Professional Information for ADACEL®

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

ADACEL® suspension for injection

Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 mL dose contains:

Tetanus toxoid (T)	5 Lf (not less than 20 IU*)
Diphtheria toxoid (d)	2 Lf (not less than 2 IU*)
Pertussis toxoid (PT)	2,5 micrograms
Filamentous haemagglutinin (FHA)	5 micrograms
Pertactin (PRN)	3 micrograms
Fimbriae types 2 and 3 (FIM)	5 micrograms

* As lower confidence limit (p = 0,95) of activity measured according to the assay described in the European Pharmacopoeia.

Sugar free.

ADACEL may contain traces of formaldehyde and glutaral, which are used during the manufacturing process (see section 4.4 and 6.1).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ADACEL is a sterile, uniform, cloudy, white suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADACEL (Tdap) is indicated for active booster immunesation for the prevention of tetanus, diphtheria and pertussis (whooping cough) in persons 4 years of age and older, according to local immunisation recommendations.

Passive immunisation against pertussis in early infancy following maternal immunisation during pregnancy (see sections 4.2, 4.6 and 5.1).

Persons who have had pertussis, tetanus or diphtheria, should still be immunised since these clinical infections do not always confer immunity.

ADACEL can be used in the management of tetanus prone injuries with or without concomitant administration of tetanus immunoglobulin in accordance with official recommendations.

4.2 Posology and method of administration

ADACEL (0,5 mL) should be administered as a booster injection 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.

ADACEL may be administered to pregnant women during the second and third trimester to provide passive immunity to infants against pertussis (see sections 4.1, 4.6 and 5.1).

The use of ADACEL in management of tetanus-prone wounds should follow local recommendations. A thorough attempt must be made to determine whether a patient has completed primary immunisation. Persons who have completed primary immunisation 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, faeces, soil and saliva, puncture wounds, avulsions and wounds resulting from measles, 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:

Administer the total volume of 0,5 mL intramuscularly (IM). The preferred site of injection is the deltoid muscle. Fractional doses (doses < 0,5 mL) should not be given.

Do not administer ADACEL intravenously. ADACEL should not be administered into the gluteal area; intradermal or subcutaneous routes should not be used (for exception see section 4.4).

For instructions on handling of ADACEL before administration see section 6.6.

Separate syringes, separate injection sites and preferably separate limbs must be used in case of concomitant administration (see section 4.5).

4.3 Contraindications

Hypersensitivity:

ADACEL should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine (sections 2 and 6.1) or after a previous administration of the vaccine or a vaccine containing the same components or constituents.

Febrile or acute disease:

Generally, vaccination must be postponed in cases of moderate or severe febrile and/or acute disease. Low-grade fever does not constitute a contraindication.

Neurological disorders:

Encephalopathy within 7 days of a previous dose of pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with ADACEL.

4.4 Special warnings and precautions for use

General:

Before immunisation, health care providers should inform the recipient or their parent/guardian of the benefits and risks of immunisation, inquire about the recent health status of the recipient, review the recipient's immunisation history including possible hypersensitivity to ADACEL or a similar vaccine, presence of contraindications to immunisation and comply with local requirements regarding information to be provided to the recipient or parent/guardian before immunisation.

It is extremely important that the recipient or parent/guardian be questioned concerning any signs or symptoms of an adverse reaction after a previous dose of vaccine. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.
The rates and severity of adverse events in recipients of tetanus toxoid are influenced by the number or prior doses and level of pre-existing antitoxins.

Hypersensitivity:

Formaldehyde and glutaraldehyde have been used in the manufacturing process of ADACEL and trace residual amounts may be present in the final product. Therefore, a hypersensitivity

reaction may occur.

Neurological disorders:

If Guillain-Barré syndrome or brachial neuritis has occurred following receipt of prior vaccine containing tetanus toxoid, the decision to give any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

ADACEL should not be administered to individuals with progressive or unstable neurological disorders, uncontrolled epilepsy or progressive encephalopathy until a treatment regimen has been established, the condition has stabilised and the benefit clearly outweighs the risk.

Protection:

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

Special patient groups:

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment.

Nevertheless, vaccination of subjects 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 intravascular injection: ensure that the needle does not penetrate a blood vessel.

As with all injectable vaccines, the vaccine must be administered with caution to subjects with thrombocytopaenia or a bleeding disorder, since bleeding may occur following an intramuscular administration to these subjects.

Syncope:

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.

4.5 Interactions with other medicines and other forms of interaction

Concomitant administration with other vaccines:

ADACEL may be administered concurrently with influenza vaccine, hepatitis B vaccine, inactivated or oral poliomyelitis vaccine and human papillomavirus vaccine (see section 4.8).

In accordance with national recommendations, other live or inactivated parenteral vaccines may be administered simultaneously, as appropriate for the recipient's age and previous vaccination status.

Separate injection sites and separate syringes must be used in case of concomitant administration. ADACEL must not be mixed with other vaccines or medicines.

Vaccine-medicine interaction:

Immunosuppressive treatment may interfere with the development of the expected immune response to ADACEL.

4.6 Fertility, pregnancy and lactation

Pregnancy:

ADACEL can be used during the second or third trimester of pregnancy in accordance with official recommendations (see section 4.2).

Safety data from 4 randomised controlled trials (310 pregnancy outcomes), 1 prospective observational studies (546 pregnancy outcomes), 5 retrospective observational studies (124 810 pregnancy outcomes), and from passive surveillance of women who received ADACEL or ADACEL QUADRA (Tdap-IPV; containing the same amounts of tetanus, diphtheria and pertussis antigens as ADACEL) during the second or third trimester have shown no vaccine-related adverse effect on pregnancy or on the health of the fetus/new born child. As with other inactivated vaccines, it is not expected that vaccination with ADACEL during any trimester would harm the fetus.

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

For information on immune responses to vaccination during pregnancy and its effectiveness at preventing pertussis in infants, see section 5.1.

Breastfeeding:

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.

The effect of administration of ADACEL during lactation has not been assessed. As ADACEL is inactivated, any risk to the mother or the infant is improbable.

The risks and benefits of vaccination should be assessed before making the decision to immunise a nursing woman.

Fertility:

ADACEL has not been evaluated in fertility studies.

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Data from clinical studies

In clinical studies of ADACEL conducted on individuals ≥ 4 years of age, pain at the injection site was the most common solicited injection site reaction. Most injection site reactions occurred within 3 days following vaccination and their mean duration was less than 3 days.

The most frequent systemic reaction was tiredness in children and headache in adolescents and adults (18 – 64 years). Myalgia was the most frequently reported systemic reaction among older adults ≥ 65 years of age. Fever was reported in less than 10 % of vaccinees.

These reactions were usually transient and of mild to moderate intensity.
The frequency of the solicited injection site and systemic reactions reported in 3 clinical studies following a single dose of ADACEL are shown in Table 1.

Table 1. Frequency (%) of solicited reactions observed within 0 to 14 days in clinical trials in children, adolescents and adults, following a single dose with ADACEL

Solicited reactions	Children (4 – 6 years) (N = 298)	Adolescents (11 – 17 years) (N = 1 184)	Adults (18 – 64 years) (N = 1 752)	Adults (≥ 65 years) (N = 1 153)
Injection site reactions:				
Pain	39,6	77,8	65,7	43,0
Swelling	24,2	20,9	21,0	18,1

Solicited reactions	Children (4 – 6 years) (N = 298)	Adolescents (11 – 17 years) (N = 1 184)	Adults (18 – 64 years) (N = 1 752)	Adults (≥ 65 years) (N = 1 153)
Erythema	34,6	20,8	24,7	24,3
Systemic reactions:				
Fever (≥ 38,0 °C)	8,7	5,0	1,4	0,5
Headache	16,4	43,7	33,9	18,2
Nausea	9,4	13,3	9,2	N.S.*
Diarrhoea	14,4	10,3	10,3	N.S.*
Vomiting	8,1	4,6	3,0	N.S.*
Anorexia	21,5	N.S.*	N.S.*	N.S.*
Rash	8,4	2,7	2,0	N.S.*
Body ache or muscle weakness † / myalgia‡	6,4	30,4	21,9	28,4*
Sore or swollen joints	4,0	11,3	9,1	N.S.*
Tiredness§ / malaise**	31,5	30,2	24,3	17.2
Chills	7,1	15,1	8,1	N.S.*
Axillary lymph node swelling	5,4	6,6	6,5	N.S.*

* Not solicited

† Body ache or muscle weakness was the solicited term in the trials in children, adolescents and adults 18 – 64 years of age.

‡ Myalgia was the solicited term in the trial in adults ≥ 65 years of age.

§ Tiredness was the solicited term in the trials in children, adolescents and adults 18 – 64 years of age.

** Malaise was the solicited term in the trial in adults ≥ 65 years of age.

The safety and tolerability of revaccination with ADACEL at 5 and 10 years after a previous dose of the vaccine was evaluated in 2 clinical studies. In adolescents and adults, pain at the

injection site was the most common solicited injection site reaction, while myalgia was the most frequently reported systemic reaction. Fever was reported in less than 7 % of vaccinees. The frequency of the solicited injection site and systemic reactions observed in adolescents and adults following re-administration of ADACEL at 5 and 10 years are shown in Table 2.

Table 2. Frequency of solicited reactions observed in adolescents and adults following re-administration of ADACEL at 5 and 10 years, respectively

Solicited reactions	**Re-administration of ADACEL**	
	After 5 years*	**After 10 years†**
	Adolescents and adults 16 – 69 years (N = 544)	**Adults 20 – 72 years (N = 361)**
Injection site reactions:		
Pain	87,6	87,8
Erythema/ Redness	28,6	23,1
Swelling	25,6	20,5
Systemic reactions:		
Fever	6,5	4,2
Headache	53,2	40,6
Myalgia	61,0	60,1
Malaise	38,2	29,4

* Adverse reactions observed within 0 to 14 days after vaccination.

† Adverse reactions observed within 0 to 7 days after vaccination.

Safety analysis was conducted in 1 042 healthy adolescent males and females aged 10 to 17 years during a clinical trial. They received recombinant HPV vaccine 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 recombinant HPV vaccine injection site, bruising and pain at ADACEL injection site 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.

Data from post-marketing experience

The following additional adverse events have been spontaneously reported during the post-marketing use of ADACEL worldwide. Because these 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. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to ADACEL.

Immune system disorders

Hypersensitivity (anaphylactic) reaction (angioedema, edema, rash, hypotension)

Nervous system disorders

Paraesthesia, hypoesthesia, Guillain-Barré syndrome, brachial neuritis,
facial palsy, convulsion, syncope, myelitis.

Cardiac disorders

Myocarditis

Skin and subcutaneous tissue disorders

Pruritus, urticaria

Musculoskeletal and connective tissue disorders

Myositis

General disorders and administration site conditions

Large injection site reactions (> 50 mm) and 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.

Injection site bruising, injection site nodule, sterile abscess.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: Email: za.drugsafety@sanofi.com or Tel: 011 256-3700, or
- SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

None known.

5. PHARMACOLOGICAL PROPERTIES

A 30.2 Antigens

Pharmacotherapeutic group: Pertussis, purified antigen, combination with toxoids.

ATC code: J07AJ52

5.1 Pharmacodynamic properties

Efficacy:

Tetanus and diphtheria:

Serological correlates of protection have been defined for tetanus and diphtheria. The efficacy of the tetanus toxoid and diphtheria toxoid used in ADACEL was inferred by the demonstration that the immune responses to these antigens attain levels previously established as protective (≥ 0,1 IU/mL).

Pertussis:

The efficacy of the pertussis antigens used in ADACEL was inferred based on a comparison of pertussis antibody levels achieved in recipients of a single booster dose of ADACEL with those obtained in infants after a 3-dose primary series with Sanofi Pasteur Limited's (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine adsorbed – DtaP) infant formulation in a pertussis efficacy trial (Sweden I Efficacy Trial). The acellular pertussis formulations for ADACEL and the infant DTaP formulation differ only in the amount of (PT) (2,5 microgram in ADACEL versus 10 microgram in the infant DTaP formulation).

Immunogenicity:

Tetanus and diphtheria:

In clinical studies, 100 % of children, adolescents and adults and 98,4 % of older adults (≥ 65-years-old) achieved seroprotective tetanus antitoxin levels of ≥ 0,1 IU/mL one month after vaccination with ADACEL vaccine. A seroprotective antitoxin level (≥ 0,1 IU/mL) against diphtheria was achieved one month after vaccination with ADACEL vaccine in 100 % of children, 99,8 % of adolescents, 94,1 % of adults and 77,4 % of older adults ≥ 65 years of age.

Pertussis:

The pertussis antibody responses in the clinical studies conducted in children, adolescents and adults 19 – 64 years of age demonstrate that a booster dose of ADACEL results in robust antibody responses to all pertussis antigens and post-immunisation antibody levels that are 2- to 5-fold higher than those found to be protective in the Sweden I Efficacy Trial. Older adults (≥ 65 years of age) vaccinated with a single dose of ADACEL achieved lower geometric mean concentrations (GMCs) for some of the pertussis antibodies than did infants who had received 3 or 4 doses of the infant DTaP formulation. Nevertheless, their post-immunisation anti-pertussis antibody levels were 4,4- to 15,1-fold higher than pre-immunisation levels, suggesting an improved degree of protection against pertussis.

Duration of immunity:

Adolescents and adults:

Long-term follow-up of serum antibody levels in adolescents and adults who received a single dose of ADACEL show that protective levels of tetanus antitoxin (≥ 0,01 IU/mL) and diphtheria antitoxin (≥ 0,01 IU/mL) persist in 99,2 % and 92,6 % of participants, respectively, 10 years post-vaccination.

While protective levels of pertussis antibodies have not yet been clearly defined, these antibody levels remain 2- to 9-fold higher than pre-immunisation levels after 5 years. However, at 10 years post-vaccination, pertussis antibody levels were observed to decline towards pre-vaccination levels.

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 randomised controlled trials demonstrate higher pertussis antibody concentrations at birth and at 2 months of age, (i.e. 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 1 867,0 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.

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 QUADRA 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 or ADACEL QUADRA vaccination in pregnancy may be associated with blunting of the infant immune response to active immunisation 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 or ADACEL QUADRA and the infants' or toddlers' responses to diphtheria, tetanus, *Haemophilus influenzae* type b, inactivated poliovirus or pneumococcal antigens.

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 2: Vaccine effectiveness (VE) against pertussis disease in young infants born to mothers vaccinated during pregnancy with ADACEL or ADACEL QUADRA in 3 retrospective studies.

Location	**Vaccine**	**VE (95 % CI)**	**VE estimation method**	**Infant follow-up period**
UK	ADACEL QUADRA	93 % (81, 97)	unmatched case-control	2 months
US	ADACEL*	91,4 % (19,5; 99,1)	cohort regression model	2 months
UK	ADACEL QUADRA	93 % (89,95)	screening (case-coverage)	3 months

Approximately 99 % of women were vaccinated with ADACEL

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

Aluminum phosphate (adjuvant) 1,5 mg (0,33 mg Al^{3+})

2-phenoxyethanol (not as preservative) 3,3 mg (0,6 % *v/v*)

Water for injection

Other ingredients per dose include ≤ 5 micrograms residual formaldehyde and < 50 nanograms residual glutaral.

6.2 Incompatibilities

ADACEL must not be mixed with other vaccines or medicines (see section 4.5).

6.3 Shelf life

36 months.

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. Protect from light. Keep the vial in the outer carton until required for use.

6.5 Nature and contents of container

ADACEL is packed in a single dose 2,0 mL glass vial. The vial is Type 1 clear borosilicate glass. The stopper is a 13 mm grey stopper made of halobutyl elastomer. The aluminium seal has an orange plastic flip-off cap.

Marketed in pack sizes of 5 or 10 vials. Not all pack sizes may be marketed.

Components are latex free.

The vials are packed in an outer carton.

6.6 Special precautions for disposal and other handling

Inspect the vial for extraneous particulate matter and/or discolouration before use. If these conditions exist, do not administer ADACEL.

Shake the vial well before use until a uniform, cloudy, suspension results. Aseptic technique must be used to withdraw the dose. Use a separate sterile needle and syringe, or a sterile disposable unit, for each recipient.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

8. REGISTRATION NUMBER

51/30.1/0837

MANUFACTURER:

Sanofi Pasteur Limited – 1755 Steeles Avenue West,

Toronto, Ontario,

Canada.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 December 2019

10. DATE OF REVISION OF THE TEXT

18 October 2023