1. NAME OF THE MEDICINAL PRODUCT

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

Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) 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 (PT)	2.5 micrograms
Filamentous haemagglutinin (FHA)	5 micrograms
Fimbriae types 2 + 3 (FIM)	5 micrograms
Pertactin (PRN)	3 micrograms
Poliovirus (Inactivated)**	
Type 1 (Mahoney)	40 D antigen units
Type 2 (MEF1)	8 D antigen units
Type 3 (Saukett)	32 D antigen units
Adsorbed on aluminum phosphate	1.5 mg (0.33 mg Al^{3+})

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

ADACEL POLIO may contain traces of formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B and bovine serum albumin, which are used during the manufacturing process (see sections 4.3 and 4.4).

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 uniform, cloudy, white 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)

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.

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

• ADACEL POLIO should not be administered to persons with known hypersensitivity

- to diphtheria, tetanus, pertussis or poliomyelitis vaccines

- to any other component of the vaccine (see Section 6.1)

- to any residual substances carried over from manufacture (formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B and bovine serum albumin), which may be present in undetectable trace amounts.

• ADACEL POLIO 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, administration of ADACEL POLIO should be postponed in persons suffering from an acute severe febrile illness. The presence of a minor infection (e.g., mild upper respiratory infection) is not a contraindication.

4.4 Special warnings and precautions for use

ADACEL-POLIO should not be administered into the gluteal area; intradermal or subcutaneous routes should not be used (in exceptional cases the subcutaneous route may be considered, see section 4.4).

Precautions to be taken before handling or administering the medicinal product

For instructions on handling of the medicinal product before administration, see section 6.6.

ADACEL-POLIO should not be used for primary immunization.

Regarding the interval between a booster dose of ADACEL-POLIO and preceding booster doses of diphtheria and/or tetanus containing vaccines, the official recommendations should generally be followed. Clinical data in adults have demonstrated that there was no clinically relevant difference in rates of adverse reactions associated with administration of ADACEL-POLIO 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-POLIO 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-POLIO should be based on careful consideration of the potential benefits and possible risks.

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

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

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 and following official recommendations the administration of ADACEL-POLIO 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-POLIO. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Other considerations

As with any vaccine, a protective immune response may not be elicited in all vaccines (see section 5.1).

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.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Excipients with known effects

ADACEL-POLIO contains 1.01 milligram of alcohol (ethanol) in each 0.5 mL dose. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

ADACEL-POLIO may be administered concomitantly with a dose of inactivated influenza vaccine, based on the results of a clinical trial conducted in persons 60 years of age and older.
ADACEL-POLIO may be administered concomitantly with a dose of hepatitis B vaccine.
Based on the results of concomitant use clinical studies, ADACEL-POLIO can be administered with human papilloma virus vaccine (HPV) and/or Meningococcal Polysaccharide (Serogroups A, C, Y, and W) (MenACYW) conjugate vaccines (either all three vaccines concomitantly or in pairs) (see section 4.8) according to to local recommendations.
Separate limbs must be used for the site of injection. 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-POLIO is an inactivated product it may be administered concomitantly with other vaccines or immunoglobulins at separate injection sites.
In the case of immunosuppressive therapy please refer to Section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
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), 2 prospective observational studies (2670 pregnancy outcomes), 4 retrospective observational studies (81,701 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. The benefits versus the risks of administering ADACEL-POLIO 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-POLIO 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.
Breastfeeding
The effect of administration of ADACEL-POLIO during lactation has not been assessed. Nevertheless, as ADACEL-POLIO contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering ADACEL-POLIO to breastfeeding women should be evaluated by the health-care providers.

Fertility
ADACEL-POLIO 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-POLIO 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 POLIO was given to a total of 1,384 persons including 390 children 3 through 6 years of age and 994 adolescent and adults. Most commonly reported reactions following vaccination included local reactions at the injection site (pain, redness and swelling). These signs and symptoms usually were mild in intensity and occurred within 48 hours following vaccination (Adverse Events have been observed within 24 hours and 7 days following vaccination in children 3 through 6 years). They all resolved without sequelae.

There was a trend for higher rates of local and systemic reactions in adolescents than in adults. In both age groups, injection site pain was the most common adverse reaction.

Late-onset local adverse reactions (i.e. a local adverse reaction which had an onset or increase in severity 3 to 14 days post-immunization), such as injection site pain, erythema and swelling occurred in less than 1.2%. Most of the reported adverse reactions occurred within 24 hours after the vaccination.

The safety analysis of concomitant use of either ADACEL POLIO or ADACEL administered with MenACYW (Menactra or MenQuadfi) and/or HPV (Gardasil or Gardasil 9) vaccines included 5 122 healthy male and female subjects aged 10 to 17 years from 6 clinical trials.

The overall safety profile of ADACEL POLIO or ADACEL was similar when all three vaccines were administered concomitantly compared to coadministered pairs (ADACEL and Menactra or ADACEL POLIO /ADACEL and Gardasil/Gardasil 9). The safety profile of coadministered ADACEL POLIO and Gardasil/Gardasil 9 was similar to Gardasil/Gardasil 9 administered alone.

In clinical studies, injection-site reactions (pain, erythema, swelling, and bruising), as well as headache, malaise, and myalgia were observed more frequently when all three vaccines were administered together or in pairs, compared to when they were administered alone. Overall, the differences observed in injection site reactions were < 10%, while the differences in headache, malaise, and myalgia ranged from < 10% to < 28%. The difference in fever rates across clinical studies was < 2%.
The majority of 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), including individual cases
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 POLIO worldwide. Adverse events in children were collected from clinical trials conducted in 3 to 5 years of age and 5 to 6 years of age. The highest frequency from either study is presented. 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 clinical trials and worldwide post marketing experience

System Organ Class	Frequency	Children 3 through 6 years	Adolescents and Adults
Blood and lymphatic system disorders	Not known	Lymphadenopathy*	
Immune system disorders	Not known	Anaphylactic reactions, such as urticaria, face oedema and dyspnea*	
Nervous system disorders	Very common		Headache
	Common	Headache	
	Not known	Convulsions, Vasovagal Syncope, Guillain Barré syndrome, Facial Palsy, Myelitis, Brachial Neuritis, Transient paresthesia/hypoesthesia of vaccinated limb, Dizziness*	
Gastrointestinal disorders	Very common	Diarrhoea	Nausea
	Common	Vomiting, Nausea	Diarrhoea, Vomiting
	Not known	Abdominal pain	
Skin and subcutaneous system disorders	Common	Rash	
Musculoskeletal and connective tissue disorders	Very common		Arthralgia/joint swelling, Myalgia
	Common	Arthralgia/joint swelling	
	Not known	Pain in vaccinated limb*	
General disorders and administration site conditions	Very common	Fatigue/Asthenia, Fever†	Fatigue/Asthenia, Chills
		Injection site pain, Injection site swelling, Injection site erythema	
	Common	Irritability, Injection site dermatitis, Injection site bruising, Injection site pruritus	Fever†
	Not known	Malaise§, Pallor*, Extensive limb swelling‡, Injection site induration*	

* Post marketing adverse events

† Fever was measured as temperature ≥37.5°C in Children groups and measured as temperature ≥38°C in Adolescents and Adults group

‡ See section c)

§ was observed at a frequency of very common in adolescents and adults, in studies with ADACEL (Tdap component of ADACEL-POLIO; containing the same amounts of diphtheria, tetanus and pertussis antigens)

Description of selected adverse reactions
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.

Paediatric population
The safety profile of ADACEL-POLIO in 390 children 3 to 6 years of age as presented in Table 1 is derived from two clinical studies:
- In a clinical study, 240 children were primed at 3, 5 and 12 months of age with a DTaP vaccine with no additional dose in the second year of life. These children received ADACEL-POLIO at 5 to 6 years of age.
- 150 children primed at 2, 3, and 4 months of age with a DTwP vaccine (with no additional dose in the second year of life) received ADACEL-POLIO at 3 to 5 years of age.
In both studies the rates of most systemic adverse events within 7 to 10 days following vaccination were less than 10%. Only fever (≥37.5°C) and fatigue were reported in more than 10 % of subjects 3 to 6 years of age. In addition, irritability was reported in more than 10% of subjects 3 to 5 years of age. (See Table 1).
Transient severe swelling of the injected upper arm was reported in <1% of children aged 5 to 6 years.

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: Bacterial and viral vaccines combined. Vaccine against diphtheria, tetanus, pertussis and poliomyelitis
ATC Code: J07CA02

Clinical trials
The immune responses of adults, adolescents and children 3 to 6 years of age one-month after vaccination with ADACEL POLIO are shown in the table below. The use of ADACEL POLIO in children aged 3 to 5 years is based upon studies in which ADACEL POLIO was given as the fourth dose (first booster) of diphtheria, tetanus, pertussis and poliomyelitis vaccines.

Table 2: Immune responses 4 weeks after vaccination

Antigen	Criteria	Adults and Adolescents* (n = 994)	Children 5-6 years old† (n = 240)	Children 3-5 years old‡ (n = 148)
Diphtheria	≥0.1 IU/mL	92.8%	99.4%	100%

Tetanus	≥0.1 IU/mL§	100%	99.5%	100%
Pertussis **Pertussis Toxoid** **Filamentous Haemagglutinin** **Pertactin** **Fimbriae Types 2 and 3**	 ≥5 EU/mL** ≥5 EU/mL** ≥5 EU/mL** ≥5 EU/mL**	 99.7% 99.9% 99.6% 99.8%	 91.2% 99.1% 100% 99.5%	 99.3% 99.3% 100% 100%
Polio 1 **Polio 2** **Polio 3**	≥1:8 Dilution ≥1:8 Dilution ≥1:8 Dilution	99.9% 100% 100%	100% 100% 100%	100% 100% 100%

* From the age of 10 years onwards
† Primed with DTaP at 3 and 5 months with a booster at 12 months of age
‡ Primed with DTwP at 2, 3 and 4 months of age
§ Measured by ELISA
** EU = ELISA units: Antibody levels of >5 EU/mL were postulated as possible surrogate markers for protection against pertussis by Storsaeter J. et al, Vaccine 1998;16:1907-16.

The safety and immunogenicity of ADACEL-POLIO in adults and adolescents was shown to be comparable to that observed with a single booster dose of Td adsorbed or Td Polio adsorbed vaccines containing a similar amount of tetanus and diphtheria toxoids and inactivated poliovirus types 1, 2 and 3.

The lower response to diphtheria toxoid in adults probably reflected the inclusion of some participants with an uncertain or incomplete immunization history.

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-POLIO had elicited protective immune responses.

In a subsequent study, robust immune responses were observed following a single dose of ADACEL-POLIO in UK children 3.5 to 4.0 years of age previously primed with either an acellular pertussis combination vaccine (DTaP-IPV-Hib) or whole cell pertussis combination vaccine (DTwP//Hib) and OPV.

Antibody persistence

Pivotal studies conducted with ADACEL provide serology follow-up data 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 3.

Table 3: Persistence of Seroprotection/Seropositivity Rates in Children, Adolescents and Adults at 3-, 5- and 10- years following a dose of ADACEL (Tdap component of ADACEL-POLIO) (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)								
PT	Sero-positivity[3]	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

In serology follow-up studies conducted with ADACEL-POLIO, seroprotective antibody levels (≥1:8 dilution) for each poliovirus (type1, 2 and 3) were maintained in 95% to 100% of the children, adolescents and adults at the 5-year follow-up time point, and in 100% of the adolescents at the 10-year follow-up time point.

Immunogenicity following repeat vaccination

The immunogenicity of ADACEL following repeat vaccination 10 years after a previous dose of ADACEL or ADACEL-POLIO, 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-POLIO can be used instead of a dT vaccine or dT-IPV vaccine to boost immunity to pertussis in addition diphtheria, tetanus and polio.

Immunogenicity in naive subjects

After administration of one dose of ADACEL-POLIO to 330 adults ≥40 years of age that had not received any diphtheria- and tetanus-containing vaccine in the past 20 years:

• ≥95.8% of adults were seropositive (≥ 5 IU/mL) for antibodies to all vaccine-containing pertussis antigens,

• 82.4% and 92.7% were seroprotected against diphtheria at a threshold ≥0.1 and ≥0.01 IU/mL, respectively,

• 98.5% and 99.7% were seroprotected against tetanus at a threshold ≥0.1 and ≥0.01 IU/mL, respectively,

• and ≥98.8% were seroprotected against polio (types 1, 2 and 3) at a threshold ≥1:8 dilution.

After administration of two additional doses of diphtheria- tetanus- and polio-containing vaccine to 316 subjects, one and six months after the first dose, the seroprotection rates against diphtheria were 94.6% and 100% (≥0.1 and ≥ 0.01 IU/mL, respectively), against tetanus 100% (≥0.1 IU/mL), and against polio (types 1, 2 and 3) 100% (≥1:8 dilution) (see Table 4).

Table 4: Serological immune status (seroprotection/seroresponse rates and GMC/GMT) before vaccination and after each dose of a 3 dose-vaccination schedule including ADACEL-POLIO (Dose 1) followed by 2 doses of REVAXIS 1 and 6 months later (Dose 2 and 3) in subjects vaccinated according to protocol (FAS)

Antigen	Criteria	Pre-vaccination	Post-dose 1 ADACEL-POLIO	Post-dose 2 REVAXIS	Post-dose 3 REVAXIS
		N=330	N=330	N=325	N=316
Diphtheria	GMC	0.059	0.813	1.373	1.489
(SN, IU/mL)	95%CI	[0.046; 0.077]	[0.624; 1.059]	[1.100; 1.715]	[1.262; 1.757]
	≥0.1	44.5%	82.4%	90.5%	94.6%
	95%CI	[39.1; 50.1]	[77.9; 86.4]	[86.7; 93.4]	[91.5; 96.8]
	≥0.01	72.4%	92.7%	96.0%	100%
	95%CI	[67.3; 77.2]	[89.4; 95.3]	[93.3; 97.9]	[98.8; 100]
Tetanus	GMC	0.48	6.82	7.60	5.46
(ELISA, IU/mL)	95%CI	[0.39;0.60]	[5.92;7.87]	[6.77;8.52]	[5.01;5.96]
	≥0.1	81.2%	98.5%	100%	100%
	95%CI	[76.6; 85.3]	[96.5; 99.5]	[98.9; 100]	[98.8; 100]
	≥0.01	92.4%	99.7%	100%	100%
	95%CI	[89.0; 95.0]	[98.3; 100]	[98.9; 100]	[98.8; 100]
Poliomyelitis (SN, 1/dil)					
Type 1	GMT	162.6	2869.0	2320.2	1601.9
	95%CI	[133.6; 198.0]	[2432.9; 3383.4]	[2010.9; 2677.0]	[1425.4; 1800.3]
	≥8	93.3%	99.4%	100%	100%
	95%CI	[90.1; 95.8]	[97.8; 99.9]	[98.9; 100]	[98.8; 100]
Type 2	GMT	164.5	3829.7	3256.0	2107.2
	95%CI	[137.6;196.8]	[3258.5;4501.1]	[2818.2;3761.7]	[1855.7;2392.8]
	≥8	95.5%	100%	100%	100%
	95%CI	[92.6; 97.4]	[98.9; 100]	[98.9; 100]	[98.8; 100]
Type 3	GMT	69.0	5011.4	3615.6	2125.8
	95%CI	[56.9; 83.6]	[4177.4; 6012.0]	[3100.5; 4216.4]	[1875.5; 2409.6]
	≥8	89.1%	98.8%	99.7%	100%
	95%CI	[85.2; 92.2]	[96.9; 99.7]	[98.3; 100]	[98.8; 100]
Pertussis (ELISA, EU/mL)					
PT	GMC	7.7	41.3		
	95%CI	[6.8; 8.7]	[36.7; 46.5]		
	≥5	-	96.3%	-	-
	95%CI		[93.6; 98.1]		
FHA	GMC	28.5	186.7		
	95%CI	[25.5; 31.8]	[169.6; 205.6]		
	≥5	-	100%	-	-
	95%CI		[98.9; 100]		
PRN	GMC	7.7	328.6		

Antigen	Criteria	Pre-vaccination	Post-dose 1 ADACEL-POLIO	Post-dose 2 REVAXIS	Post-dose 3 REVAXIS
	95%CI	[6.7; 8.9]	[273.0; 395.6]		
	≥5	-	99.4%	-	-
	95%CI		[97.8; 99.9]		
FIM2&3	GMC	6.1	149.6		
	95%CI	[5.2; 7.1]	[123.6; 181.0]		
	≥5	-	95.8%	-	-
	95%CI		[93.0; 97.7]		

GMC: Geometric mean of antibody concentrations; GMT: Geometric mean of antibody titres; CI: Confidence Interval; SN: seroneutralisation; ELISA: Enzyme Linked Immunoassay; dil: dilution
FAS: Full Analysis Set – includes all subjects who received the study vaccine dose and for whom the post-vaccination immunogenicity evaluation was available.

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 doses toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

2-Phenoxyethanol, Ethanol, Aluminum phosphate, Polysorbate 80, Water for injection.

For adjuvant see section 2.

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 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 container in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 mL of suspension in pre-filled syringe (glass) with a plunger stopper (chlorobutyl elastomer), without attached needle, with a tip-cap (synthetic isoprene-bromobutyl elastomer) - pack size of 1, 10 or 20.
0.5 mL of suspension in pre-filled syringe (glass) with a plunger stopper (chlorobutyl elastomer), without attached needle, with a tip-cap (synthetic isoprene-bromobutyl elastomer) and 1 or 2 separate needles - pack size of 1 or 10.
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 discoloration 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 prefilled syringe well to uniformly distribute the suspension before administering the vaccine.
For needle free syringes, the needle should be pushed firmly on to the end of the prefilled syringe and rotated through 90 degrees.
Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Needles should not be recapped.

7. MARKETING AUTHORISATION HOLDER:
Sanofi Israel Ltd., Greenwork Complex, P.O box 47, Yakum

8. MARKETING AUTHORISATION NUMBER
142-60-31938-00

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