Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tetravac, suspension for injection in prefilled syringe Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine, (adsorbed).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:
Diphtheria Toxoid1 not less than 20 IU 2,3 (30 Lf)
Tetanus Toxoid1 not less than 40 IU 3,4 (10 Lf)
Bordetella pertussis antigens
Pertussis Toxoid 1 25 micrograms
Filamentous Haemagglutinin1 25 micrograms
Poliovirus (Inactivated)[5]
Type 1 (Mahoney) 29 D-antigen units[6]
Type 2 (MEF-1) 7 D-antigen units[6]
Type 3 (Saukett) 26 D-antigen units[6]

1 Adsorbed on aluminium hydroxide, hydrated (0.3 mg Al3+)
2 As lower confidence limit (p= 0.95) and not less than 30 IU as mean value
3 Or equivalent activity determined by immunogenicity evaluation
4 As lower confidence limit (p = 0.95)
5 Cultivated on Vero cells
6 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.

The vaccine may contain traces of glutaraldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process (see section 4.4).

Excipients with known effect
Phenylalanine.....12.5 micrograms
(See section 4.4)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in prefilled syringe
Tetravac is a whitish turbid suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tetravac is indicated for primary and booster vaccination of infants and children from 2 months of age against diphtheria, tetanus, pertussis and poliomyelitis.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Tetravac (DTaP-IPV) is a full antigen(s) content formulation.

Posology

Primary vaccination and first booster:

The primary vaccination consists of 2 doses (with an interval of at least 2 months) or 3 doses (with an interval of at least 1 month) followed by a booster dose from the age of 12 months, in accordance with the official recommendations.

Additional booster vaccination:
For individuals of 4 through 13 years of age, one single dose should be given for booster vaccination, in accordance with the official recommendations.

Method of administration

Tetravac must be administered intramuscularly.
Administration should preferably be performed in the antero-lateral side of the upper thigh in infants and in the deltoid area in older children.

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

Known systemic hypersensitivity reaction to any component of Tetravac listed in section 6.1 or a vaccine containing the same substances or to pertussis vaccines (acellular or whole cell pertussis).

- Evolving encephalopathy.
- Encephalopathy within 7 days of administration of a previous dose of any vaccine containing pertussis antigens (whole cell or acellular pertussis vaccines).

4.4 Special warnings and precautions for use

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.

Special warnings prior to immunization

- As each dose may contain undetectable traces of glutaraldehyde, neomycin, streptomycin and polymyxin B, caution should be exercised when the vaccine is administered to subjects with hypersensitivity to these substances.
- Vaccination must be postponed in case of febrile or acute disease.
- If Guillain-Barré Syndrome or brachial neuritis has occurred in subjects 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 of vaccination. Vaccination is usually justified for infants whose primary immunisation schedules are incomplete (i.e., fewer than three doses administered).
- The immunogenicity of Tetravac may be reduced by immunosuppressive treatment or immunodeficiency. It is then recommended to wait until the end of the treatment or disease before vaccinating. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the immune response may be limited.
- Vaccination must be preceded by medical history screening (especially with regard to vaccination history and any occurrence of undesirable events) and a clinical examination.
- If any of the following events are known to have occurred in temporal relation to receipt of vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered:
- Fever ≥ 40°C within 48 hours not due to another identifiable cause,
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination,
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination,
- Convulsions with or without fever, occurring within 3 days of vaccination.
- A history of febrile convulsions not related to a previous vaccine injection is not a contraindication to vaccination.

In this respect, it is particularly important to monitor temperature in the 48 hours following vaccination and to give antipyretic treatment regularly for 48 hours.
A history of a febrile convulsions not related to a previous vaccine injection should be assessed by a specialist before deciding to vaccinate.

In the event of oedematous reactions occurring in the lower limbs after injection of a *Haemophilus influenzae* type b-containing vaccine, the two vaccines, diphtheria-tetanus-pertussis-poliomyelitis vaccine and the *Haemophilus influenzae* type b conjugate vaccine should be administered in two separate injection sites and on two different days.

Special population

- The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Precautions for use

- Do not inject by the intravascular route. Do not inject by the intradermal route.
- As with all injectable vaccines, Tetravac must be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.
- Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

- As with all injectable vaccines, appropriate medical treatment should always be readily available and close supervision in case of a rare anaphylactic reactions following administration of the vaccine.

Tetravac contains phenylalanine, ethanol and sodium
Tetravac contains 12.5 micrograms phenylalanine in each 0.5 mL dose. Phenylalanine may be harmful for individuals with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
Tetravac contains 2 mg of alcohol (ethanol) in each 0.5 mL dose. The small amount of alcohol in this medicine will not have any noticeable effects.
Tetravac contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

This vaccine may be administered concomitantly or in combination with the *Haemophilus influenzae* type b conjugate vaccine (Act-HIB), see section 4.8.

This vaccine may be administered concomitantly with measles-mumps-rubella (MMR), varicella-containing vaccines or HepB vaccine, at separate injection sites.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Summary of the safety profile
In three clinical studies, over 2800 infants were vaccinated with Tetravac, administered simultaneously with Act-Hib at one or two injection sites.
Over 8400 doses were administered as a primary series and the most frequently reported reactions included: irritability (20.2%), local reactions at the injection site such as redness >2 cm (9%) and induration >2 cm (12%).
These signs and symptoms usually occur within 48 hours following the vaccination and may continue for 48-72 hours. They resolve spontaneously without requiring specific treatment.
After the primary series, the frequencies of injection site reactions tend to increase with the booster dose.

Tetravac safety profile does not differ significantly between the different age groups however some adverse events such as myalgia, malaise and headache are specific to children ≥ 2 years of age.

Tabulated list of adverse reactions

The adverse events are ranked under headings of frequency using the following convention:

- Very common: ≥1/10
- Common: ≥1/100 and <1/10
- Uncommon: ≥ 1/1,000 and <1/100
- Rare: ≥1/10,000 and <1/1,000
- Very rare: <1/10,000
- Not known: frequency cannot be estimated from the available data.

Table 1: Adverse Reactions from clinical trials and post marketing surveillance.

System Organ Class	Frequency	Adverse Events
Blood and lymphatic system disorders	Not known	Lymphadenopathy
Immune system disorders	Not known	Anaphylactic reactions such as face oedema, Quincke's oedema
Metabolism and nutrition disorders	Very common	Appetite loss (feeding disturbances)
Psychiatric disorders	Very common	Nervousness (irritability) Abnormal crying
	Common	Insomnia (sleep disturbances)
	Uncommon	Prolonged inconsolable crying
Nervous system disorders	Very common	Somnolence (drowsiness) Headache
	Not known	Convulsions with or without fever Syncope
Gastro-intestinal disorders	Very common	Vomiting
	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Not known	Allergy-like symptoms, such as various types of rash, erythema and urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
General disorders and administration site conditions	Very common	Redness at the injection site Pain at the injection site Injection site swelling Pyrexia (fever) ≥ 38°C Malaise
	Common	Induration at the injection site
	Uncommon	Redness and swelling ≥ 5 cm at the injection site Pyrexia (fever) ≥ 39°C
	Rare	Pyrexia (fever) > 40°C
	Not known	Large injection site reactions (> 50 mm), including extensive limb swelling from the injection site beyond one or both joints. *

*These reactions start within 24-72 hours after vaccination and may be associated with symptoms such as erythema, warmth, tenderness or pain at the injection site. They resolve spontaneously within 3-5 days.
The risk appears to be dependent on the number of prior doses of acellular pertussis-containing vaccines, with a greater risk following the 4th and 5th doses.

Oedematous reaction affecting one or both lower limbs may occur following vaccination with *Haemophilus influenzae* type b containing vaccines. If this reaction occurs, it does so after primary injections and is observed within the first few hours

following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolve spontaneously without sequelae within 24 hours.
This reaction may occur when Tetravac and *Haemophilus influenzae* type b conjugate vaccine are administered concomitantly (see section 4.5).

When Tetravac is indicated for administration to children aged from 4 to 13 years as a late booster, reactions to Tetravac in children in this age group are less or equally frequently reported than after administration of DTP-IPV (whole-cell pertussis) or DT-IPV, respectively, at the same age.

Potential adverse events
(i.e., they have not been reported directly with Tetravac, but with other vaccines containing one or more of the antigenic constituents of Tetravac):

- Guillain-Barré Syndrome and brachial neuritis have been reported after administration of a tetanus toxoid-containing vaccine.
- Apnoea in very premature infants (born ≤ 28 weeks of gestation) (see section 4.4).
- Hypotonic-hyporesponsive episodes.

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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combined bacterial and viral vaccines (diphtheria-pertussis- poliomyelitis-tetanus),
ATC code: J07C A02

Mechanism of action:
Protection after vaccination is provided by the induction of neutralising antibodies against diphtheria-tetanus-pertussis-poliomyelitis vaccine.

For diphtheria, tetanus and polio, there are established correlate of protection which were evaluated in the clinical studies *(See below)*. The mechanism of protection from pertussis disease is not well understood. However, the efficacy of the acellular pertussis antigens contained in Tetravac was demonstrated in a study in Senegal *(See Efficacy and effectiveness in protecting against pertussis)*.

Immune response after primary vaccination:
Immunogenicity studies have shown that all infants (100%) vaccinated with three doses of vaccine from 2 months of age developed a seroprotective antibody titre (> 0.01 IU/mL) to both diphtheria and tetanus antigens.

For pertussis, more than 87% of infants achieved a four-fold rise in PT and FHA antibody titres one to two months after completion of a three-dose primary vaccination.

Following primary vaccination, at least 99.5% of children had seroprotective antibody titres to poliomyelitis virus types 1, 2 and 3 (≥ 5 as expressed by reciprocal of dilution in seroneutralisation) and were considered protected against poliomyelitis.

Immune response after booster injection:
After the first booster dose (16-18 months), all the toddlers developed protective antibodies against diphtheria (> 0.1 IU/mL), tetanus (> 0.1 IU/mL) and 87.5% against poliomyelitis viruses (≥ 5 as expressed by reciprocal of dilution in seroneutralisation). The seroconversion rate in pertussis antibodies (titres higher than four-fold the pre-vaccinal titres) is 92.6% for PT and 89.7% for FHA.

Immune responses after booster injection in individuals aged 4 through 13 years:
In clinical studies with Tetravac in individuals 4 through 13 years of age, the booster responses against diphtheria, tetanus, poliovirus types 1, 2, 3 and pertussis antigens were high and above seroprotective levels for diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL) and poliovirus types 1, 2, 3 (≥8 as expressed by reciprocal of dilution in seroneutralisation).
In a study performed in individuals aged 11 through 13 years of age, anamnestic responses to tetanus, diphtheria and poliovirus components were demonstrated.

Efficacy and effectiveness in protecting against pertussis:
Vaccine efficacy of acellular pertussis (aP) antigens contained in Tetravac against the most severe WHO-defined typical pertussis (≥21 days of paroxysmal cough) is documented in a randomized double-blind study among infants with a 3 dose primary series in a highly endemic country (Senegal).
The long-term capability of the aP antigens contained in Tetravac to reduce pertussis incidence and control pertussis disease has been demonstrated in a 10- year national pertussis surveillance in Sweden with the Pentaxim/Pentavac vaccine.

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Formaldehyde
- Acetic acid glacial and/or sodium hydroxide for pH adjustment
- Phenoxyethanol
- Ethanol anhydrous
- Medium 199 Hanks without phenol red [complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other substances (such as glucose)]
- Water for injections.

For adsorbent: see section 2.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except the *Haemophilus influenzae* type b conjugate vaccine [Act-HIB] see section 6.6.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

0.5 mL single dose prefilled syringe (type 1 glass) with plunger-stopper (bromobutyl or chlorobutyl), attached needle and needle shield (elastomer).

0.5 mL single dose prefilled syringe (type 1 glass) with plunger-stopper (bromobutyl or chlorobutyl) and tip cap (elastomer), without needle.

0.5 mL single dose prefilled syringe (type 1 glass) with plunger-stopper (bromobutyl or chlorobutyl) and tip cap (elastomer), with 1 separate needle (for each syringe).

0.5 mL single dose prefilled syringe (type 1 glass) with plunger-stopper (bromobutyl or chlorobutyl) and tip cap (elastomer), with 2 separate needles (for each syringe).

Packs of 1 or 10.

Not all pack sizes and presentations may be marketed.

6.6 Special precautions for disposal and other handling

For syringes without attached needles, the separate needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.

Shake before injection until a homogeneous whitish-turbid suspension is obtained.

The suspension should be visually inspected prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the prefilled syringe.

Tetravac may be administered by reconstituting the Act-HIB (*Haemophilus influenzae* type b conjugate) vaccine as follows:

Shake the prefilled syringe until the contents become homogeneous and reconstitute the solution by injecting the suspension of the combined diphtheria, tetanus, acellular pertussis and poliomyelitis vaccine into the vial with the powder of the *Haemophilus* type b conjugate vaccine.

- Gently shake the vial until complete dissolution of the powder. After reconstitution, the whitish-turbid appearance of the suspension is normal.
- Withdraw immediately the reconstituted suspension into the syringe.
- The whitish cloudy suspension must be used immediately after reconstitution and shaken before injection.
- After reconstitution and withdrawing into the syringe, the separation of the suspension into a transparent phase and gel-like phase can appear.

In that case, the syringe should be again vigorously shaken before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
Gentilly
94250
France

8 MARKETING AUTHORISATION NUMBER

PA23458/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2001

Date of last renewal: 13 July 2012

10 DATE OF REVISION OF THE TEXT

January 2025