SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

ADACEL QUADRA® suspension for injection

Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (0,5 mL) contains:

Diphtheria toxoid*	2 Lf (not less than 2 IU)
Tetanus toxoid*	5 Lf (not less than 20 IU)
Pertussis toxoid (PT)	2,5 micrograms
Filamentous haemagglutinin (FHA)	5 micrograms
Fimbriae types 2 + 3 (FIM)	5 micrograms
Pertactin (PRN)	3 micrograms
Poliomyelitis virus type 1** (Mahoney)	40 D-antigen units
Poliomyelitis virus type 2** (MEF)	8 D-antigen units
Poliomyelitis virus type 3** (Saukett)	32 D-antigen units

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

** Produced on Vero cells.

Sugar (glucose): trace amounts.

ADACEL QUADRA contains, as residues from the manufacturing process, trace amounts of formaldehyde, glutaraldehyde, neomycin, streptomycin, polymyxin B and bovine serum albumin, as well as Hanks' medium, a mixture of amino acids (including phenylalanine), salts, vitamins and other compounds (including glucose) (see sections 4.4 and 6.1).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADACEL QUADRA is indicated for active immunisation against diphtheria, tetanus, pertussis and poliomyelitis in persons aged 3 years and older as a booster dose following primary immunisation.

ADACEL QUADRA has been used in clinical studies in elderly persons aged 59 to 91 years of age.

Passive protection against pertussis in early infancy following maternal immunisation during pregnancy (see sections 4.2, 4.4, 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. Although well-documented pertussis disease is likely to confer immunity, the duration of protection is unknown.

ADACEL QUADRA is not to be used for the treatment of disease caused by *B. pertussis, C. diphtheriae* or *C. tetani,* or poliomyelitis infections.

HIV-infected persons, both asymptomatic and symptomatic, should be immunised against diphtheria, tetanus, pertussis and poliomyelitis according to standard schedules.

4.2 Posology and method of administration

Posology

ADACEL QUADRA should be administered as a single injection of one dose (0,5 mL) by the intramuscular route.

ADACEL QUADRA should not be used for primary immunisation.
In adolescents and adults with an unknown or incomplete diphtheria or tetanus vaccination status against diphtheria or tetanus, one dose of ADACEL QUADRA can be administered as part of a vaccination series to protect against pertussis and poliomyelitis and in most cases also against tetanus and diphtheria. One additional dose of a diphtheria- and tetanus- (dT) containing vaccine can be administered one month later followed by a third dose of a diphtheria- or dT-containing vaccine 6 months after the first dose to optimise protection against disease (see section 5.1). The number and schedule of doses should be determined according to local recommendations.
ADACEL QUADRA can be used for repeat vaccination to boost immunity to diphtheria, tetanus and pertussis at 5 to 10-year intervals (see section 5.1).

ADACEL QUADRA can be used in the management of tetanus-prone injuries with or without concomitant administration of tetanus Immunoglobulin according to official recommendations.

ADACEL QUADRA may be administered to pregnant women during the second and third trimester to provide passive protection to infants against pertussis (see sections 4.1, 4.4, 4.6 and 5.1).

Method of administration

Administer the vaccine intramuscularly. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area. Do not administer ADACEL QUADRA intravenously. The subcutaneous route should not be used (see section 4.4 for exceptions).
Fractional doses (doses < 0,5 mL) should not be given. The effect of fractional doses on the frequency of serious adverse events and on efficacy has not been determined.
For instructions on handling of ADACEL before administration, see section 6.6.

4.3 Contraindications

Known systemic hypersensitivity reaction or a life-threatening reaction to any component of ADACEL QUADRA after previous administration of the vaccine or a vaccine containing the same components are contraindications to the administration of ADACEL QUADRA (see sections 2, 4.4

and 6.1).

Vaccination should be postponed in case of an acute or febrile illness. However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

Encephalopathy (e.g. coma, decreased level of consciousness or prolonged seizures) within 7 days of a previous dose of pertussis-containing vaccine, not attributable to another identifiable cause, is a contraindication to vaccination with ADACEL QUADRA.

4.4 Special warnings and precautions for use

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.

Anaphylaxis has been reported after receipt of some preparations containing diphtheria toxoid, tetanus toxoid, and/or pertussis antigens.

A review by the 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 or brachial neuritis has occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give any vaccine containing tetanus toxoid, including ADACEL QUADRA, should be based on careful consideration of the potential benefits and possible risks, such as whether or not the primary immunisation schedule has been completed.

ADACEL QUADRA 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 stabilised.

ADACEL QUADRA contains as residues, trace amounts of formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B and bovine serum albumin, as well as Hanks' medium, a mixture of amino acids (including phenylalanine), salts, vitamins and other compounds (including glucose).

Phenylalanine may be harmful if the patient suffers from phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

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

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 treatment if practical. Nevertheless, vaccination of HIV-infected subjects or subjects with chronic immunodeficiency, such as AIDS, is recommended even if the antibody response might be limited.

Do not administer by intravascular or intradermal injection – ensure that the needle does not penetrate a blood vessel.

Because any intramuscular injection can cause an injection site haematoma in persons with any bleeding disorders, such as haemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with ADACEL QUADRA 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 haematoma formation following injection. In these situations, and following official recommendations, the administration of ADACEL QUADRA by deep subcutaneous injection may be considered, although there is a risk of increased local reactions.

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.

Prior to administration of ADACEL QUADRA, the parent or guardian of the recipient or the adult recipient must be asked about personal history, family history and recent health status, including immunisation history, current health status and any adverse event after previous immunisations. In persons who have a history of serious or severe reactions within 48 hours of a previous injection with a vaccine containing similar components, administration of ADACEL QUADRA vaccine must be carefully considered.

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

As a precautionary measure adrenaline (epinephrine) injection (1:1 000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

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

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

Effects on ability to drive and use machines

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

4.5 Interactions with other medicines and other forms of interaction

ADACEL QUADRA may be administered concomitantly with hepatitis B vaccine.

ADACEL QUADRA 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 QUADRA may be administered concurrently with a dose of recombinant human papillomavirus (HPV) vaccine with no significant interference with antibody response to any of the components of either vaccine. However, a trend of lower anti-HPV GMTs was observed in the concomitant group. The clinical significance of this observation is not known.

Interaction studies have not been carried out with other vaccines, biological products or therapeutic medications. However, ADACEL QUADRA is an inactivated vaccine and theoretically there is no reason why it should not be administered concomitantly with other vaccines or immunoglobulins at separate sites.

Separate limbs must be used for the site of injection when co-administering vaccines.

In 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 randomised controlled trials (310 pregnancy outcomes), 2 prospective observational studies (2 670 pregnancy outcomes), 4 retrospective observational studies (81 701 pregnancy outcomes), and from passive surveillance of women who received ADACEL QUADRA or ADACEL (Tdap component of ADACEL QUADRA; containing the same amounts of diphtheria, tetanus and pertussis antigens) during the second or third 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 QUADRA during any trimester would

harm the fetus. The benefits versus the risks of administering ADACEL QUADRA 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 QUADRA 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

It is not known whether the active substances included in ADACEL QUADRA are excreted in human milk.

The effect on breastfed infants of the administration of ADACEL QUADRA to their mothers has not been studied. ADACEL QUADRA 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 QUADRA 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 trials

In clinical trials ADACEL QUADRA was given to a total of 1 384 children, adolescent and adult subjects. Most commonly reported reactions following vaccination include local reactions at the injection site (pain, redness and swelling). These signs and symptoms were mild in intensity and occurred within 48 hours following vaccination. They all resolved without sequelae.

Side effects 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.

Adolescents and adults (994 subjects)

In clinical studies in which ADACEL QUADRA was administered to adolescents and adults, the most frequently reported adverse reactions occurring over all age groups during the first 24 hours after vaccination included the following:

Nervous system disorders

Very common: headache

Gastrointestinal disorders

Very common: nausea

Common: vomiting, diarrhoea

Musculoskeletal and connective tissue disorders

Very common: arthralgia/joint swelling, myalgia

General disorders and administration site conditions

Very common: asthenia, chills, injection site pain, swelling, erythema

Common: fever > 38 °C.

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-immunisation), such as injection site pain, erythema and swelling occurred in less than 1,2 % of subjects.

In a clinical trial of 843 healthy adolescent males and females 11 – 17 years of age, administration of the first dose of HPV vaccine concomitantly with ADACEL QUADRA showed that there was more injection site swelling and headache reported following concomitant administration. The differences observed were < 10 % and in the majority of subjects, the adverse events were reported as mild to moderate in intensity.

Children 5 to 6 years old (240 subjects)

In a clinical study, 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 QUADRA at 5 to 6 years of age. The most frequently reported adverse reactions occurring during the first 24 hours, included the following:

Gastrointestinal disorders

Uncommon: vomiting, diarrhoea

General disorders and administration site conditions

Very common: fatigue, injection site pain, swelling

Common: fever > 38 °C, injection site erythema and pruritis

The rates of general symptoms after the first day but within 10 days after vaccination were low; only fever (> 38 °C) and fatigue were reported in > 10 % of subjects. Transient severe swelling of the upper arm was reported in < 1 % of subjects.

Children 3 to 5 years old (150 subjects)

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 QUADRA at 3 to 5 years of age. The most frequently

reported adverse reactions occurring during the first 7 days included the following:

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea

General disorders and administration site conditions

Very common: fatigue, fever > 37,5 °C, irritability, injection site pain, swelling, erythema

Common: injection site bruising and dermatitis.

Data from post-marketing experience

In addition to the data from clinical studies, the following adverse events have been reported during the commercial use of ADACEL QUADRA. All the adverse events have been very rarely reported (< 0,01 %); however, the exact incidence rates cannot precisely be calculated.

Blood and lymphatic system disorders

Lymphadenopathy.

Immune system disorders

Anaphylactic reactions such as urticaria, face oedema and dyspnoea.

Nervous system disorders

Convulsions, vasovagal syncope, Guillain-Barré syndrome, facial palsy, myelitis, brachial neuritis, transient paraesthesia/hypaesthesia of vaccinated limb, dizziness.

Gastrointestinal disorders

Abdominal pain.

Musculoskeletal and connective tissue disorders

Pain in vaccinated limb.

General disorders and administration site conditions:

Extensive limb swelling which may extend from the injection site beyond one or both joints and is frequently associated with erythema, and sometimes with blisters, has been reported following administration of ADACEL QUADRA. 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 fourth and fifth doses.

Malaise, pallor, injection site induration.

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

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

A.30.2 Antigens

5.1 Pharmacodynamic properties

Active immunising agent against diphtheria, tetanus, pertussis and poliomyelitis.

Clinical trials:

Immune responses of adults, adolescents and children 3 to 6 years of age one month post vaccination with ADACEL QUADRA are shown below.

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 PT	> 5 EU/mL	99,7 %	91,2 %	99,3 %

Antigen	Criteria	Adults and adolescents* (n = 994)	Children 5 – 6 years old+ (n = 240)	Children 3 – 5 years old$ (n = 148)
PT				
FHA	> 5 EU/mL	99,9 %	99,1 %	99,3 %
PRN	> 5 EU/mL	99,6 %	100 %	100 %
FIM	> 5 EU/mL	99,8 %	99,5 %	100 %
Polio 1	> 1:8 dilution	99,9 %	100 %	100 %
Polio 2	> 1:8 dilution	100 %	100 %	100 %
Polio 3	> 1:8 dilution	100 %	100 %	100 %

* From the age of 10 years.

+ 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.

The safety and immunogenicity profile of ADACEL QUADRA in adults and adolescents was shown to be comparable to that observed with a single dose booster of diphtheria-tetanus vaccine or diphtheria-tetanus-inactivated polio vaccine containing similar amounts of tetanus and diphtheria toxoids and inactivated polio virus type 1, 2 and 3. The lower response to diphtheria toxoid in adults probably reflected the inclusion of some participants with an uncertain or incomplete immunisation history.

Serological correlates for protection against pertussis have not been established. On comparison with data from the two separate pertussis efficacy trials conducted in Sweden between 1992 and 1996, where primary immunisation with Sanofi Pasteur Limited's acellular pertussis infant DTaP formulations conferred a protective efficacy of 85 % against pertussis disease, it was considered that ADACEL QUADRA had elicited protective immune responses.

In a subsequent study, robust immune responses were observed following a single dose of

ADACEL QUADRA 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.

Serology follow-up studies were conducted in children, adolescents and adults immunised with a single booster dose of ADACEL QUADRA.

At the 5-year follow-up time point, seroprotective antibody levels (≥ 0,01 IU/mL) were maintained in 100 % of participants of all age groups, for tetanus, and in 96 – 100 % of the children and adolescents and > 79 % of the adults, for diphtheria.

For poliovirus, the seroprotective levels (≥ 1:8 dilution) for each type (1, 2 and 3) were maintained for 95 – 100 % of the children, adolescents and adults at the 5-year follow-up time point.

GMTs for all pertussis antigens at 5 years remained several fold higher than pre-immunisation levels, indicating a sustained long-term immune response for all age groups.

The long-term antibody profile observed indicates that long-term protection against diphtheria, tetanus and polio clinical disease is maintained for at least 5 years following administration of ADACEL QUADRA in all age groups. The pertussis responses for all age groups were indicative of long-term persistence and suggested ongoing protection against pertussis.

Based on findings from multiple studies of ADACEL QUADRA administered to pregnant women primarily during the 2nd or 3rd trimester of gestation:

- Pertussis antibody responses in pregnant women are generally similar to those in non-pregnant women.
- Maternal antibody directed against pertussis antigens persists for 2 to 4 months after birth and may be associated with blunting of the infant immune response to active immunisation against pertussis (see section 4.4).

- The effectiveness of maternal immunisation against pertussis in the first 3 months of life has been estimated to be > 90 %.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium phosphate	1,5 mg (0,33 mg Al)
Phenoxyethanol not as preservative	3,3 mg (0,6 % *v/v*)
Polysorbate 80	≤ 0,01 % *m/v*

Water for injections.

ADACEL QUADRA contains as residues, trace amounts of formaldehyde, glutaraldehyde, streptomycin, neomycin, polymyxin B and bovine serum albumin, as well as Hanks' medium, a mixture of amino acids (including phenylalanine), salts, vitamins and other compounds (including glucose) (see sections 2 and 4.4).

6.2 Incompatibilities

ADACEL QUADRA must not be mixed with other vaccines or medicine products (see section 4.5).

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store between 2 °C and 8 °C. DO NOT FREEZE.

Discard product if it has been exposed to freezing.

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

6.5 Nature and contents of container

The vaccine is either available in a pre-filled syringe or a vial.

0,5 mL in a type 1 glass pre-filled syringe with a chlorobromobutyl plunger stopper, co-packaged with 1 separate needle,

or

0,5 mL in a type 1 glass vial with an elastomer stopper and aluminium seal with flip-off cap.

6.6 Special precautions for disposal and other handling

Inspect visually for extraneous particulate matter and/or discolouration before use. In the event of either being observed, discard the ADACEL QUADRA.

SHAKE THE PRE-FILLED SYRINGE OR VIAL WELL to uniformly distribute the suspension before administering the vaccine.

Needle should not be recapped and should be disposed of properly.

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

42/30.1/0118

MANUFACTURER

Sanofi Pasteur Limited

1755 Steeles Avenue West

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Canada

9. DATE OF FIRST AUTHORISATION

Date of registration: 14 August 2009

10. DATE OF REVISION OF THE TEXT

02 November 2020

BOTSWANA: S2

Registration number: BOT1402607

NAMIBIA: NS2

Registration number: 10/30.1 /0381