Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TRIAXIS, suspension for injection.

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

Triaxis appears as a cloudy white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

TRIAXIS is indicated for active immunization against tetanus, diphtheria and pertussis in persons from 4 years of age as a booster following primary immunization.

The use of TRIAXIS should be determined on the basis of official recommendations.

4.2 Posology and method of administration

Posology

A single injection of one (0.5 mL) dose is recommended in all indicated age groups.

TRIAXIS is a vaccine containing low-dose diphtheria-, tetanus- and pertussis-antigens indicated for booster vaccinations. When administering the vaccine, indications and dosing intervals according to the official recommendations should be considered for all antigens contained in the vaccine.

Individuals with an incomplete, or no history of a primary series of diphtheria and tetanus toxoids should not be vaccinated with TRIAXIS.

TRIAXIS is not precluded in persons with an incomplete, or no history of previous pertussis vaccination. However, a booster response will only be elicited in individuals who have been previously primed by vaccination or by natural infection.
TRIAXIS
TRIAXIS can be used for repeat vaccination to boost immunity to diphtheria, tetanus and pertussis at 5 to 10 year intervals (see section 5.1). Repeat vaccination should be performed according to official recommendations.

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

Paediatric population

Children from the age of 4 years onwards and adolescents should receive the same dosage as adults.

Method of administration

A single injection of one dose (0.5 mL) of TRIAXIS should be administered intramuscularly. The preferred site is into the deltoid muscle.

TRIAXIS
TRIAXIS 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.

4.3 Contraindications

- TRIAXIS 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.
- TRIAXIS 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, TRIAXIS 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

TRIAXIS should not be used for primary immunization.

Regarding the interval between a booster dose of TRIAXIS 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 TRIAXIS 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 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.

TRIAXIS 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 TRIAXIS by deep subcutaneous injection may be considered, although there is a risk of increased local reactions.

Other considerations

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

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, TRIAXIS 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 TRIAXIS 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

Data on a limited number of exposed pregnancies indicated no adverse effect of TRIAXIS on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

TRIAXIS should be given to a pregnant woman only if clearly needed, based on an assessment of the benefits versus the risks.

Breast-feeding

It is not known whether the active substances included in TRIAXIS are excreted in human milk but antibodies to the

vaccine antigens have been found to be transferred to the suckling offspring of rabbits. An animal developmental study conducted in rabbits has 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 TRIAXIS to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunize a nursing woman.

Fertility

TRIAXIS 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. TRIAXIS 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 TRIAXIS 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 TRIAXIS 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 TRIAXIS 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 TRIAXIS 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)
		Hypersensitivity (Anaphylactic) reaction (Angioedema, Oedema,		

Immune system disorders	Not known	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
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 TRIAXIS 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 TRIAXIS 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. Healthcare professionals are asked to report any suspected adverse reactions via the Health Products Regulatory Authority (HPRA) at HPRA Pharmacovigilance,

Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 TRIAXIS 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 TRIAXIS

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 Filamentous haemagglutinin Pertactin Fimbriae Types 2 and 3	Booster Response*	91.9 88.1 94.6 94.3	92.0 85.6 94.5 94.9	84.4 82.7 93.8 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 TRIAXIS 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 TRIAXIS had elicited protective immune responses. The pertussis antibody levels for all antigens following a booster dose of TRIAXIS 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 TRIAXIS 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
	TRIAXIS*/DTaP† GMCs Ratio (95% CIs)	**TRIAXIS†/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 TRIAXIS.
† 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 TRIAXIS.
§ GMCs following TRIAXIS were non-inferior to GMCs following DTaP (lower limit of 95% CI on the ratio of GMCs for TRIAXIS 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 TRIAXIS. 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 TRIAXIS (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 TRIAXIS

[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 TRIAXIS following repeat vaccination 10 years after a previous dose of TRIAXIS or REPEVAX (Tdap-IPV; containing the Tdap component of TRIAXIS), 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, TRIAXIS 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/foetal 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, Triaxis must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

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

6.5 Nature and contents of container

0.5 mL suspension for injection in a vial (type I glass) with a stopper (elastomer) and seal (aluminium) with a plastic flip-off cap.

Pack sizes 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 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 to uniformly distribute the suspension before administering the vaccine.

When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place.

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 Pasteur Europe
14 Espace Henry Vallée
69007 Lyon
FRANCE

8 MARKETING AUTHORISATION NUMBER

PA2131/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th May 2010
Date of last renewal: 19th January 2014

10 DATE OF REVISION OF THE TEXT

January 2018