

1 NAME OF THE MEDICINAL PRODUCT

TETRAXIM, 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 toxoid ⁽¹⁾ ≥ 30 IU^{(2) (3)}

Tetanus toxoid ⁽¹⁾ ≥ 40 IU^{(3) (4)}

Bordetella pertussis antigens:

Pertussis toxoid ⁽¹⁾ 25 micrograms

Filamentous haemagglutinin ⁽¹⁾ 25 micrograms

Poliomyelitis virus (inactivated)

- type 1 (Mahoney strain)⁽⁵⁾ 40 DU ^{(6) (7)}

- type 2 (MEF-1 strain)⁽⁵⁾ 8 DU ^{(6) (7)}

- type 3 (Saukett strain)⁽⁵⁾ 32 DU ^{(6) (7)}

⁽¹⁾ Adsorbed on aluminium hydroxide, hydrated 0.3 mg Al³⁺

⁽²⁾ As mean value

⁽³⁾ Or equivalent activity determined by evaluation of immunogenicity

⁽⁴⁾ As lower confidence limit (p = 0.95)

⁽⁵⁾ Produced on VERO cells

⁽⁶⁾ DU: D-antigen unit

⁽⁷⁾ Or equivalent antigenic quantity determined by a suitable immunochemical method.

TETRAXIM may contain traces of glutaraldehyde, neomycin, streptomycin and polymyxin B (see section 4.3).

Excipient 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.

Whitish-turbid suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This vaccine is indicated in the joint prevention of diphtheria, tetanus, pertussis and poliomyelitis according to official recommendations:

- for primary vaccination in infants from the age of 2 months,
- for booster vaccination

4.2 Posology and method of administration

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

Posology

Primary vaccination: Primary immunization can be given as 3 doses at an interval of 1-2 months starting at the age of 2 or 3 months i.e., according to the official schedule, at the age of 2, 3, 4 months or 3, 4, 5 months or 2, 4, 6 months.

Booster vaccination: 1 injection in the second year of life, i.e., usually, between 16 and 18 months.

Tetraxim can also be administered to children aged 4 through 13 years who were previously immunized with an acellular vaccine or a whole-cell pertussis vaccine. Tetraxim is a high dose diphtheria vaccine. A low dose diphtheria vaccine is usually recommended at this age as per official recommendation.

Booster doses in 4 through 13 years old individuals should be given in accordance with official recommendation.

For primary vaccination and for the first booster dose, this vaccine may be administered by reconstituting the *Haemophilus influenzae* type b conjugate vaccine (Act-HIB) or administered at the same time as this vaccine, but at two separate injection sites.

Method of administration

Administer via the intramuscular route.

Administration should preferably be performed in the antero-lateral side of the thigh (middle third) in infants and in the deltoid area in children aged between 4 through 13 years.

4.3 Contraindications

- Hypersensitivity:
 - to any of the active substances of TETRAXIM,
 - to any of the excipients listed in section 6.1,
 - to glutaraldehyde, neomycin, streptomycin, or polymyxin B (used during the manufacturing process and which may be present in trace amounts)
 - to a pertussis vaccine (acellular or whole cell).

- Life-threatening reaction after previous administration of the same vaccine or a vaccine containing the same substances.
- Vaccination must be postponed in case of febrile or acute disease.
- 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

The immunogenicity of TETRAXIM 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.

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).

Do not inject via the intravascular route: make sure the needle does not penetrate a blood vessel.

Do not inject via the intradermal route.

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

Vaccination must be preceded by medical history screening (especially with regard to vaccination history and any occurrence of undesirable events) and a clinical examination.

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.

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 $\geq 40^{\circ}\text{C}$ 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 afebrile 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.

As with all injectable vaccines, appropriate medical treatment must be readily available and close supervision provided should a rare anaphylactic reaction occur following administration of the vaccine.

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.

TETRAXIM contains phenylalanine, ethanol and sodium

TETRAXIM contains 12.5 micrograms of phenylalanine in each 0.5 mL dose. Phenylalanine may be harmful for people who have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

TETRAXIM 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.

TETRAXIM contains less than 1 mmol sodium (23 mg) 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 interaction

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

This vaccine can be associated or combined with the *Haemophilus influenzae* type b conjugate vaccine (Act-HIB).

Except in the case of immunosuppressive therapy (see section 4.4), no significant clinical interaction with other treatments or biological products has been documented.

4.6 Fertility, pregnancy and lactation

TETRAXIM is intended for paediatric use only.

4.7 Effects on ability to drive and use machines

TETRAXIM is intended for paediatric use only.

4.8 Undesirable effects

Paediatric population

a) Summary of the safety profile

In clinical studies in children who received TETRAXIM as a primary series, stand alone or combined with the Act-HIB vaccine, the most frequently reported reactions are local injection-site reactions, abnormal crying, loss of appetite 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.

The frequency of injection-site reactions tends to increase at booster vaccination compared with the frequency observed for primary series.

The safety profile of TETRAXIM does not differ significantly according to age groups. However, certain reactions (myalgia, malaise, headache) are specific to children aged 2 years or more.

b) Tabulated list of adverse reactions

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

Very common: $\geq 1/10$

Common: $\geq 1/100$ and $< 1/10$

Uncommon: $\geq 1/1\ 000$ and $< 1/100$

Rare: $\geq 1/10\ 000$ and $< 1/1\ 000$

Very rare: $< 1/10\ 000$

Not known: cannot be estimated from the available data.

Based on spontaneous reporting, certain undesirable events were very rarely reported following the use of TETRAXIM. 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. This is why these undesirable events are ranked under the “ Not known “ frequency.

Blood and lymphatic system disorders

Reactions for which the frequency is not known

- Lymphadenopathy.

Immune system disorders

Reactions for which the frequency is not known

- Immediate hypersensitivity reactions, such as face oedema, angioedema, Quincke's oedema, anaphylactic reactions.

Metabolism and nutrition disorders

Very common reactions

- Loss of appetite.

Psychiatric disorders

Very common reactions

- Nervousness, irritability.
- Abnormal crying.

Common reactions

- Insomnia, sleep disturbances.

Uncommon reactions

- Prolonged, inconsolable crying.

Nervous system disorders

Very common reactions

- Somnolence.
- Headache.

Reactions for which the frequency is not known

- Convulsions with or without fever.
- Syncope.

Gastrointestinal disorders

Very common reactions

- Vomiting.

Common reactions

- Diarrhoea.

Skin and subcutaneous tissue disorders

Reactions for which the frequency is not known

- Rash, erythema, urticaria.

Musculoskeletal and connective tissue disorders

Very common reactions

- Myalgia.

General disorders and administration site conditions

Very common reactions

- Injection-site erythema.
- Injection-site pain.
- Injection-site oedema.
- Fever $\geq 38^{\circ}\text{C}$.
- Malaise.

Common reactions

- Injection-site induration.

Uncommon reactions

- Injection-site redness and oedema ≥ 5 cm.
- Fever $\geq 39^{\circ}\text{C}$.

Rare reactions

- Fever $> 40^{\circ}\text{C}$.

Reactions for which the frequency is 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.
- Hypotonic-hyporesponsive episodes have been reported after administration of pertussis-containing vaccines.
- Oedematous reactions on one or on both lower limbs may occur after vaccination with a *Haemophilus influenzae* type b conjugate-containing vaccine. These reactions generally occur after primary series, within hours of the vaccination, and resolve without sequelae within 24 hours. These reactions may be accompanied with cyanosis, erythema, transient purpura and severe crying. These reactions may be observed if TETRAXIM is administered simultaneously with the *Haemophilus influenzae* type b conjugate vaccine.

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

- Guillain-Barré Syndrome and brachial neuritis after administration of a tetanus toxoid-containing vaccine.

Additional information concerning specific populations

Apnoea in very premature infants (born ≤ 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.

4.9 Overdose

Not documented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bacterial and viral vaccines, combined, ATC code: J07CA02.

Diphtheria and tetanus toxins are detoxified using formaldehyde and then purified.

The poliomyelitis vaccine is obtained from the propagation of poliomyelitis virus types 1, 2 and 3 on Vero cells, purified, then inactivated using formaldehyde.

The acellular pertussis components (PT and FHA) are extracted from *Bordetella pertussis* cultures, then purified.

The pertussis toxin (PT) is detoxified by glutaraldehyde and corresponds to the pertussis toxoid (PTxd). The FHA is native.

It has been shown that PTxd and FHA are two components of major importance for protection against pertussis.

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.

As for pertussis, one to two months after the third dose of the primary vaccination, more than 87% of infants achieved a four-fold increase in PT and FHA antibody titres.

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 as protected against poliomyelitis.

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 people aged 4 to 13 years:

In clinical studies with TETRAXIM in people aged 4 to 13 years, booster responses against diphtheria, tetanus, poliomyelitis virus types 1, 2 and 3, and pertussis antigens were elevated and greater than seroprotective levels against diphtheria (≥ 0.1 IU/mL), tetanus (≥ 0.1 IU/mL) and poliomyelitis virus types 1, 2 and 3 (≥ 8 as expressed by reciprocal of dilution in seroneutralisation).

In a study in people aged 11 to 13 years, anamnestic responses to the components tetanus, diphtheria and poliomyelitis virus were demonstrated.

Vaccine efficacy and field efficacy against pertussis:

The vaccine efficacy of the acellular pertussis (Pa) antigens contained in TETRAXIM against the most severe form of characteristic pertussis as defined by the WHO (≥ 21 days of paroxysmal cough), is documented in a randomised, double-blind study conducted in infants who received a three-dose primary vaccination in a highly endemic country (Senegal).

The ability of the acellular pertussis (Pa) antigens in TETRAXIM to decrease the incidence of pertussis in the long term and to control the disease has been demonstrated in a 10-year national pertussis surveillance study with the PENTAXIM vaccine in Sweden.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional acute toxicity, repeat dose toxicity and local tolerance studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hanks' medium 199 (without phenol red)
- Glacial acetic acid and/or sodium hydroxide (for pH adjustment)
- Formaldehyde
- Phenoxyethanol
- Anhydrous ethanol
- Water for injections

Hanks' medium 199 is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other components (such as glucose) diluted in water for injections.

Concerning the adsorbent, see section 2.

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products, except those listed in section 6.6.

6.3 Shelf life

3 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 of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (bromobutyl or chlorobutyl). Box of 1, 10 or 20.

0.5 mL of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (bromobutyl or chlorobutyl) and a tip-cap, without needle. Box of 1 and 20.

0.5 mL of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (bromobutyl or chlorobutyl) and a tip-cap, with a separate needle. Box of 1.

0.5 mL of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (bromobutyl or chlorobutyl) and a tip-cap, with two separate needles. Box of 1 or 10.

Not all pack sizes 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.

TETRAXIM can be used to reconstitute the *Haemophilus Influenzae* type b conjugate vaccine (Act-HIB).

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

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

7 PRODUCT OWNER

SANOFI PASTEUR

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France

8 DATE OF REVISION OF THE TEXT

24 March 2023