Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

REPEVAX, 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[1] (2 Lf)
Tetanus Toxoid ..... Not less than 20 IU[1] (5 Lf)
Pertussis Antigens
Pertussis Toxoid ..... 2.5 micrograms
Filamentous Haemagglutinin ..... 5 micrograms
Pertactin ..... 3 micrograms
Fimbriae Types 2 and 3 ..... 5 micrograms
Poliovirus (Inactivated)[2]
Type 1 (Mahoney) ..... 29 D antigen units[3]
Type 2 (MEF1)..... 7 D antigen units[3]
Type 3 (Saukett)..... 26 D antigen units[3]
Adsorbed on aluminium phosphate ..... 1.5 mg (0.33 mg Al^{3+})

[1] As lower confidence limit (p = 0.95) of activity measured according to the assay described in the European Pharmacopoeia.
[2] Cultivated on Vero cells.
[3] These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method.

REPEVAX 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).

Excipient(s) with known effect
Polysorbate 80 (E 433) ≤ 5 µg in each 0.5 mL pre-filled syringe, which is equivalent to 10 µg/mL (see section 4.4)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in a pre-filled syringe.
REPEVAXappears as a uniform, cloudy, white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

REPEVAX (Tdap-IPV) is indicated for:

Active immunization against diphtheria,tetanus, pertussis and poliomyelitis in persons from 3 years of ageas a booster following primary immunization.

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

REPEVAX should be used in accordance with 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.

In adolescents and adults with an unknown or incomplete diphtheria or tetanus vaccination status against diphtheria or tetanus, one dose of REPEVAX® 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 3rd dose of a diphtheria or dT containing vaccine 6 months after the first dose to optimize protection against disease (see section 5.1). The number and schedule of doses should be determined according to local recommendations.

REPEVAX can be used for repeat vaccination to boost immunity to diphtheria, tetanus and pertussis at 5 to 10 year intervals (see section 5.1).

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

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

Method of administration

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

REPEVAX 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

- REPEVAX 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.
- REPEVAX 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 REPEVAX 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

REPEVAX should not be used for primary immunization.

Regarding the interval between a booster dose of REPEVAX 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 REPEVAX 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 REPEVAX 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 REPEVAX should be based on careful consideration of the potential benefits and possible risks.

REPEVAX 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 REPEVAX 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 REPEVAX. 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).
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 and the batch number of the administered product should be clearly recorded.

Excipients with known effects
REPEVAX 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.

Polysorbate 80 (E 433)
This medicine contains ≤ 5 µg of polysorbate 80 in each 0.5 mL pre-filled syringe, which is equivalent to 10 µg/mL.
Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

REPEVAX 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.

REPEVAX may be administered concomitantly with a dose of hepatitis B vaccine.

Based on the results of concomitant use clinical studies, REPEVAX 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 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 REPEVAX 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
REPEVAX can be used during the second or third trimester of pregnancy in accordance with official recommendations (see section 4.2).
Safety data from 4 randomized controlled trials (310 pregnancy outcomes), 1 prospective observational study (546 pregnancy outcomes), 5 retrospective observational studies (124, 810 pregnancy outcomes), and from passive surveillance of women who received REPEVAX or TRIAXIS (Tdap; containing the same amounts of tetanus, diphtheria and pertussis antigens as REPEVAX) 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 REPEVAX 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
The effect of administration of REPEVAX during lactation has not been assessed. Nevertheless, as REPEVAX contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering REPEVAX to breastfeeding women should be evaluated by the health-care providers.

Fertility
REPEVAX 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. REPEVAX 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 REPEVAX 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 REPEVAX or TRIAXIS 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 REPEVAX or TRIAXIS was similar when all three vaccines were administered concomitantly compared to coadministered pairs (TRIAXIS and Menactra or REPEVAX/TRIAXIS and Gardasil/Gardasil 9). The safety profile of coadministered REPEVAX 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 (³1/10)
Common (³1/100 to <1/10)
Uncommon (³1/1,000 to <1/100)
Rare (³1/10,000 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 REPEVAX 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	Very common	Fatigue/Asthenia, Fever†	Fatigue/Asthenia, Chills

administration site conditions			
		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

§ was observed at a frequency of very common in adolescents and adults, in studies with TRIAXIS (Tdap component of REPEVAX; 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 REPEVAX. 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 REPEVAX 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 REPEVAX 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 REPEVAX 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. Healthcare professionals are asked to report any suspected adverse reactions via the Health Products Regulatory Authority (HPRA) Pharmacovigilance Website: www.hpra.ie.

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 children 3 to 6 years of age, adolescents and adults one-month aftervaccination with REPEVAX are shown in the table below.

Table 2: Immune responses 4 weeks after vaccination with REPEVAX

Antibody	Criteria	Children 3-5 years old[1] (n = 148)	Children 5-6 years old[2] (n = 240)	Adults and Adolescents[3] (n = 994)
Diphtheria (SN, IU/mL)	[3]0.1	100%	99.4%	92.8%
Tetanus (ELISA, IU/mL or EU/mL)[4]	[3]0.1	100%	99.5%	100%
Pertussis (ELISA, EU/mL) Pertussis Toxoid	[3]5[5]	99.3%	91.2%	99.7%
Filamentous Haemagglutinin		99.3%	99.1%	99.9%
Pertactin		100%	100%	99.6%
Fimbriae Types 2 and 3		100%	99.5%	99.8%
IPV (SN, titre)				
Type 1	[3]1:8 Dilution	100%	100%	99.9%
Type 2	[3]1:8 Dilution	100%	100%	100%
Type 3	[3]1:8 Dilution	100%	100%	100%

ELISA: Enzyme Linked Immunoassay; EU: ELISA units; IPV: inactivated polio vaccine; IU: international units; n: number of participants who received REPEVAX; SN: seroneutralisation.

[1] Studies U01-Td5I-303 and U02-Td5I-402 were conducted in UK with children previously primed with DTwP and OPV at 2, 3 and 4 months of age. U01-Td5I-303 enrolled children 3.5-5 years of age. U02-Td5I-402 enrolled children 3-3.5 years of age.

[2] The Sweden 5.5 study was conducted in Swedish with children 5-6 years of age previously primed with DTaP and IPV at 3, 5, and 12 months of age.

[3] Studies TD9707 and TD9809 were conducted in Canada. TD9707 enrolled adolescents 11-17 years of age and adults 18-64 years of age. Study TD9809 enrolled adolescents 11-14 years of age.

[4] Tetanus units differed by the testing lab. Results were in IU/mL for the Sweden 5.5 study and in EU/mL for the other studies.

[5] 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 use of REPEVAX in children aged 3 to 6 years is based upon studies in which REPEVAX was given as the fourth dose (first booster) of diphtheria, tetanus, pertussis and poliomyelitis vaccines. Robust immune responses were observed following a single dose of REPEVAX in children primed with either a whole cell pertussis vaccine (DTwP) and OPV (UK studies; ages 3-5 years) or an acellular pertussis vaccine (DTaP) and IPV (Sweden study; ages 5-6 years) during infancy.

The safety and immunogenicity of REPEVAX 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 of 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's acellular pertussis infant DTaP formulation confirmed a protective efficacy of 85% against pertussis disease, it is considered that REPEVAX had elicited protective immune responses in children, adolescents, and adults in clinical trials.

Antibody persistence

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

Table 3: Persistence of Seroprotection/Seropositivity Rates (%) in Children, Adolescents and Adults at 3-, 5- and 10-years following a dose of TRIAXIS (Tdap component of REPEVAX) (PPI Population[1])

		Children (4-6 years)[2]	**Adolescents** (11-17 years)[3]			**Adults** (18-64 years)[3]		
Time since TRIAXIS dose		**5 years**	**3 years**	**5 years**	**10 years**	**3 years**	**5 years**	**10 years**
Participants		N=128-150	N=300	N=204-206	N=28-39	N=292	N=237-238	N=120-136
Antibody		**% Seroprotection/Seropositivity**						
Diphtheria (SN, IU/mL)	≥ 0.1	86.0	97.0	95.1	94.9	81.2	81.1	84.6
	≥ 0.01	100	100	100	100	95.2	93.7	99.3
Tetanus	≥ 0.1	97.3	100	100	100	99.0	97.1	100

(ELISA, IU/mL)								
Pertussis (ELISA, EU/mL)	Sero-positivity[4]							
PT		63.3	97.3	85.4	82.1	94.2	89.1	85.8
FHA		97.3	100	99.5	100	99.3	100	100
PRN		95.3	99.7	98.5	100	98.6	97.1	99.3
FIM		98.7	98.3	99.5	100	93.5	99.6	98.5

ELISA: Enzyme Linked Immunoassay; EU: ELISA units; IU: international units; N: number of participants with available data; PPI: per protocol immunogenicity; SN: seroneutralisation;

[1]Eligible participants for whom immunogenicity data were available for at least one antibody at the specified time-point.

[2] Study Td508 was conducted in Canada with children 4-6 years of age.

[3] Study Td506 was conducted in the United States with adolescents 11-17 years of age and adults 18-64 years of age.

[4] Percentage of participants with antibodies ≥ 5 EU/mL for PT, ≥ 3 EU.mL for FHA and PRN, and ≥ 17 EU/mL for FIM for the 3 year follow-up; ≥ 4 EU/mL for PT, PRN and FIM, and ≥ 3 EU/mL for FHA for the 5-year and 10-year follow-up

Follow-up studies conducted with REPEVAX provide serology data at 1, 3, 5 and 10 years in individuals previously immunized with a single booster dose of REPEVAX. Persistence of seroprotection to diphtheria and tetanus, seropositivity to pertussis and seroprotective antibody levels (≥1:8 dilution) for each poliovirus (types 1, 2 and 3) are summarized in Table 4.

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

		Children (3.5-5 years)[2]			**Adolescents** (11-17 years)[2]				**Adults** (18-64 years)[2]			
Time since REPEVAX dose		**1 year**	**3 years**	**5 years**	**1 year**	**3 years**	**5 years**	**10 years**	**1 year**	**3 years**	**5 years**	**10 years**
Participants		N=36 -37	N=36	N=38 -48	N=64	N=117	N=108	N=97 -107	N=32	N=135 -136	N=127	N=67 -79
Antibody		**% Seroprotection/Seropositivity**										
Diphtheria (SN, IU/mL)	≥ 0.1	89.2	72.2	75.0	71.9	85.2	77.1	68.5	62.5	55.6	35.2	32.9
	≥ 0.01	100	100	100	100	99.1	96.2	99.1	90.6	91.9	79.2	84.8
Tetanus (ELISA, IU/mL)	≥ 0.1	100	100	100	100	100	100	97.2	100	97.8	98.4	93.7
Pertussis (ELISA, EU/mL)	Sero-positivity[3,4]											
PT		89.2	61.1	55.3	98.4	96.6	99.1	87.6	100	97.1	97.6	91.0
FHA		100	94.4	100	100	99.1	99.1	98.1	100	100	100	100
PRN		97.3	91.7	95.7	100	99.1	100	88.8	100	99.3	98.4	93.7
FIM		100	100	95.7	98.4	98.3	98.1	100	93.8	94.1	93.7	98.7
IPV (SN, titre)	≥ 1:8											
Type 1		100	100	97.9	98.4	100	100	NA	100	100	100	NA
Type 2		100	100	100	100	100	100	NA	100	100	100	NA
Type 3		100	97.2	95.7	98.4	100	98.2	NA	100	100	100	NA

ELISA: Enzyme Linked Immunoassay; EU: ELISA units; IPV: inactivated polio vaccine; ITT: intention to treat; IU: international units; N: number of participants with available data; NA: not analysed; SN: seroneutralisation.

[1] ITT population: Study U01-Td5I-303-LT: Eligible participants for whom immunogenicity data were available for at least one antibody at the specified time point and at year 5. Study TD9707-LT: Eligible participants for whom immunogenicity data were available for at least one antibody at the specified time point.

[2] Study U01-Td5I-303-LT conducted in UK with children 3.5-5 years of age; Study TD9707-LT conducted in Canada with adolescents 11-17 years of age and adults 18-64 years of age.

[3] For U01-Td5I-303-LT: percentage of participants with antibodies ≥ 5 EU/mL for PT, ≥ 3 for FHA and ≥ 4 for PRN and for FIM for the 1-year follow-up; ≥ 4 EU/mL for PT, FIM and PRN, and ≥ 3 EU/mL for FHA for the 3-year and 5-year follow-up.

[4] For TD9707-LT: percentage of participants with antibodies ≥ 5 EU/mL for PT, ≥ 3 EU/mL for FHA and PRN, and ≥ 17 EU/mL for FIM for all time points except 10 years; ≥ 4 EU/mL for PT, FIM and PRN and ≥ 3 EU/mL for FHA for 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, 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 (Lower Limit Of Quantification) 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, REPEVAX 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 naïve subjects
After administration of one dose of REPEVAX 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 EU/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 5: Serological immune status (seroprotection/seroresponse rates and GMC/GMT) before vaccination and after each dose of a 3 dose-vaccination schedule including REPEVAX® (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 REPEVAX®**	**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		
	95%CI	[6.7; 8.9]	[273.0; 395.6]		
	≥5	-	99.4%	-	-
	95%CI		[97.8; 99.9]		
FIM	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.

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 randomized controlled trials demonstrate higher pertussis antibody concentrations at birth and at 2 months of age, (ie, prior to the start of their primary vaccinations) in infants of women vaccinated with TRIAXIS during pregnancy compared with infants of women not vaccinated against pertussis during pregnancy.

In the first study, 33 pregnant women received TRIAXIS 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 1867.0 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 (TRIAXIS/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.

In the second study, 134 pregnant women received TRIAXIS and 138 received a tetanus and diphtheria control vaccine at a mean gestational age of 34.5 weeks. The GMCs (EU/mL) for the anti-pertussis antibodies to the PT, FHA, PRN, and FIM antigens in infants of vaccinated women were, respectively, 54.2, 184.2, 294.1, and 939.6 at birth, and 14.1, 51.0, 76.8, and 220.0 at 2 months of age. In the control-group infants, the corresponding GMCs were 9.5, 21.4, 11.2, and 31.5 at birth, and 3.6, 6.1, 4.4, and 9.0 at 2 months. The GMC ratios (TRIAXIS/control group) were 5.7, 8.6, 26.3, and 29.8 at birth, and 3.9, 8.4, 17.5, and 24.4 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 REPEVAX or TRIAXIS 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 REPEVAX or TRIAXIS vaccination in pregnancy may be associated with blunting of the infant immune response to active immunization 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 REPEVAX or TRIAXIS and the infants' or toddlers' responses to diphtheria, tetanus, *Haemophilusinfluenzae* 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 6: Vaccine effectiveness (VE) against pertussis disease in young infants born to mothers vaccinated during pregnancy with REPEVAX or TRIAXIS in 3 retrospective studies.

Location	Vaccine	VE (95% CI)	VE estimation method	Infant follow-up period
UK	REPEVAX	93% (81, 97)	unmatched case-control	2 months
US	TRIAXIS*	91.4% (19.5, 99.1)	cohort regression model	2 months
UK	REPEVAX	93% (89, 95)	screening (case-coverage)	3 months
* Approximately 99% of women were vaccinated with TRIAXIS				

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

Phenoxyethanol
Ethanol
Polysorbate 80
Water for injections
For adjuvant see section 2

6.2 Incompatibilities

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

6.3 Shelf life

4 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.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period, REPEVAX should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

0.5 mL of suspension in pre-filled syringe (glass) with a plunger stopper (chlorobutyl elastomer), with a tip-cap (synthetic isoprene-bromobutyl elastomer).

Pack size of 1, 10 or 20 pre-filled syringe(s) without needle(s)
Pack size of 1 or 10 pre-filled syringe(s) with 1 or 2 separate needle(s).

0.5 mL of suspension in pre-filled syringe (glass) with a plunger stopper (chlorobutyl elastomer), and a Luer Lock adaptor with a tip-cap (synthetic isoprene-bromobutyl + polypropylene elastomer).

Pack of 1 or 10 pre-filled syringe(s) without needle(s).
Pack of 1 or 10 pre-filled syringe(s) with separate needle(s) (stainless steel).
Pack of 1 or 10 pre-filled syringe(s) with separate needle(s) (stainless steel) and safety shield (polycarbonate).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

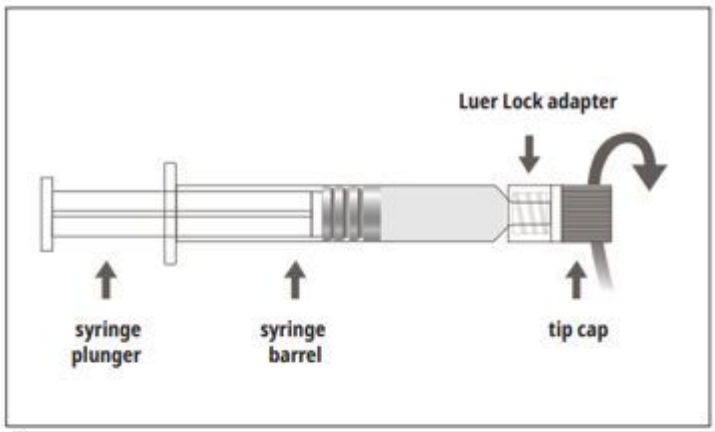
Instructions for use
Parenteral products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration. In the event of either being observed, discard the medicinal product.

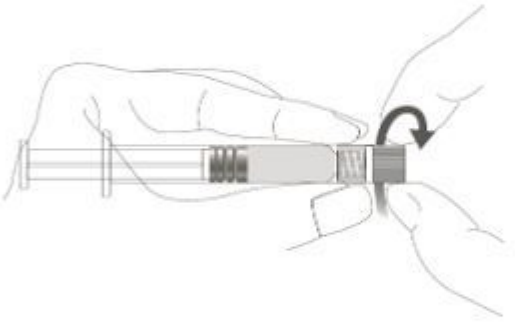
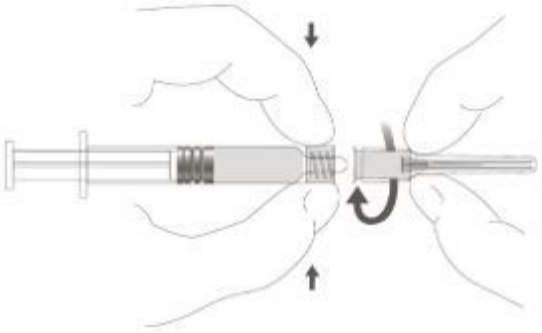
The normal appearance of the vaccine is a uniform cloudy, white suspension which may sediment during storage. Shake the prefilled syringe well to uniformly distribute the suspension before administering the vaccine. If aggregates are present, the product can be shaken again until a uniform suspension is obtained.

For needle free syringes, the needle should be pushed firmly on to the end of the prefilled syringe and rotated through 90 degrees.

Preparation for administration
The pre-filled syringe can be supplied with a Luer Lock with Rigid Tip Cap (Picture A). The syringe with suspension for injection should be visually inspected prior to administration. In the event of any foreign particulate matter, leakage, premature activation of the plunger or faulty tip seal, discard the pre-filled syringe. The syringe is intended for single use only and must not be reused.

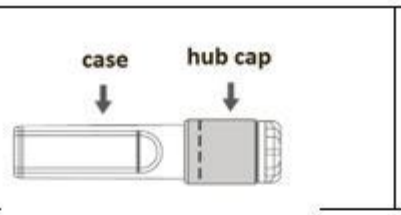
Instructions for use of Luer Lock pre-filled syringe:
Picture A: Luer Lock Syringe with Rigid Tip Cap

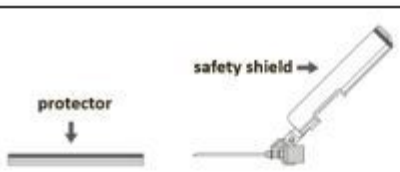


Step 1: Holding the Luer Lock adapter in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it.	
Step 2: To attach the needle to the syringe, gently twist the needle into the Luer Lock adapter of the syringe until slight resistance is felt.	

<Instructions for use of Safety Needle with Luer Lock pre-filled syringe:
Follow Step 1 and 2 above to prepare the Luer Lock syringe and needle for attachment.

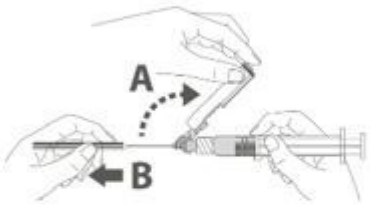
Picture B: Safety Needle (inside case)	**Picture C: Safety Needle Components (prepared for use)**





Step 3: Pull the safety needle's case straight off. The needle is covered by the safety shield and protector.

Step 4:
A: Move the safety shield away from the needle and toward the syringe barrel to the angle shown.
B: Pull the protector straight off.

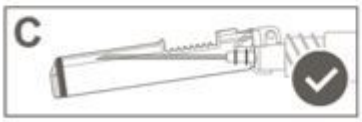


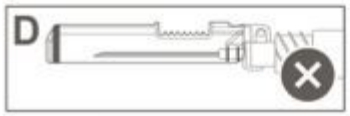
Step 5: After injection is complete, lock (activate) the safety shield using one of the three (3) **one-handed** techniques illustrated: surface, thumb or finger activation.
Note: Activation is verified by an audible and/or tactile "click."



Step 6: Visually inspect the safety shield activation. The safety shield should be **fully locked (activated)** as shown in Figure C.

Figure D shows the safety shield is **NOT fully locked (not activated).**





Caution: Do not attempt to unlock (deactivate) the safety device by forcing the needle out of the safety shield.

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 Winthrop Industrie
82 Avenue Raspail
Gentilly
94250
France

8 MARKETING AUTHORISATION NUMBER

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