Package Insert

ADACEL®-POLIO

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine

Suspension for injection

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

Singapore Package Insert

Version: SG/ADE-POL/0923/EUSmPC1221

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Intramuscular injection

Suspension for injection

DESCRIPTION

ADACEL®-POLIO (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine) is a sterile, uniform, cloudy, white suspension of tetanus and diphtheria toxoids and acellular pertussis vaccine adsorbed separately on aluminum phosphate, combined with inactivated poliomyelitis vaccine (vero cell origin) types 1, 2 and 3, and suspended in water for injection. The acellular pertussis vaccine is composed of five purified pertussis antigens (PT, FHA, PRN and FIM).

INDICATIONS AND CLINICAL USE

ADACEL®-POLIO is indicated for active booster immunization for the prevention of tetanus, diphtheria, pertussis (whooping cough) and poliomyelitis in persons 4 years of age and above.

In children 4 to 6 years of age, ADACEL®-POLIO may be considered as an alternative for the fifth dose of diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine (DTaP-IPV).

Persons who have had tetanus, diphtheria or pertussis should still be immunized since these clinical infections do not always confer immunity. Human Immunodeficiency Virus (HIV)-infected persons, both asymptomatic and symptomatic, should be immunized against tetanus, diphtheria and pertussis according to standard schedules.

ADACEL®-POLIO is not to be used for the treatment of disease caused by *Bordetella pertussis, Corynebacterium diphtheriae, Clostridium tetani* or poliomyelitis infections.

Pediatrics

ADACEL®-POLIO has been used in clinical studies in children as young as 3 years of age.

Geriatrics

ADACEL®-POLIO has been used in clinical studies in persons up to 91 years of age.

Tetanus Prophylaxis in Wound Management

The need for active immunization with a tetanus toxoid-containing preparation (such as Td Adsorbed vaccine, ADACEL® or ADACEL®-POLIO) with or without passive immunization with Tetanus Immune Globulin, depends on both the condition of the wound and the patient's vaccination history. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Hypersensitivity

Known systemic hypersensitivity reaction to any component of ADACEL®-POLIO 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. 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

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 is a contraindication to administration of any pertussis-containing vaccine, including ADACEL®-POLIO.

WARNINGS AND PRECAUTIONS

General

Before administration of ADACEL®-POLIO, health-care providers should inform the recipient or parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the patient to be immunized, review the patient'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 regarding information to be provided to the patient/guardian before immunization.

It is extremely important that the recipient, 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.)

Syncope (fainting) has been reported following vaccination with ADACEL®-POLIO. Procedures should be in place to prevent falling injury and manage syncopal 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.

As with any vaccine, ADACEL®-POLIO may not protect 100% of vaccinated persons.

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

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

ADACEL®-POLIO should not be administered into the buttocks.

Febrile and Acute Disease: Vaccination should be postponed in cases of an acute or febrile disease. However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

Hematologic

Because any intramuscular injection can cause an injection site hematoma in persons with any bleeding disorders, such as haemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with ADACEL®-POLIO 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 ADACEL®-POLIO even in persons with no prior history of hypersensitivity to the product components.

As with all other products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. 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.

Immunocompromised persons (whether from disease or treatment) may not achieve the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. Nevertheless, vaccination of persons with chronic immunodeficiency, such as HIV infection, is recommended even if the immune response might be limited.

Neurologic

ADACEL®-POLIO should not be administered to individuals with progressive neurological disorder, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give ADACEL®-POLIO or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

Pregnant Women

Safety
No teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus has been observed following use in pregnant women.

Safety data from 4 randomized controlled trials (310 pregnancy outcomes), 1 prospective observational study (546 pregnancy outcomes), 5 retrospective observational studies (124,810 pregnancy outcomes), and from passive surveillance of women who received ADACEL®-POLIO or ADACEL® (Tdap component of ADACEL®-POLIO; containing the same amounts of diphtheria, tetanus and pertussis antigens) during the 2nd or 3rd trimester have shown no vaccine-related adverse effect on pregnancy or on the health of the fetus/newborn child. As with other inactivated vaccines, it is not expected that vaccination with ADACEL®-POLIO during any trimester would harm the fetus.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born to women vaccinated with ADACEL®-POLIO during pregnancy. The clinical relevance of this observation is unknown.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

The benefits versus the risks of administering ADACEL®-POLIO during pregnancy should be evaluated.

Nursing Women

The effect of administration of ADACEL®-POLIO during lactation has not been assessed. As ADACEL®-POLIO is inactivated, any risk to the mother or the infant is improbable. However, the effect on breast-fed infants of the administration of ADACEL®-POLIO to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunize a nursing woman.

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.

The safety of ADACEL®-POLIO has been evaluated in a total of 1,636 participants who received a single dose of ADACEL®-POLIO in 7 clinical trials (644 children 3 to 7 years of age, 992 adolescents and adults 11 to 60 years of age). Pain was the most common injection site reaction in all age groups. Most injection site reactions occurred within 3 days following vaccination. The most frequent systemic reaction was headache in adolescents and adults and tiredness in children. These reactions were usually transient and of mild to moderate intensity.

Table 1 presents the frequencies of the solicited injection site and systemic adverse events reported in 3 UK clinical trials in which children previously primed with 3 doses of PEDIACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine and Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] or a whole-cell pertussis combination vaccine, received a pre-school booster dose of ADACEL®-POLIO at 3 to 5 years of age. In addition, adverse events of irritability (7.3%), injection site bruising (3.3%), injection site pruritus (2.7%) and dermatitis (1.3%) were reported within 7 days of vaccination in two of these studies.

In clinical trials in children ADACEL®-POLIO showed a comparable safety profile to that of ADACEL

® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed]. Therefore, the safety of ADACEL®-POLIO, in particular for use as a 4 to 6 years-old booster dose is further supported by a study conducted with ADACEL® in 298 children.

The frequency of the solicited injection site and systemic adverse events reported in a Canadian clinical trial in adolescents and adults are also presented in Table 1.

Table 1: Frequency (%) of Solicited Reactions Observed in Clinical Trials in Children, Adolescents and Adults, Following a Single Booster Dose of ADACEL®-POLIO

Solicited Reactions	Children 3 to 5 Years of Age* (N = 307)	Adolescents 12 to 18 Years of Age† (N = 350)	Adults 19 to 60 Years of Age† (N = 366)
Injection Site Reactions			
Pain	46.5 – 71.3	88.3	86.3
Swelling	20.4 – 34.0	21.2	16.7
Redness	35.7 – 48.7	17.5	23.0
Systemic Reactions			
Fever‡	7.0 – 12.7	14.2	2.7
Headache	N.S.	41.3	37.7
Nausea	N.S.	17.5	14.5
Diarrhea	7.6 – 10.0	5.4	15.8
Vomiting	2.5 – 6.7	3.2	2.5
Body Ache	N.S.	26.1	24.0
Sore or Swollen Joints	1.3	11.2	11.2
Tiredness	35.7 – 52.7	37.2	29.8
Chills	N.S.	17.5	11.2
Rash	7.0 – 8.7	N.S.	N.S.

* Adverse reactions reported within 7 days of vaccination. Range of frequencies across 3 UK studies.

† Adverse reactions reported within 14 days of vaccination

‡ Fever was defined as temperature ≥37.5°C in children, ≥38.0°C in adolescents and adults. Fever was solicited up to 7 days post-vaccination in children, up to 72 hours in adolescents and adults.

N.S. Not solicited

Post-Market Adverse Drug Reactions

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

Blood and Lymphatic Disorders

Lymphadenopathy

Immune System Disorders

Anaphylactic reactions, such as urticaria, face edema and dyspnea

Nervous System Disorders

Convulsions, vasovagal syncope, Guillain-Barré syndrome, facial palsy, myelitis, brachial neuritis, transient paresthesia/ hypoesthesia of vaccinated limb, dizziness

Musculoskeletal and Connective Tissue Disorders

Pain in vaccinated limb

Gastrointestinal Disorders

Abdominal pain

General Disorders and Administration Site Conditions

Extensive limb swelling, which may extend from the injection site beyond one or both joints and is frequently associated with erythema, and sometimes with blisters, has been reported following administration of ADACEL®-POLIO. The majority of these reactions appeared within 48 hours of vaccination and spontaneously resolved over an average of 4 days without sequelae. The risk appears to be dependent on the number of prior doses of d/DTaP vaccine, with a greater risk following the 4th and 5th doses.

Malaise, pallor, injection site induration

DRUG INTERACTIONS

Vaccine-Drug Interactions

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

Concomitant Vaccine Administration

ADACEL®-POLIO may be administered concurrently with a dose of hepatitis B vaccine. Supportive data from a study conducted with ADACEL® suggests that ADACEL®-POLIO may be used concomitantly with trivalent influenza vaccine. ADACEL®-POLIO has been safely administered concomitantly with measles-mumps-rubella vaccine in non-controlled clinical studies in children 3 to 5 years of age. Data are not available on concomitant use of ADACEL®-POLIO and varicella vaccine.

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 concomitantly 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.

ADACEL®-POLIO should not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

ADACEL®-POLIO should be administered as a single injection of 1 dose (0.5 mL) by the intramuscular route. The preferred site is the deltoid muscle.

ADACEL®- POLIO may be administered to pregnant women during the second or third trimester to provide passive immunization of infants against pertussis (see sections WARNINGS AND PRECAUTIONS - Pregnant Women and ACTION AND CLINICAL PHARMACOLOGY- Immunogenicity).

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

Health-care professionals should refer to the National Advisory Committee on Immunization (NACI) guidelines for tetanus prophylaxis in routine wound management shown in Table 2.

Table 2: NACI Recommended Use of Immunizing Agents in Wound Management

	Clean, minor wounds		**All other wounds**	
History of Tetanus Immunization	**Td***	**TIG† (Human)**	**Td***	**TIG† (Human)**
Uncertain or <3 doses of an immunization series‡	Yes	No	Yes	Yes
≥3 doses received in an immunization series‡	No§	No	No**	No††

* Adult-type tetanus and diphtheria toxoid

† Tetanus immune globulin, given at a separate site from the Td

‡ Primary immunization is at least 3 doses at age appropriate intervals.

§ Yes, if >10 years since last booster.

** Yes, if >5 years since last booster.

†† Yes, if persons are known to have a significant humoral immune deficiency state (e.g., HIV, agammaglobulinemia) since immune response to tetanus toxoid may be suboptimal.

A thorough attempt must be made to determine whether a patient has completed primary immunization. Persons who have completed primary immunization against tetanus and who sustain wounds that are minor and uncontaminated, should receive a booster dose of a tetanus toxoid-containing preparation if they have not received tetanus toxoid within the preceding 10 years. For tetanus-prone wounds (e.g., wounds contaminated with dirt, feces, soil and saliva, puncture wounds, avulsions and wounds resulting from missiles, crushing, burns or frostbite), a booster is appropriate if the patient has not received a tetanus toxoid-containing preparation within the preceding 5 years.

For adults who have not previously received a dose of acellular pertussis vaccine, a single Tetanus-diphtheria (Td) booster dose should be replaced by a combined tetanus-diphtheria-acellular pertussis vaccine (Tdap).

Administration

Inspect for extraneous particulate matter and/or discolouration before use. (See DESCRIPTION.) If these conditions exist, the product should be discarded.

Shake the vial or syringe well until a uniform, cloudy, suspension results. When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. 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 0.5 mL **intramuscularly** (IM). The preferred site of injection is the deltoid muscle.

ACTION AND CLINICAL PHARMACOLOGY

Immunogenicity

Immunogenicity in pregnant women

Pertussis antibody responses in pregnant women are generally similar to those in non-pregnant women. Vaccination during the second or third trimester of pregnancy is optimal for antibody transfer to the developing fetus.

Immunogenicity against pertussis in infants (<3 months of age) born to women vaccinated during pregnancy

Data from 2 published randomized controlled trials demonstrate higher pertussis antibody concentrations at birth and at 2 months of age, (ie, prior to the start of their primary vaccinations) in infants of women vaccinated with ADACEL® during pregnancy compared with infants of women not vaccinated against pertussis during pregnancy.

In the first study, 33 pregnant women received ADACEL® and 15 received saline placebo at 30 to 32 weeks gestation. The geometric mean concentrations (GMC) in EU/mL for the anti-pertussis

antibodies to the PT, FHA, PRN, and FIM antigens in infants of vaccinated women were, respectively, 68.8, 234.2, 226.8, and 1867.0 at birth, and 20.6, 99.1, 75.7, and 510.4 at 2 months of age. In the control-group infants, the corresponding GMCs were 14.0, 25.1, 14.4, and 48.5 at birth, and 5.3, 6.6, 5.2, and 12.0 at 2 months. The GMC ratios (ADACEL® /control group) were 4.9, 9.3, 15.8, and 38.5 at birth, and 3.9, 15.0, 14.6, and 42.5 at 2 months.

In the second study, 134 pregnant women received Tdap and 138 received a tetanus and diphtheria control vaccine at a mean gestational age of 34.5 weeks. The GMCs (EU/mL) for the anti-pertussis antibodies to the PT, FHA, PRN, and FIM antigens in infants of vaccinated women were, respectively, 54.2, 184.2, 294.1, and 939.6 at birth, and 14.1, 51.0, 76.8, and 220.0 at 2 months of age. In the control-group infants, the corresponding GMCs were 9.5, 21.4, 11.2, and 31.5 at birth, and 3.6, 6.1, 4.4, and 9.0 at 2 months. The GMC ratios (ADACEL® /control group) were 5.7, 8.6, 26.3, and 29.8 at birth, and 3.9, 8.4, 17.5, and 24.4 at 2 months.

These higher antibody concentrations should provide passive immunity against pertussis for the infant during the first 2 to 3 months of life, as has been shown by observational effectiveness studies.

Immunogenicity in infants and toddlers born to women vaccinated during pregnancy

For infants of women vaccinated with ADACEL® or ADACEL®-POLIO during pregnancy, the immunogenicity of routine infant vaccination was assessed in several published studies. Data on the infant response to pertussis and non-pertussis antigens were evaluated during the first year of life.

Maternal antibodies derived after ADACEL® and ADACEL®-POLIO vaccination in pregnancy may be associated with blunting of the infant immune response to active immunization against pertussis. Based on current epidemiological studies, this blunting may not have clinical relevance.

Data from several studies did not show any clinically relevant blunting from vaccination in pregnancy with ADACEL® and ADACEL®-POLIO and the infants' or toddlers' responses to diphtheria, tetanus, *Haemophilus influenzae* type b, inactivated poliovirus, or pneumococcal antigens.

Effectiveness

Effectiveness against pertussis in infants born to women vaccinated during pregnancy

The vaccine effectiveness in the first 2-3 months of life for infants born to women vaccinated against pertussis during the third trimester of pregnancy has been evaluated in 3 observational studies. The overall effectiveness is > 90%.

Table 5: Vaccine effectiveness (VE) against pertussis disease in young infants born to mothers vaccinated during pregnancy with ADACEL®-POLIO and ADACEL® in 3 retrospective studies.

Location	Vaccine	VE (95% CI)	VE estimation method	Infant follow-up period
UK	ADACEL®-POLIO	93% (81, 97)	unmatched case-control	2 months
US	ADACEL®*	91.4% (19.5, 99.1)	cohort regression model	2 months
UK	ADACEL®-POLIO	93% (89, 95)	screening (case-coverage)	3 months

* Approximately 99% of women were vaccinated with Adacel

INCOMPATIBILITIES

This vaccine must not be mixed with other vaccines or medicinal products.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do Not Freeze**. Discard product if exposed to freezing

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ADACEL®-POLIO is supplied as a sterile, uniform, cloudy, white suspension in a vial or prefilled syringe.

Composition

Each dose (0.5 mL) is formulated to contain:

Active Ingredients

Tetanus Toxoid	Not less than 20 International Units (5 Lf)
Diphtheria Toxoid	Not less than 2 International Units (2 Lf)
Acellular Pertussis:	
Pertussis Toxoid (PT)	2.5 µg
Filamentous Haemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Inactivated Poliomyelitis Vaccine	

Type 1 (Mahoney)	40 D-antigen units*
Type 2 (MEF-1)	8 D-antigen units*
Type 3 (Saukett)	32 D-antigen units*

*or 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	<5 µg
Water for Injection	q.s. 0.5 mL

Manufacturing Process Residuals

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

Packaging

ADACEL®-POLIO is presented as a suspension for injection in pre-filled syringes (0.5 mL):

1 single dose syringe without attached needle and with 1 separate needle (1 x 25G 1" 0.5 x 25mm)

The syringes are made of USP Type 1 glass. The container closure system for the syringe presentation of ADACEL®-POLIO is free of latex (natural rubber).

Manufactured by:

Sanofi Pasteur Limited
Toronto, Ontario, Canada

Product Owner:
Sanofi Pasteur
Lyon, France

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