1 NAME OF THE MEDICINAL PRODUCT

ADACEL® suspension for injection in a glass vial.
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine (adsorbed, reduced antigen(s) content)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Diphtheria Toxoid	Not less than 2 IU* (2 Lf)
Tetanus Toxoid	Not less than 20 IU* (5 Lf)
Pertussis Antigens	
Pertussis Toxoid	2.5 micrograms
Filamentous Haemagglutinin	5 micrograms
Pertactin	3 micrograms
Fimbriae Types 2 and 3	5 micrograms
Adsorbed on aluminium phosphate	1.5 mg (0.33 mg aluminium)

* As lower confidence limit (p = 0.95) of activity measured according to the assay described in the European Pharmacopoeia.

This vaccine may contain traces of formaldehyde and glutaraldehyde which are used during the manufacturing process (see sections 4.3 and 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in 0.5 mL single dose glass vial.

ADACEL® appears as a cloudy white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADACEL® is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis in children, adolescents and adults aged 4 to 64 years.
ADACEL® is not to be used for the treatment of disease caused by *B.ordetella pertussis, C.-orynebacterium diphtheriae* or *Clostridium tetani* infections.

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4.2 Posology and method of administration

Posology

Recommended Dose
The immunization schedule with ADACEL® should follow local recommendations. ADACEL® (0.5mL) should be administered as a booster dose by the intramuscular route.
Re-dosing with ADACEL® can be used to boost immunity to diphtheria, tetanus and pertussis at 5 to 10 year intervals.
The preferred site is into the deltoid muscle.
Fractional doses (doses <0.5 mL) should not be given. The effect of fractional doses on the safety and efficacy has not been determined.
The use of ADACEL® in management of tetanus-prone wounds should follow local recommendations. Canada's National Advisory Committee on Immunization (NACI) and US Advisory Committee on Immunization Practices (ACIP) have issued guidelines for tetanus prophylaxis in routine wound management as shown in the Table below

NACI Recommended Use of Immunizing Agents in Wound Management

History of Tetanus Immunization	Clean, Minor Wounds		All Other Wounds	
	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.

Method of administration

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.

Shake the vial well until a uniform, cloudy, suspension results. Cleanse the vial stopper with a suitable germicide prior to withdrawing the dose. Do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual recipient, 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.

4.3 Contraindications

ADACEL® should not be administered to person with known hypersensitivity

- to diphtheria, tetanus or pertussis vaccines
- to any other component of the vaccine (see section 6.1)
- to any residual substances carried over from manufacture (formaldehyde and glutaraldehyde), which may be present in undetectable trace amounts.

ADACEL® should not be administered to persons who experienced an encephalopathy of unknown origin within 7 days of previous immunization with a pertussis-containing vaccine.

As with other vaccines, ADACEL® should be postponed in persons suffering from an acute severe febrile illness. The presence of a minor infection is not a contraindication.

4.4 Special warnings and precautions for use

ADACEL® should not be used for primary immunization.

Regarding the interval between a booster dose of ADACEL® and preceding booster doses of diphtheria and/or tetanus containing vaccines, the official recommendations should generally be followed. Clinical data have demonstrated that there was no clinically relevant difference in rates of adverse reactions associated with administration of a tetanus-, diphtheria- and pertussis-containing booster vaccine as early as 4 weeks, compared to at least 5 years, after a preceding dose of tetanus and diphtheria-containing vaccine.

Prior to immunization

Vaccination should be preceded by a review of the person's medical history (in particular previous vaccinations and possible adverse events). In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of ADACEL® vaccine must be carefully considered.

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine.

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

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

The immunogenicity of the vaccine could be reduced by immunosuppressive treatment or immunodeficiency. It is recommended to postpone the vaccination until the end of such disease or treatment if practical. Nevertheless, vaccination of HIV infected persons or persons with chronic immunodeficiency, such as AIDS, is recommended even if the antibody response might be limited.

Administration precautions

Do not administer by intravascular or intradermal injection.

Intramuscular injections should be given with care in patients on anticoagulant therapy or suffering from coagulation disorders because of the risk of haemorrhage. In these situations, administration of ADACEL® by deep subcutaneous injection may be considered, although there is a risk of increased local reactions.

Syncope (fainting) can occur following, or even before, administration of injectable vaccines, including ADACEL®. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Other considerations

As with any vaccine, vaccination with ADACEL® may not protect 100% of susceptible individuals.

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® during pregnancy. The clinical relevance of this observation is unknown.

A persistent nodule at the site of injection may occur with all adsorbed vaccines particularly if administered into the superficial layers of the subcutaneous tissue.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of concomitant use clinical studies, ADACEL® can be administered concomitantly with any of the following vaccines: inactivated Influenza vaccine, Hepatitis B vaccine, Inactivated or Oral Poliomyelitis vaccine and recombinant Human Papillomavirus vaccine (See section 4.8) according to local recommendations.

Separate limbs must be used for the site of injection of concomitant parenteral vaccines. Interaction studies have not been carried out with other vaccines, biological products, or therapeutic medications. However, in accordance with commonly accepted immunization guidelines, since ADACEL® is an inactivated product it may be administered concomitantly with other vaccines or immunoglobulins at a separate injection site.

In the case of immunosuppressive therapy please refer to section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety data from 4 randomized controlled trials (310 pregnancy outcomes), 2 prospective observational studies (2670 pregnancy outcomes), 4 retrospective observational studies (81,701 pregnancy outcomes), and from passive surveillance of women who received ADACEL® or REPEVAX (Tdap-IPV; containing the Tdap component of ADACEL®) 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® during any trimester would harm the fetus. The benefits versus the risks of administering ADACEL® during pregnancy should be evaluated.

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

Limited clinical data have shown there is interference with the immune response to other antigens (i.e. diphtheria, tetanus, polio, pneumococcal, meningococcal) in infants born to women vaccinated with ADACEL® during pregnancy. However, in most of the cases, the antibody concentrations remain above the thresholds established as protective. The clinical relevance of this observation is unknown.

Breast-feeding

It is not known whether the active substances included in ADACEL® are excreted in human milk but antibodies to the vaccine antigens have been found to be transferred to the suckling offspring of rabbits. Two animal developmental studies conducted in rabbits have not shown any harmful effects of maternal antibodies induced by the vaccine on offspring postnatal development.

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

Fertility

ADACEL® has not been evaluated in fertility studies.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. ADACEL® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials ADACEL® was given to a total of 4,546 persons, including 298 children (4 to 6 years), 1,313 adolescents (11 to 17 years) and 2,935 adults (18 to 64 years). Most commonly reported reactions following vaccination included local reactions at the injection site (pain, redness and swelling) that occurred in 21% - 78% of the vaccinees, headache and tiredness that occurred in 16% - 44% of vaccinees.

These signs and symptoms usually were mild in intensity and occurred within 48 hours following vaccination. They all resolved without sequelae.

Safety analysis was conducted in 1,042 healthy adolescent males and females aged 10 to 17 years during a clinical trial. They received quadrivalent human papillomavirus types 6/11/16/18 vaccine (Gardasil) concurrently with a dose of ADACEL® and a dose of quadrivalent meningococcal conjugate vaccine serogroup A, C, Y and W135. The safety profiles were similar in both concomitant and non concomitant groups. Higher frequencies of swelling at the Gardasil injection site, bruising and pain at ADACEL® injection sites were observed in the concomitant administration group. The differences observed between concomitant and non concomitant groups were less than 7% and in a majority of subjects the adverse events were reported as mild to moderate in intensity.

Tabulated list of adverse reactions

Adverse reactions are ranked under headings of frequency using the following convention:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	cannot be estimated from the available data

Table 1 presents adverse reactions observed in clinical trials and also includes additional adverse events which have been spontaneously reported during the post-marketing use of ADACEL® worldwide. Because post-marketing adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Therefore, the frequency category "Not known" is assigned to these adverse events.

Table 1: Adverse events from trials and worldwide post-marketing experience

System Organ Class	Frequency	Children (4 to 6 Years)	Adolescents (11 to 17 Years)	Adults (18 to 64 Years)
Immune system disorders	Not known	Hypersensitivity (Anaphylactic) reaction (Angioedema, Oedema, Rash, Hypotension)*		
Metabolism and nutrition disorders	Very common	Anorexia (decreased appetite)		
Nervous system disorders	Very common	Headache		
	Not known	Paraesthesia*, Hypoaesthesia*, Guillain-Barré Syndrome*, Brachial Neuritis*, Facial Palsy*, Convulsions*, Syncope*, Myelitis*		
Cardiac disorders	Not known	Myocarditis*		
Gastrointestinal disorders	Very common	Diarrhoea	Diarrhoea, Nausea	Diarrhoea
	Common	Nausea, Vomiting	Vomiting	Nausea, Vomiting

System Organ Class	Frequency	Children (4 to 6 Years)	Adolescents (11 to 17 Years)	Adults (18 to 64 Years)
Skin and subcutaneous system disorders	Common	Rash		
	Not known	Pruritus*, Urticaria*		
Musculoskeletal and connective tissue disorders	Very common		Generalized aching or Muscular weakness, Arthralgia or Joint swelling	Generalized aching or Muscular weakness
	Common	Generalized aching or Muscular weakness, Arthralgia or Joint swelling		Arthralgia or Joint swelling
	Not known	Myositis*		
General disorders and administrative site conditions	Very common	Fatigue/Asthenia	Fatigue/Asthenia, Malaise, Chills	Fatigue/Asthenia, Malaise
		Injection site pain, Injection site erythema, Injection site swelling		
	Common	Pyrexia, Chills, Axillary adenopathy	Pyrexia, Axillary adenopathy	Pyrexia, Chills, Axillary adenopathy
	Not known	Injection site bruising*, Injection site sterile abscess*		

* Post-marketing Adverse Events

Description of selected adverse reactions

General Disorders and Administration Site Conditions:
Large injection site reactions (>50 mm), including extensive limb swelling from the injection site beyond one or both joints occur after administration of ADACEL® in adolescents and adults. These reactions usually start within 24 - 72 hours after vaccination, may be associated with erythema, warmth, tenderness or pain at the injection site and resolve spontaneously within 3 - 5 days.

Paediatric population

The safety profile of ADACEL® as presented in Table 1 includes data from a clinical trial in 298 children 4 to 6 years of age who had previously received a total of 4 doses, including primary immunization, with DTaP-IPV combined with Hib, at approximately 2, 4, 6 and 18 months of age. In this clinical study, the most common adverse events reported within 14 days post-vaccination were pain at the injection site (in 39.6 % of subjects) and tiredness (in 31.5 % of subjects).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pertussis, purified antigen, combination with toxoids.
ATC code: J07AJ52

Clinical trials

The immune responses observed one month after vaccination with ADACEL® in 265 children, 527 adolescents and 743 adults are shown in the table below.

Table 2: Immune response of children, adolescents and adults one month after vaccination with ADACEL®

Antigen	Immune Response	Children (4 to 6 Years) 265 Persons %	Adolescents (11 to 17 Years) 527 Persons %	Adults (18 to 64 Years) 743 Persons %
Diphtheria toxoid	≥0.1 IU/mL	100.0	99.8	94.1
Tetanus toxoid	≥0.1 IU/mL	100.0	100.0	100.0
Pertussis toxoid	Booster Response*	91.9	92.0	84.4
Filamentous haemagglutinin		88.1	85.6	82.7
Pertactin		94.6	94.5	93.8
Fimbriae Types 2 and 3		94.3	94.9	85.9

* For children 4-6 years of age previously primed with DTaP (diphtheria toxoid [paediatric dose], tetanus and acellular pertussis) at 2, 4, 6 and 18 months of age, a booster response is defined as a 4-fold increase in concentration of anti-pertussis antibodies.
For adolescents and adults, a booster response is defined as a 2-fold increase in concentration of anti-pertussis antibodies in participants with high pre-vaccination concentration and a 4-fold increase in participants with low pre-vaccination concentration.

The safety and immunogenicity of ADACEL® in adults and adolescents was shown to be comparable to that observed with a single dose of an adult formulation diphtheria-tetanus (Td) adsorbed vaccine containing the same amount of tetanus and diphtheria toxoids.

Serological correlates for protection against pertussis have not been established. On comparison with data from the Sweden I pertussis efficacy trials conducted between 1992 and 1996, where primary immunization with Sanofi Pasteur Limited's acellular pertussis infant DTaP formulation confirmed a protective efficacy of 85% against pertussis disease, it is considered that ADACEL® had elicited protective immune responses. The pertussis antibody levels for all antigens following a booster dose of ADACEL® in adolescents and adults exceeded those observed in a household contact study nested within the efficacy trial.

Table 3: Ratio of pertussis antibody GMCs observed one month after a dose of ADACEL® in adolescents and adults compared with those observed in infants one month following vaccination at 2, 4 and 6 months of age in the Sweden I efficacy trial with DTaP**

	Adolescents	**Adults**
	ADACEL®*/DTaP† GMCs Ratio (95% CIs)	**ADACEL®‡/DTaP† GMCs Ratio (95% CIs)**
Anti-PT	3.6 (2.8, 4.5)§	2.1 (1.6, 2.7)§
Anti-FHA	5.4 (4.5, 6.5)§	4.8 (3.9, 5.9)§
Anti-PRN	3.2 (2.5, 4.1)§	3.2 (2.3, 4.4)§
Anti-FIM	5.3 (3.9, 7.1)§	2.5 (1.8, 3.5)§

* N = 524 to 526, number of adolescents in the per-protocol population with available data for ADACEL®.

† N = 80, number of infants who received DTaP at 2, 4 and 6 months of age with available data post-dose 3 (sera from the Sweden I Efficacy Trial tested contemporaneously with samples from Clinical Trial Td506).

‡ N = 741, number of adults in the per-protocol population with available data for ADACEL®.

§ GMCs following ADACEL® were non-inferior to GMCs following DTaP (lower limit of 95% CI on the ratio of GMCs for ADACEL® divided by DTaP >0.67).

** Antibody GMCs, measured in ELISA units were calculated separately for infants, adolescents and adults.

Antibody persistence

Serology follow-up studies were conducted at 3, 5 and 10 years, in individuals previously immunized with a single booster dose of ADACEL®. Persistence of seroprotection to diphtheria and tetanus, and seropositivity to pertussis is summarised in Table 4.

Table 4: Persistence of Seroprotection/Seropositivity Rates in Children, Adolescents and Adults at 3-, 5- and 10- years following a dose of ADACEL® (PPI Population[1])

		Children (4-6 years)[2]	**Adolescents** (11-17 years)[2]			**Adults** (18-64 years)[2]		
Time point		**5 years**	**3 years**	**5 years**	**10 years**	**3 years**	**5 years**	**10 years**
Antibody		N=128-150	N=300	N=204-206	N=28-39	N=292	N=237-238	N=120-136
Diphtheria (SN, IU/mL)	≥ 0.1	86.0	97.0	95.1	94.9	81.2	81.1	84.6
	≥ 0.01	100.0	100.0	100.0	100.0	95.2	93.7	99.3
Tetanus (ELISA, IU/mL)	≥ 0.1	97.3	100.0	100.0	100.0	99.0	97.1	100.0
Pertussis (ELISA, IU/mL)	Sero-positivity[3]							
PT		63.3	97.3	85.4	82.1	94.2	89.1	85.8
FHA		97.3	100.0	99.5	100.0	99.3	100.0	100.0
PRN		95.3	99.7	98.5	100.0	98.6	97.1	99.3
FIM		98.7	98.3	99.5	100.0	93.5	99.6	98.5

N = number of subjects with available data; SN: seroneutralisation; ELISA: Enzyme Linked Immunoassay
[1]Eligible subjects for whom immunogenicity data was available for at least one antigen at the specified time-point.
[2]Age at which subjects received a dose of ADACEL®
[3]Percentage of subjects with antibodies ≥ 4 EU/mL for PT, FHA and PRN, and ≥ 17 EU/mL for FIM for the 3 year follow-up; ≥ 4 EU/mL for PT, FIM and PRN, and ≥ 3 EU/mL for FHA for the 5-year and 10-year follow-up

Immunogenicity following repeat vaccination

The immunogenicity of ADACEL® following repeat vaccination 10 years after a previous dose of ADACEL® or REPEVAX, has been evaluated. One month post-vaccination ≥ 98.5% of study participants achieved seroprotective antibody levels (≥ 0.1 IU/ml) for diphtheria and tetanus, and ≥ 84% achieved booster responses to the pertussis antigens. (A pertussis booster response was defined as a post-vaccination antibody concentration ≥ 4 times the LLOQ if the pre-vaccination level was < LLOQ; ≥ 4 times the pre-vaccination level if that was ≥ LLOQ but < 4 times LLOQ; or ≥ 2 times the pre-vaccination level if that was ≥ 4 times the LLOQ).

Based on the serology follow-up and repeat vaccination data, ADACEL® can be used instead of a dT vaccine to boost immunity to pertussis in addition to diphtheria and tetanus.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity and toxicity in pregnancy, embryonal/fetal development, parturition and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenoxyethanol
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, ADACEL® must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

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.
Keep the syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

ADACEL® is supplied in 0.5 mL single dose glass vials.
The vials are made of Type 1 glass. The container closure system of ADACEL® is free of latex (natural rubber).
ADACEL® is available in a package of:
1 single dose vial
5 single dose vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

Parenteral products should be inspected visually for extraneous particulate matter and/or discolouration prior to administration. In the event of either being observed, discard the medicinal product.

The normal appearance of the vaccine is a uniform, cloudy, white suspension which may sediment during storage.

Shake the vial well until a uniform, cloudy, suspension results. Cleanse the vial stopper with a suitable germicide prior to withdrawing the dose. Do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual recipient, 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.

Disposal

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

7. MANUFACTURER:

SANOFI PASTEUR LTD, CANADA, 1755 STEELS AVEUE WEST-TORONTO ONTARIO,CANADA

8. LICENSE HOLDER:

Medici Medical LTD., 3 HAMACHSHEV ST., NETANYA 4250713, ISRAEL

9. MARKETING AUTHORISATION NUMBER

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