Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose of vaccine contains:

Purified diphtheria toxoid[1] not less than 30 I.U.[2 3]
Purified tetanus toxoid[1] not less than 40 I.U. [3 4]
Purified pertussis toxoid (PTxd) [1] 25 microgram
Purified filamentous haemagglutinin (FHA) [1] 25 microgram
Inactivated type 1 poliovirus[2] D antigen[6]: 40 units
Inactivated type 2 poliovirus[2] D antigen[6]: 8 units
Inactivated type 3 poliovirus[2] D antigen[6]: 32 units

[1] Adsorbed on aluminium hydroxide, hydrated (0.3 mg Al3+)
[2] As mean value
[3] Or equivalent activity determined by immunogenicity evaluation
[4] As lower confidence limit (p = 0.95)
[5] Produced on Vero cells
[6] Or equivalent antigenic quantity determined by a suitable immunochemical method

The vaccine may contain traces of glutaraldehyde, neomycin, streptomycin and polymyxin B (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.
Tetravac is a sterile and whitish turbid suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Active immunisation against diphtheria, tetanus, pertussis and poliomyelitis
- for primary vaccination in infants,
- for booster in children who have previously received a primary vaccination with a diphtheria-tetanus-whole-cell or acellular pertussis-poliomyelitis vaccine.

4.2 Posology and method of administration

Tetravac (DTaP-IPV) is a full dose formulation.

Posology

Primary vaccination:
Primary immunisation can be given as 3 doses at an interval of 1-2 months starting at the age of
2 or 3 months or as 2 doses at an interval of 2 months starting at the age of 3 months and a third dose at the age of 12 months [according to national vaccination policies].

Booster:
A fourth dose should be administered within the second year of life to children who received Tetravac (or a diphtheria-tetanus-whole-cell or acellular pertussis-poliomyelitis vaccine, whether mixed or not with the freeze-dried conjugate *Haemophilus influenzae*type b vaccine) as a three-dose primary series between the ages of 2-6 months.

Tetravac can also be administered to children aged 4 through 13 years who were previously immunised with an acellular vaccine or four doses of whole-cell vaccine.
Booster doses in 4 through 13 years old individuals should be given in accordance with national vaccination policies.

Tetravac is a high dose diphtheria vaccine. The use of a low dose diphtheria may be recommended at an earlier age than 13 years in some countries depending on national policies.

Method of administration

Tetravac must be administered intramuscularly. The recommended injection sites are the antero-lateral aspect of the upper thigh in infants and the deltoid muscle in older children.

The intradermal or intravenous routes must not be used. Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

4.3 Contraindications

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

As with other vaccines, the vaccination with Tetravac should be postponed in case of :
- fever or an acute illness.
- 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

Special warnings

- 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.

- The immunogenicity of the vaccine may be reduced by immunosuppressive treatment or immunodeficiency. It is recommended to postpone vaccination until the end of such treatment or disease. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.

- 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, such as whether or not the primary immunisation schedule has been completed. Vaccination is usually justified for infants whose primary immunisation schedules are incomplete (i.e., fewer than three doses have been received).

- The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administration 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 never be withheld of delayed.

- Tetravac contains phenylalanine which may be harmful to people with phenylketonuria (PKU).

- Tetravac contains small amounts of ethanol (alcohol), less than 100 mg per dose.

Precautions for use

- Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

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

- Prior to administration of any dose of Tetravac, the parent or guardian of the recipient must be asked about the personal history of the recipient, family history and recent health status, including immunisation history, current health status and any adverse event after previous immunisations.

- If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered:

    - Temperature of ≥40.0°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.

- Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

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 sodium per dose, that is to say essentially "sodium-free".

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.

4.5 Interaction with other medicinal products and other forms of interactions

Except in the case of an immunosuppressive therapy (see section 4.4) no significant clinical interaction with other treatments or biological products has been reported. A specific interaction study has been done on co-administration of Tetravac, used to reconstitute freeze-dried Act-HIB vaccine (Haemophilus influenzae type b), and MMR.

4.6 Fertility, pregnancy and lactation

Not applicable. This vaccine is intended only for paediatric use.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

- Very common: ≥1/10
- Common: ≥1/100 and <1/10
- Uncommon: ≥ 1/1000 and <1/100

- Rare: ≥1/10 000 and <1/1000
- Very rare: <1/10 000
- Not known: cannot be estimated from the available data. Based on spontaneous reporting, these adverse events have been very rarely reported following commercial use of Tetravac. Because 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.

In clinical studies infants who received Tetravac administered alone or simultaneously with Act-HIB® as a primary series the most frequently reported reactions include local reactions at the injection site, abnormal crying, anorexia, and irritability.
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.

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:*

- Anorexia (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

Musculoskeletal and connective tissue disorders

- *Very common:*

- Myalgia

Skin and subcutaneous tissue disorders

- *Not known*:

- Allergy-like symptoms, such as various types of rash, erythema and urticaria

General disorders and administration site conditions

- *Very common:*

- Redness at the injection site
- Pain at the site injection
- 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 > 40°C (high fever)

- *Not known*:

- Large injection site reactions (> 50 mm), including extensive limb swelling from the injection site beyond one or both joints have been reported in children. These reactions 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. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine, with a greater risk following the 4th and 5th doses.
Hypotonic hyporesponsive episodes have not been reported following the use of Tetravac during clinical studies but have been reported for other pertussis vaccines.
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 mainly 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.
One such case has been reported during clinical trials performed with diphtheria-tetanus-acellular pertussis-poliomyelitis vaccine Tetravac administered simultaneously with the conjugate *Haemophilus influenzae* type b vaccine in two separate injection sites.
When Tetravac is indicated for administration to children aged from 5 to 12 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.
There have been very rare reports of brachial neuritis and Guillain-Barré Syndrome after administration of other tetanus toxoid containing vaccines.

Additional information on special populations:
Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4).

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

Immuneresponseafter primary vaccination:

Immunogenicity studies in infants given three doses of Tetravac starting at 2 months of age have shown that all (100%) developed a seroprotective antibody level (≥ 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 the primary vaccination.

At least 99.5% of children had post-immunisation titres above the threshold of 5 (reciprocal of dilution in seroneutralisation) against poliovirus types 1, 2 and 3, and were considered protected against poliomyelitis.

In the Senegal efficacy trial following a 3 dose primary regimen and after 18 months without booster, the protective efficacy of this acellular pertussis vaccine was found to be lower than the Pasteur Mérieux whole cell pertussis control vaccine. However, lower reactogenicity was demonstrated for this acellular pertussis vaccine in 2 controlled clinical studies when compared to this same whole cell pertussis vaccine.

Immuneresponseafter booster injection:
Immunogenicity studies in toddlers in the second year of life who had received a 3-dose primary vaccination series with Tetravac have shown high antibody responses to all components following a fourth dose (booster).

Studies in children 12 to 24 months of age who were given a 3-dose primary immunisation course with whole-cell pertussis vaccines, DTP-IPV (Tetracoq) or DTP-IPV-ACT-HIB (Pentact-HIB/PENTACOQ), have shown that a booster dose with Tetravac is safe and immunogenic for all components of the vaccine.

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

None stated.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Formaldehyde
- 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)]
- Acetic acid glacial and/or sodium hydroxide (for pH adjustment)
- Water for injections.

For adsorbent: see section 2.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *section 6.6*.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

0.5 ml single dose prefilled syringe (glass) with plunger (chlorobromobutyl elastomer or bromobutyl rubber or chlorobutyl rubber), attached needle and needle shield (elastomer).

0.5 ml single dose prefilled syringe (glass) with plunger (chlorobromobutyl elastomer or bromobutyl rubber or chlorobutyl rubber) and tip cap (elastomer), without needle.

0.5 ml single dose prefilled syringe (glass) with plunger (chlorobromobutyl elastomer or bromobutyl rubber or chlorobutyl rubber) and tip cap (elastomer), with 1 separate needle (for each syringe).

0.5 ml single dose prefilled syringe (glass) with plunger (chlorobromobutyl elastomer or bromobutyl rubber or chlorobutyl rubber) 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 needle free syringes, the needle should be pushed firmly to the end of the prefilled syringe and rotated through 90 degrees.

Shake before using to obtain a homogeneous white turbid suspension.

Tetravac can be used to dissolve the freeze-dried conjugate *Haemophilus influenzae* type b vaccine (Act-HIB). Shake the pre-filled syringe so that the contents become homogeneous. Add the suspension to the vial and shake carefully until the freeze-dried substance is completely dissolved. The suspension must be white turbid after reconstitution.

The vaccine must be injected immediately after reconstitution.

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

7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur Europe
14 Espace Henry Vallée
69007
Lyon
France

8 MARKETING AUTHORISATION NUMBER

PA2131/009/001

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

August 2021