1. NAME OF THE MEDICINAL PRODUCT

ADACEL®-POLIO, suspension for injection in a pre-filled syringe

Diphtheria (reduced antigen content), Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:	
Diphtheria toxoid adsorbed	Not less than 2 IU*
Tetanus toxoid adsorbed	5Lf
Pertussis antigens adsorbed:	
Pertussis toxoid adsorbed	2.5 micrograms
Filamentous haemagglutinin adsorbed	5 micrograms
Fimbriae types 2 + 3 adsorbed	5 micrograms
Pertactin adsorbed	3 micrograms
Poliomyelitis virus type 1** (inactivated)	40 D antigen units
Poliomyelitis virus type 2** (inactivated)	8 D antigen units
Poliomyelitis virus type 3** (inactivated)	32 D antigen units
Adsorbed on aluminum phosphate	1.5 mg (0.33 mg Al)

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

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe.

ADACEL®-POLIO appears as a cloudy whitish suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADACEL®-POLIO is indicated for active immunization against diphtheria, tetanus, pertussis and poliomyelitis in persons from the age of four years as a booster following primary immunization.

ADACEL®-POLIO is not intended for primary immunization.

ADACEL®-POLIO is not to be used for the treatment of disease caused by *B. pertussis, C. diphtheriae* or *C. tetani* or Poliomyelitis infections.

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.

The use of ADACEL®-POLIO should be determined on the basis of official recommendations.

4.2 Posology and method of 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.

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 1.

Table 1: NACI Recommended Use of Immunizing Agents in Wound Management (1)

	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).

Method of administration

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

A single injection of one dose (0.5 mL) of ADACEL®-POLIO should be administered by intramuscular route. Administration should preferably be performed in the deltoid muscle.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substances, to any of the excipients or any residual component carried over from manufacture (formaldehyde, gluteraldehyde, streptomycin, neomycin, polymyxin B and bovine serum albumin (trace)).
- Anaphylactic or other allergic reactions to a previous dose of a vaccine containing diphtheria or tetanus toxoids, poliomyelitis viruses or pertussis (acellular or whole cell).
- Encephalopathy: ADACEL®-POLIO should not be administered to subjects who experienced an encephalopathy of unknown origin within 7 days of previous immunization with a pertussis-containing vaccine, or to subjects who have experienced other neurological complications following previous immunization with any of the antigens in ADACEL®-POLIO.

4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE

General

The administration of ADACEL®-POLIO, should be preceded by asking parents/guardians of the recipient about his/her personal and family history concerning possible hypersensitivity to the vaccine or similar vaccine , including vaccination history, current health status and the presence of any contra-indications to immunization or any undesirable effects following previous vaccinations

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.

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.

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. A review by the US Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. 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.

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.

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.

Administration Route Related Precautions

Do not administer by the intravascular route. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

A clinical study has shown that ADACEL®-POLIO can be administered concomitantly with hepatitis B vaccine, using a separate limb for the site of injection.

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.

Immunosuppressive treatments may interfere with the development of the expected immune response.

4.6 Pregnancy and lactation

The effect of ADACEL®-POLIO on embryo-foetal development has not been assessed.

Limited post-marketing data is available following administration of ADACEL®-POLIO in pregnant women. Vaccination in pregnancy is not recommended unless there is a definite risk of acquiring pertussis. As the vaccine is inactivated, risk to the embryo or the fetus is improbable. The benefits versus the risks of administering ADACEL®-POLIO during pregnancy should be carefully evaluated when there is a high probable risk of exposure to a household contact or during an outbreak in the community.

Use in lactation

The effect of ADACEL®-POLIO administration during lactation has not been assessed. However, as ADACEL®-POLIO contains toxoids or inactivated antigens, there should be no expected risk for breastfed children. The benefits compared the risk of administering ADACEL®-POLIO to lactating women should be assessed by the health-care professionals.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive or to use operate machines.

4.8 Undesirable effects

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 2 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 2.

Table 2: 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

In addition to the data obtained from clinical studies, the following adverse events have been reported during the commercial 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

Nervous system disorders:

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

General disorders and administrative site conditions:

Extensive limb swelling which may extent from the injection site beyond one or both joints and frequently associated with erythema, sometimes with blisters has been reported after the administration of ADACEL®-POLIO. Most reactions appeared within 48 hours of vaccination and spontaneously resolved without sequelae within 4 days on average.

The risk seems to be dependent on the number of doses of d/DtaP vaccine previously administered, with a risk increased after the 4th and 5th doses.

Malaise, Pallor, Injection site indurations

Musculoskeletal and connective tissue disorders:

Pain in vaccinated limb

Immune system disorders:

Anaphylactic reactions, such as urticaria, face oedema and dyspnea

Gastrointestinal Disorders:

Abdominal pain

4.9 Overdose

No case of overdose has been reported

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Vaccine against diphtheria, tetanus, pertussis and poliomyelitis

ATC Code:J07CA02

Tetanus and Diphtheria: 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. One month after a single booster dose of ADACEL®-POLIO, seroprotective tetanus antitoxin levels were achieved in 100% of adults and adolescents, and 100% of children 3.5 to 4.1 years of age.

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 for diphtheria. 83.8% of adults, 97.1% of adolescents and at least 97.6% of children 3.5 to 4.1 years of age achieved a seroprotective antitoxin level of 0.1 IU/mL against diphtheria.

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) using TRIPACEL® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed], the same pertussis components as present in ADACEL®-POLIO (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 established. 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. The acellular pertussis formulations of ADACEL®-POLIO and ADACEL® compared to TRIPACEL® differ only in the amount of PT (2.5 µg in ADACEL®-POLIO and ADACEL® versus 10 µg in TRIPACEL®) and the amount of diphtheria toxoid (2 Lf in ADACEL®-POLIO and ADACEL® versus 15 Lf in TRIPACEL®). Furthermore, the IPV antigens present in ADACEL®- POLIO are not included in the formulation of TRIPACEL®.

The efficacy of ADACEL®-POLIO is based on a comparison of pertussis antibody levels achieved in ADACEL®-POLIO recipients with those measured with TRIPACEL® in the Sweden I Efficacy Trial. In particular, ADACEL®-POLIO was demonstrated, both in children and in adolescents and adults, to elicit antibody levels against pertussis antigens, which were consistently higher than those found to be protective in the Sweden I Efficacy Trial. In addition, in a clinical study with ADACEL® among Canadian 4 to 6 year-olds, it was demonstrated that, in the context of the Canadian immunization schedule, the pertussis antigens formulation of ADACEL®-POLIO also elicited serum antibody levels that were consistently higher than those measured in the Sweden I Efficacy Trial.

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. In all clinical trials, 99.0% to 100% of vaccines in all age groups achieved seroprotective levels (≥1:8 dilution) of anti-poliovirus antibodies for all three types.

Duration of Effect

Long-term follow-up of serum antibody levels in adolescents and adults who received a single dose of ADACEL®-POLIO shows that protective levels for tetanus antitoxin (≥0.01 IU/mL) and diphtheria antitoxin (≥0.01 IU/mL) persist in 100% and at least 79.2% of participants, respectively, after at least 5 years. Protective levels of anti-poliovirus antibodies (≥1:8) persist in 98.2% to 100.0% of both adolescents and adults after 5 years. While protective levels against pertussis have not yet been clearly defined, pertussis antibody levels remain several-fold higher than pre-immunization levels after 5 years.

Long-term follow-up of serum antibody levels in children who received a single dose of ADACEL®-POLIO at 3.5 to 5 years of age shows that protective levels for tetanus antitoxin (≥0.01 IU/mL) and diphtheria antitoxin (≥0.01 IU/mL) persist in 100.0% of participants, 3 years after immunization. Protective levels of anti-poliovirus antibodies (≥1:8) persist in 97.9 to 100.0% of participants after 3 years. While protective levels against pertussis have not yet been clearly defined, after 3 years, pertussis antibody levels remain higher than pre-immunization levels.

According to NACI, tetanus and diphtheria toxoid boosters are recommended every 10 years, however, the optimal interval for administering subsequent booster doses with ADACEL®-POLIO has not been determined. Nevertheless, a clinical study conducted with ADACEL® demonstrated that the incidence and severity of adverse events reported after administration of ADACEL® as early as 2 years after the last dose of tetanus and diphtheria vaccine were similar to those observed after administration at greater time intervals, up to 10 years.

5.2 Pharmacokinetic properties

As for all vaccines, pharmacokinetic data being non-relevant, no pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Preclinical data revealed no unexpected findings and no target organ toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenoxyethanol, Aluminum phosphate, Polysorbate 80, Water for injections

Manufacturing Process Residuals:

The final product may contain trace amount of formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B, bovine serum albumin (trace).

6.2 Incompatibilities

In the absence of compatibility studies, ADACEL®-POLIO must not be mixed with any vaccine or other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (at 2°C to 8°C).

Do not freeze. Discard the vaccine if it has been frozen.

6.5 Special precautions for disposal and other handling

Instructions for Use

All biological products for parenteral use should be visually inspected visually for extraneous particles and/or discoloration prior to administration. In the event of either being observed, the vaccine should be disposed of.

The vaccine's normal appearance is a cloudy white suspension, which may sediment during storage. Shake the prefilled syringe well to obtain a homogeneous suspension before administering the vaccine.

For syringes without attached needles, the needle must be fitted firmly to the prefilled syringe, rotating it by one quarter of a turn.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Needles should not be reprocessed.

7. LICENSE HOLDER:

Medici Medical Ltd., 3 Hamachshev St. Netanya

8. MANUFACTURER:

Sanofi Pasteur, 14 Espace Henry Vallee, LYON- FRANCE

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