have been associated with similar antigen containing vaccines.

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

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

ACTacel® should not be administered into the buttocks.

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

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 ACTacel® 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 ACTacel® 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 ACTacel® even in persons with no prior history of hypersensitivity to the product components. Cases of allergic or anaphylactic reaction have been reported after receiving some preparations containing diphtheria and tetanus toxoids and/or pertussis antigens. (4)

As recommended by NACI, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. (1) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. (1) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

According to NACI, immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. (1) 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)

Anaphylactic reaction, hives and urticaria have been associated with similar antigen containing vaccines.

Neurologic

A review by the US Institute of Medicine (IOM) found evidence for a causal relationship between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome (GBS). (5) ACIP recommends that if GBS occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give ACTacel® or any vaccine containing tetanus toxoid should be based on careful consideration of potential benefits and possible risks. (2)

ACIP recommends that, for infants or children at higher risk for seizures than the general population that an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including ACTacel®) and for the following 24 hours, to reduce the possibility of post-vaccination fever. (2)

Hypotonic-hyporesponsive episodes (HHEs) rarely follow vaccination with whole-cell pertussis-containing DTP vaccines and occur even less commonly after acellular pertussis-containing DTP vaccines and DT vaccines. NACI states that a history of HHEs is not a contraindication to the use of acellular pertussis vaccines but recommends caution in these cases. (1)

Febrile convulsions, convulsions (partial seizures, grand mal convulsion), polyradiculopathies and demyelinating diseases (including Guillain-Barré syndrome) have been associated with similar antigen containing vaccines.

Pregnant Women

This vaccine is not indicated for persons 7 years of age and older.

Nursing Women

This vaccine is not indicated for persons 7 years of age and older.

Pediatrics

The potential risk of apnea and the need for respiratory monitoring for 48 – 72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

In a randomized partially blinded multicentre controlled clinical trial conducted in Canada, 545 children who had previously received a primary series at 2, 4 and 6 months of age with Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] and one of two different formulations of TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed] given separately, were administered the same vaccines at 17 - 21 months of age either

as a single injection with ACTacel® where Act-HIB® was reconstituted with TRIPACEL® or with both vaccines given separately. The two formulations of TRIPACEL® differed only in the quantity of PT and FHA antigens contained in the pertussis component. One had 10 µg PT and 5 µg FHA, while the other had 20 µg of both antigens. The lower antigen formulation was given to a total of 77 children with 27 of these being vaccinated with the combined vaccines. The higher antigen formulation was administered to 468 children and 155 of these received the combined vaccines. No statistically significant differences between the rates of solicited injection site and systemic adverse events were observed after vaccination with either ACTacel® formulation compared to when the Act-HIB® and TRIPACEL® were given separately. In addition there were no differences in the adverse event rates observed with either formulation of ACTacel®. There were no reports of HHEs in this study and no serious adverse events after vaccination with ACTacel®. A summary of the solicited injection site and systemic adverse event rates that were observed with either formulation of ACTacel® is shown in Table 1. (6) (7)

Table 1: Adverse Event Rates (%) Observed in a Canadian Clinical Trial within 72 Hours of Vaccination with ACTacel® at 17 to 21 Months (6) (7)

Adverse Event	**n = 180**
Injection Site Reactions	
Redness	37.8
Swelling	28.9
Tenderness	27.8
Systemic Reactions	
Fussiness	33.3
Less Active	17.2
Eating Less	17.2
Crying	13.9
Vomiting	5.6
Diarrhea	11.7
Fever	32.8

In a randomized partially blinded multicentre controlled clinical trial conducted in Taiwan, 68 infants received Act-HIB® reconstituted with the formulation of TRIPACEL® containing greater amounts of PT and FHA and a control group of 67 received the same vaccines administered at separate sites at 2, 4, 6 and 18 months of age. Reaction rates at the injection site were comparable whether the vaccines were given combined as ACTacel® or given separately as TRIPACEL® and Act-HIB®. No serious adverse events were observed during this study. Systemic adverse events were usually mild. There were no reports of fever ≥40°C. Few systemic reactions were reported after the fourth dose (Table 2). (8) (9)

Table 2: Adverse Event Rates (%) Observed in a Taiwanese Clinical Trial within 48 Hours of Vaccination with ACTacel® at 2, 4, 6 and 18 Months (8) (9)

Adverse Event	2 months	4 months	6 months	18 months
	n = 67	n = 66	n = 64	n = 61
Injection Site Reactions				
Redness	19.4	10.6	15.6	0.0
Swelling	22.4	16.7	7.2	0.0
Tenderness	28.4	13.6	15.6	0.0
Systemic Reactions				
Fussiness	35.8	24.2	18.8	3.3
Less Active	6.0	3.0	1.6	0.0
Eating Less	20.9	10.6	10.9	1.6
Crying	22.4	13.6	1.6	0.0
Vomiting	4.5	3.0	0.0	0.0
Diarrhea	4.5	0.0	1.6	1.6
Fever	8.7	9.8	5.1	0.0

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of ACTacel® worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not 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 ACTacel®.

Psychiatric Disorders

Irritability, screaming, prolonged or unusual high-pitched crying, restlessness

Nervous System Disorders

Hypotonic-hyporesponsive episodes, hypotonia, encephalopathy,

Vascular Disorders

Pallor

Gastro-intestinal Disorders

Nausea

Skin and Subcutaneous Tissue Disorders

Erythema, rash, pruritus

General Disorders and Administration Site Conditions

Injection site reactions, including pain and inflammation; very rarely, large injection site reactions, including limb swelling which may extend from the injection site beyond one or both joints.

Somnolence, sleepiness

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

DRUG INTERACTIONS

Vaccine-Drug Interactions

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

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) (10) Simultaneous administration is suggested, particularly when there is concern that a person may not return for subsequent vaccination. (10) Simultaneous administration of childhood vaccines such as ACTacel®, MMR, varicella, pneumococcal conjugate and hepatitis B vaccines, is encouraged for children who are at the recommended age to receive these vaccines and for whom no contraindications exist.

ACTacel® 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 *Haemophilus influenzae* type b disease within two weeks of immunization. (11)

DOSAGE AND ADMINISTRATION

Recommended Dose

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

If for any reason this schedule is delayed, it is recommended that 3 doses be administered with an interval of 2 months between each dose, followed by a fourth dose administered approximately 6 to12 months after the third dose.

Whenever feasible, ACTacel® should be used for all 4 doses in the vaccination series as there are no clinical data to support the use of ACTacel® with any other licensed acellular pertussis combination vaccine in a mixed sequence. For situations where a different brand of DTaP, DTaP-IPV or DTaP-IPV/Hib vaccine was originally used, or where the brand is unknown, please refer to the latest edition of the Canadian Immunization Guide.

NACI recommends that premature infants whose clinical condition is satisfactory should be immunized with full doses of vaccine at the same chronological age and according to the same schedule as full-term infants regardless of birth weight. (1)

Fractional doses (<0.5 mL) should not be given. The effect of fractional doses on safety and efficacy has not been determined. (12)

In compliance with NACI's recommended immunization schedule, the childhood immunization series should be completed with a single 0.5 mL dose of TRIPACEL® between 4 and 6 years of age. A dose of IPV [Inactivated Poliomyelitis Vaccine] should be administered concomitantly at a separate site. Alternatively, Sanofi Pasteur Limited's QUADRACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine] or ADACEL® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed] accompanied with IPV, may be used for this booster dose. This booster dose is unnecessary if the fourth dose of ACTacel® was administered after the child's fourth birthday. (1)

ACTacel® should not be administered to persons less than 2 months of age 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.

Reconstitution of Freeze-Dried Product and Withdrawal from Stoppered Vial

Reconstitute Act-HIB® with the TRIPACEL® vaccine.

Cleanse the TRIPACEL® and Act-HIB® vial stoppers with a suitable germicide before reconstitution. Do not remove from either vial, the stoppers or the metal seals holding them in place. Thoroughly but gently shake the vial of TRIPACEL®, withdraw the entire contents of the liquid vaccine and inject slowly into the vial of lyophilized Act-HIB®. Swirl the vial now containing ACTacel® thoroughly until a uniform, cloudy, white to off-white suspension results. Withdraw the total volume of reconstituted, combined vaccine. ACTacel® should be used immediately after reconstitution. Refer to Figures 1, 2, 3, 4 and 5.

INSTRUCTIONS FOR RECONSTITUTION OF TRIPACEL® WITH Act-HIB®

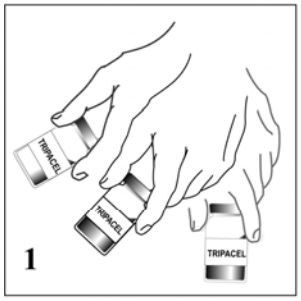

Figure 1
Gently shake the vial of TRIPACEL®.

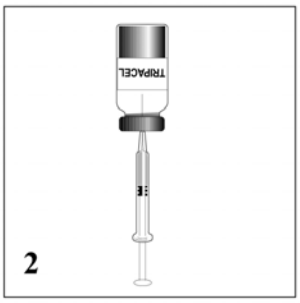

Figure 2
Withdraw the entire liquid content.

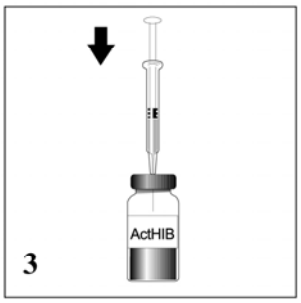

Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

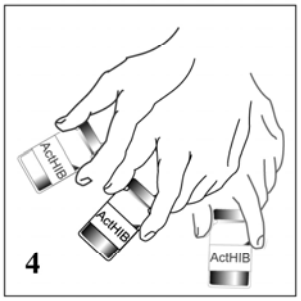

Figure 4
Swirl vial gently.

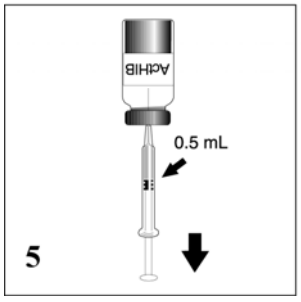

Figure 5
After reconstitution, immediately withdraw 0.5 mL of ACTacel® and administer intramuscularly.
ACTacel® should be used immediately after reconstitution.

Aseptic technique must be used. Use a separate sterile needle and syringe, 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 reconstituted vaccine **intramuscularly** (I.M.). In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for injection.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

Overdosage

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

ACTION AND CLINICAL PHARMACOLOGY

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

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *C. tetani*. The toxin causes neuromuscular dysfunction, with rigidity and spasms of skeletal muscles. Protection against disease attributable to *C. tetani* is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay, is considered the minimum protective level. (2) (3) A tetanus antitoxin level of at least 0.1 IU/mL as measured by the ELISA used in clinical studies of ACTacel® is considered protective for tetanus. Levels of 1.0 IU/mL have been associated with long-term protection. In a clinical trial in Taiwan, after 3 doses of ACTacel®, 100% (N = 68) 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 4 doses. (9)

After completion of the childhood immunization series, circulating antibodies to diphtheria and tetanus toxoids gradually decline but are thought to persist at protective levels for up to 10 years. NACI recommends Diphtheria and Tetanus Toxoid 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 ACTacel® (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. (13) (14) (15) (16) (17) (18) In a controlled clinical trial in Sweden (Sweden II Trial), the efficacy of a DTaP vaccine with a

similar formulation of five pertussis antigens as ACTacel® was demonstrated to provide a two-fold to three-fold higher protection against pertussis with any cough compared to the vaccine containing three pertussis antigens. The observed difference supports the role of FIM in the protection against colonization of *B. pertussis* and mild disease. (19)

***Haemophilus influenzae* type b:** The response to the Act-HIB® component of the vaccine is typical of a T-dependent immune response with induction of immunologic 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 ACTacel® in 68 infants, after 3 doses, 100% of vaccinated children achieved protective antibody titres ≥0.15 µg/mL and 95.3% achieved protective antibody levels ≥1.0 µg/mL. All vaccinated children achieved protective antibody levels ≥1.0 µg/mL after 4 doses. (9)

Duration of Effect

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

STORAGE AND STABILITY

Store at 2º to 8ºC (35º to 46ºF). **Do not freeze**. Discard product if exposed to freezing.

The vaccine should be used immediately after reconstitution.

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

After reconstitution, ACTacel® (Act-HIB® reconstituted with TRIPACEL®) is supplied as a sterile, uniform, cloudy, white to off-white suspension. Each component is supplied in a monodose vial.

Composition

Each single dose (0.5 mL) after reconstitution contains:

Active Ingredients

Purified Polyribosylribitol Phosphate Capsular Polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to 18-30 µg of Tetanus Protein	10 µg
Diphtheria Toxoid	15 Lf
Tetanus Toxoid	5 Lf
Acellular Pertussis	
Pertussis Toxoid (PT)	10 µg
Filamentous Haemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg

Other Ingredients:

Excipients:

Aluminum Phosphate (adjuvant) (Aluminum 0.33 mg)	1.5 mg
2-phenoxyethanol	0.6% v/v
Sucrose	42.5 mg
Tris (Hydroxymethyl) Aminomethane	0.6 mg

Manufacturing Process Residuals:

Formaldehyde and glutaraldehyde are present in trace amounts.

Packaging

Both components of ACTacel® (TRIPACEL® and Act-HIB®) are supplied in single dose vials.

The vials are made of Type 1 glass. The vial stoppers for this product do not contain latex (natural rubber).

ACTacel® is supplied in a package of:

1 x 0.5 mL (single dose) vial of TRIPACEL® for reconstituting 1 x 1 dose of Act-HIB®

5 x 0.5 mL (single dose) vials of TRIPACEL® for reconstituting 5 x 1 dose of Act-HIB®

Vaccine Information Service: 1-888-621-1146 or 416-667-2779
Business hours: 8:00 a.m. to 5:00 p.m. Eastern Time, Monday to Friday
Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of November 2011

Manufactured by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada
and
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R8-1111 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine

Product Characteristics

ACTacel® is supplied in two vials: one vial containing lyophilized Haemophilus b conjugate vaccine consisting of the *Haemophilus influenzae* type b capsular polysaccharide (PRP), covalently bound to tetanus protein, and one vial containing a suspension of diphtheria and tetanus toxoids adsorbed on aluminum phosphate and acellular pertussis and suspended in water for injection. The acellular pertussis vaccine is composed of 5 purified pertussis antigens (PT, FHA, PRN and FIM). After reconstitution, the vaccine is a sterile, uniform, cloudy, white to off-white suspension.

C. diphtheriae is grown in modified Mueller's growth medium. (21) After ammonium sulfate fractionation, the diphtheria toxin is detoxified with formalin 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 sulfate 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. 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 with aluminum phosphate (as adjuvant), 2-phenoxyethanol and water for injection.

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 mice to PT, FHA, PRN and FIM, measured by enzyme-linked immunosorbent assay (ELISA).

Act-HIB® is a sterile, lyophilized vaccine that is reconstituted at the time of use with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed. Act-HIB® consists of the Haemophilus b capsular polysaccharide 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) Act-HIB® contains no preservative. The tetanus protein is prepared by ammonium sulfate purification and formalin inactivation of the toxin from cultures of *C. tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (25) The toxoid is filter sterilized before the conjugation process. Potency of Act-HIB® is specified on each lot by limits on the content of

PRP polysaccharide and protein in each dose and the proportion of polysaccharide and protein that is characterized as high molecular weight conjugate.

CLINICAL TRIALS

Four pivotal clinical trials (Sweden Trial I, Sweden Trial II, Taiwan P3T02393 and Canada Phase IIC PB9301) conducted in Sweden, Taiwan and in Canada provide the clinical basis for the licensure of ACTacel® in Canada. (See Table 3.)

Table 3: Summary of Demographics and Study Design of the Trials with ACTacel®

Study	Study Design	Dosage and Route of Administration	Vaccination Schedule/ Study Population	Gender
Sweden I (26) (27)	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 (19) (28)	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
Taiwan P3T 02393 (8) (9)	Randomized, controlled, safety and efficacy when DTaP is combined with *Haemophilus influenzae* B conjugate vaccine.	0.5 mL I.M.	2, 4, 6, 18 months of age N = 135	Males N = 67 Females N = 68
Canada Phase IIC PB9301 (6) (7)	Randomized, partially blinded, controlled, multicentre safety and efficacy when DTaP is combined with *Haemophilus influenzae* B conjugate vaccine.	0.5 mL I.M.	17-19 months of age N = 545	Males N = 306 Females N = 239

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 (but with a lower content of PT and FHA per dose) present in ACTacel® (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). (Table 4) Protection against pertussis by TRIPACEL® was sustained for the 2-year follow-up period. (26) (Table 4)

Table 4: Vaccine Efficacy Against Pertussis Infection of Varying Clinical Severity (26) (27)

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 (26) (27) looked at the persistence of the protection provided by TRIPACEL® compared to placebo. High levels of protection were sustained for TRIPACEL® over the entire 2-year follow-up period. (Table 5)

Table 5: Duration of Vaccine Efficacy Compared to Placebo for TRIPACEL® Versus Whole-Cell Vaccine (26) (27)

Vaccine Efficacy (%) Compared to DT (Placebo n = 2,068)	
Interval Since 3rd 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. (26) (27)

A sub-study of this trial looked specifically at immunized children exposed to pertussis from other members of their household. (13) This formulation of TRIPACEL® was more efficacious than the any of the other acellular and whole-cell pertussis 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. (13)

Clinical Trial Canada Phase IIC PB9301

In a randomized partially blinded multicentre controlled clinical trial conducted in Canada, 545 children who had previously received a primary series at 2, 4, and 6 months of age with Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)] and one of two different formulations of TRIPACEL® given separately, the same vaccines were administered at 17 - 21 months of age either as a single injection with ACTacel® where Act-HIB® was reconstituted with TRIPACEL® or with both vaccines given separately. The two formulations of TRIPACEL® differed only in the quantity of PT and FHA antigens contained in the pertussis component. One had 10 µg PT and 5 µg FHA, while the other had 20 µg of both antigens. The lower antigen formulation was given to a total of 77 children with 27 of these being vaccinated with the combined vaccines. The higher antigen formulation was administered to 468 children and 155 of these received the combined vaccines. Antibody responses to diphtheria, tetanus, pertussis antigens, and PRP-T were comparable between the two different TRIPACEL® formulations. No clinically significant interactions were observed in the combined and separate vaccine groups. Regardless of vaccine group, seroprotective levels for diphtheria and tetanus antitoxin (≥0.10 IU/mL and ≥0.10 IU/mL, respectively) were achieved in 100% and over 99% had concentrations anti-PRP ≥1.0 µg/mL. (6) (7)

Safety

There were no reports of HHEs in this study and no serious adverse events after vaccination with ACTacel®. A summary of the solicited injection site and systemic adverse event rates that were observed with either formulation of ACTacel® is shown in Table 6. (6) (7)

Table 6: Adverse Event Rates (%) Observed in a Canadian Clinical Trial within 72 Hours of Vaccination with ACTacel® at 17 to 21 Months (6) (7)

Adverse Event	Severity	n = 180
Injection Site Reactions		
Redness	Any	37.8
	≥35 mm	26.7
Swelling	Any	28.9
	≥35 mm	22.8
Tenderness	Any	27.8
	Severe	1.1
Systemic Reactions		
Fussiness	Any	33.3
	≥3 hours	0.0
Less Active	Any	17.2
	Severe	0.6
Eating Less	Any	17.2
	Severe	0.6
Crying	Any	13.9
	≥3 hours	0.0
Vomiting	Any	5.6
	Severe	0.0
Diarrhea	Any	11.7
	Severe	0.6
Fever	Any	32.8
	≥40°C	0.0

Clinical Trial Taiwan P3T 02393

In a randomized partially blinded multicentre controlled clinical trial conducted in Taiwan, 68 infants received ACTacel® where Act-HIB® was reconstituted with the formulation of TRIPACEL® containing greater amounts of PT and FHA, and a control group of 67 received the same vaccines administered at separate sites at 2, 4, 6, and 18 months of age. No clinically significant interactions were observed in the antibody responses of combined and separate vaccine groups (Table 7). One month after the primary series all vaccinees (100%) in both vaccine groups achieved levels considered protective for diphtheria and tetanus antitoxin (≥0.01 IU/mL and ≥0.01 EU/mL, respectively) and for anti-PRP (≥0.15 µg/mL). Anti-PRP levels of ≥1.0 µg/mL were attained in 95.3% and 98.5% of the vaccinees in the combined and separate groups, respectively. One month after the 18 month booster dose, all vaccinees (100%) achieved levels for diphtheria and tetanus antitoxin ≥0.10 IU/mL and ≥0.10 EU/mL, respectively, and anti-PRP concentrations ≥1.0 µg/mL. (8) (9)

Table 7: Geometric Mean Titres after the Third and Fourth Doses of ACTacel®*, or Act-HIB® and TRIPACEL®* (8) (9)

Antibody	GMT Infants (at 7 months)		GMT Toddlers (19 - 20 months)	
	ACTacel® (n = 64)	TRIPACEL® + Act-HIB® (n = 67)	ACTacel® (n = 61)	TRIPACEL® + Act-HIB® (n = 66)
Anti-PRP (µg/mL)	11.8	13.0	58.5	55.3
Diphtheria (IU/mL)	0.48	0.64	5.3	3.3
Tetanus (EU/mL)	2.8	2.7	12.3	17.1
PT (EU/mL)	131	105	216	182
FHA (EU/mL)	116	116	203	200
PRN (EU/mL)	100	77	263	197
FIM (EU/mL)	922	702	892	732

* contains a TRIPACEL® formulation with higher amounts of PT and FHA (20 µg)

Safety

Reaction rates at the injection site were comparable whether the vaccines were given combined as ACTacel® or given separately as TRIPACEL® and Act-HIB®. No serious adverse events were observed during this study. Systemic adverse events were usually mild. There were no reports of fever ≥40°C. Few systemic reactions were reported after the fourth dose (Table 8). (8) (9)

Table 8: Adverse Event Rates (%) Observed in a Taiwanese Clinical Trial within 48 Hours of Vaccination with ACTacel® at 2, 4, 6 and 18 Months (8) (9)

Adverse Event	Severity	2 months n = 67	4 months n = 66	6 months n = 64	18 months n = 61
Injection Site Reactions					
Redness	Any	19.4	10.6	15.6	0.0
	≥30 mm	6.0	7.6	3.1	0.0
Swelling	Any	22.4	16.7	7.2	0.0
	≥30 mm	10.4	4.5	1.6	0.0
Tenderness	Any	28.4	13.6	15.6	0.0
	Severe	0.0	0.0	0.0	0.0
Systemic Reactions					
Fussiness	Any	35.8	24.2	18.8	3.3
	≥3 hours	3.0	0.0	0.0	0.0
Less Active	Any	6.0	3.0	1.6	0.0
	Severe	.5	0.0	0.0	0.0
Eating Less	Any	20.9	10.6	10.9	1.6
	Severe	0.0	0.0	0.0	0.0
Crying	Any	22.4	13.6	1.6	0.0
	≥3 hours	3.0	0.0	0.0	0.0
Vomiting	Any	4.5	3.0	0.0	0.0
	Severe	0.0	0.0	1.5	0.0
Diarrhea	Any	4.5	0.0	1.6	1.6
	Severe	0.0	0.0	0.0	0.0
Fever	Any	8.7	9.8	5.1	0.0
	≥40°C	0.0	0.0	0.0	0.0

ADDITIONAL RELEVANT INFORMATION

Simultaneous vaccination with combination vaccines during early childhood has been the cornerstone of Canada's immunization program for many years. ACTacel® combines four childhood vaccines and offers protection against diphtheria, tetanus, pertussis, 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. (1)

***Haemophilus influenzae* type b:** Before the introduction of Haemophilus b conjugate vaccines in Canada, *H. influenzae* type b 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. (29) After 1997 when routine infant immunization with PENTACEL® (same Hib conjugate as ACTacel®) 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. (30) 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. (29)

Diphtheria and Tetanus: The information provided below is consistent with NACI's guidelines. (1) Diphtheria is an acute 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. 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 occur. (1) 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. (19) (26) (27) (28) (31)

ACTacel® 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. (26) (27) (32)

REFERENCES

1 National Advisory Committee on Immunization. In: Canadian Immunization Guide, Seventh ed. Her Majesty the Queen in Right of Canada, represented by the Minister of Public Works and Government Services Canada; 2006. p. 31,74,80,82-4,94,113,117-8,126-9,166-78,247,257-65,309-15.

2 CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR-15):1-48.

3 Plotkin SA, Orenstein WA. In: Vaccines. 4th ed. Philadelphia, PA: W.B. Saunders 2004. p. 214,229-68,485,518-19,745-81.

4 CDC. Diphtheria, tetanus and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1991;40(RR-10):1-28.

5 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence bearing on causality. National Academy Press, Washington, DC: 1994. p. 78-117.

6 Halperin SA, et al. Safety and immunogenicity of an acellular pertussis, diphtheria, tetanus vaccine given as a single injection with Haemophilus influenzae b conjugate vaccine. Vaccine 1997;15(3):295-300.

7 Data on File at Sanofi Pasteur Limited - Study PB9301.

8 Lee CY, et al. An evaluation of the safety and immunogenicity of a five-component acellular pertussis, diphtheria and tetanus toxoid vaccine (DTaP) when combined with a Haemophilus influenzae type b-tetanus toxoid conjugate vaccine (PRP-T) in Taiwanese infants. Pediatrics 1999;103(1):25-30.

9 Data on file at Sanofi Pasteur Limited - Study P3T 02393.

10 CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization (ACIP) and the American Academy of Family Physicians (AAFP) MMWR 2002;51(RR-2):4.

11 Rothstein EP, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. Pediatr Infect Dis J 1991;10:311-4.

12 American Academy of Pediatrics. Active Immunization, Passive Immunization and Pertussis. In: Pickering LK, editor. Red Book: Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003. p. 34,63-6,472-86. Published erratum appears in Red Book® 2003 Report of the Committee on Infectious Diseases Errata. p. 3

13 Storsaeter J, et al. Levels of anti-pertussis antibodies related to protection after household exposure to Bordetella pertussis. Vaccine 1998;16(20):1907-16.

14 Cherry JD, et al. A search for serologic correlates of immunity to Bordetella pertussis cough illnesses. Vaccine 1998;16:1901-6.

15 Deen JL, et al. Household contact study of Bordetella pertussis infections. Clin Infect Dis 1995;21(5)1211-9.

16 Preston NW, Stanbridge TN. Efficacy of pertussis vaccines: a brighter horizon. Br Med J 1972;3:448-51.

17 Efficacy of whooping-cough vaccines used in the United Kingdom before 1968. Br Med J 1973;1:259-62.

18 Ramkissoon A, et al. Subclinical pertussis in incompletely vaccinated and unvaccinated infants. S Afr Med J 1995;85(7):662-7.

19 Olin P, et al. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet 1997;350(9091):1569-77.

20 Peltola H, et al. Prevention of Haemophilus influenzae type b bacteremic infections with the capsular polysaccharide vaccine. N Engl J Med 1984;310:1561-66.

21 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, MD. DHHS 91-1174. 1991. p. 7-11.

22 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J Bacteriol 1954;67(3):271-7.

23 Stainer DW, et al. A simple chemically defined medium for the production of phase I Bordetella pertussis. J Gen Microbiol 1971;63:211-20.

24 Chu CY, et al. Further studies on the immunogenicity of Haemophilus influenzae type b and pneumococcal type 6A polysaccharide-protein conjugates. Infect Immun 1983;40:245-56.

25 Mueller JH, et al. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. J Immunol 1941;40:21-32.

26 Gustafsson L, et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334:349-55.

27 Data on file at Sanofi Pasteur Limited. Gustafsson L, et al. Efficacy trial of acellular pertussis vaccine: technical report trial 1. Swedish Institute for Infectious Disease Control. 31 Aug 1995.

28 Greco D, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. N Engl J Med 1996;334:341-8.

29 Scheifele D, et al. Historic low Haemophilus influenzae type b case tally - Canada 2000. CCDR 2001;27(18):149-50.

30 Scheifele D, et al. Haemophilus influenzae type b disease control using PENTACEL®, Canada, 1998-1999. CCDR 2000;26(11):93-6.

31 Decker MD, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995;96(3):557-66.

32 Cherry JD. Comparative efficacy of acellular pertussis vaccines; an analysis of recent trials. Pediatr Infect Dis J 1997;16:S90-96.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779.
Business hours: 8:00 a.m. to 5:00 p.m. Eastern Time, Monday to Friday.
Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of November 2011

Manufactured by:
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and
Sanofi Pasteur SA
Lyon, France

Distributed by:
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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

ACTacel®

Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

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

ABOUT THIS VACCINE

What the vaccine is used for:

ACTacel® is a vaccine that is used to help prevent diphtheria, tetanus (lock jaw), pertussis (whooping cough) 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 ACTacel® will produce enough antibodies to help protect them against these 4 diseases. However, as with all vaccines, 100% protection cannot be guaranteed.

What the vaccine does:

ACTacel® causes the body to produce its own natural protection against diphtheria, tetanus, pertussis (whooping cough) 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 the vaccine should not be used:

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

What the important nonmedicinal ingredients are:

Aluminum phosphate (adjuvant), 2-phenoxyethanol, sucrose, TRIS (hydroxymethyl) aminomethane. Formaldehyde and glutaraldehyde are present in trace amounts.

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

What dosage forms the vaccine comes in:

ACTacel® is supplied in two vials: one vial of freeze-dried Act-HIB® vaccine and one vial of liquid dose of 0.5 mL TRIPACEL® vaccine which are then combined for injection into a muscle.

WARNINGS AND PRECAUTIONS

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

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

INTERACTIONS WITH THIS VACCINE

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

PROPER USE OF THIS MEDICATION

Usual dose:

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

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

Overdose:

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

Missed Dose:

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Serious side effects are extremely rare.

This is not a complete list of side effects. For any unexpected effects while taking ACTacel®, 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 case reports on adverse events following immunization.

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

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

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

By toll-free telephone: (1-866-844-0018)
By toll-free fax: (1-866-844-5931)
By email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9
A/L 6502A

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information. Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area). Business hours: 8:00 a.m. to 5:00 p.m. Eastern Time, Monday to Friday.

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