PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

TETRAXIM suspension for injection.

Diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine, adsorbed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 mL dose contains:

Active substances:

Purified diphtheria toxoid[1]	≥ 30 IU[2,3]
Purified tetanus toxoid[1]	≥ 40 IU[3,4]
Purified pertussis toxoid (PTxd)[1]	25 micrograms
Purified pertussis filamentous haemagglutinin (FHA)[1]	25 micrograms
Inactivated type 1 poliovirus (Mahoney)[5] D antigen	40 units[6]
Inactivated type 2 poliovirus (MEF1)[5] D antigen	8 units[6]
Inactivated type 3 poliovirus (Saukett)[5] D antigen	32 units[6]

[1] Adsorbed on aluminium hydroxide, hydrated (0,3 mg Al^{3+})

[2] As mean value

[3] Or equivalent activity determined by an 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

Preservatives:

2-phenoxyethanol – ethanol 50 % *v/v* solution

- 2-phenoxyethanol 2,5 microlitres

- ethanol anhydrous 2,5 microlitres

Formaldehyde 10 micrograms

Sugar (glucose): trace amounts.

Contains sweetener: phenylalanine 12,5 micrograms.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Whitish turbid suspension for injection in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TETRAXIM is indicated for active immunisation against diphtheria, tetanus, pertussis and poliomyelitis:

- For primary vaccination in infants.
- For booster vaccination in children who have previously received a primary vaccination with this vaccine or a diphtheria-tetanus-whole cell or acellular pertussis-poliomyelitis vaccine.

4.2 Posology and method of administration

Primary vaccination

Starting from 6 weeks of age, the three-dose primary vaccination is three successive doses of 0,5 mL given at an interval of one or two months, such as 6, 10 and 14 weeks or 2, 3, 4 months or 2, 4, 6 months or 3, 4, 5 months or 3, 5, 12 months (or according to national vaccination policies).

Booster vaccination

A fourth dose should be administered within the second year of life in children who received TETRAXIM (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.

Late booster

1 booster injection at 5 – 12 years old in children who were previously immunised with an acellular vaccine (3 or 4 doses) or 3 doses of a whole cell vaccine followed by a booster dose of either acellular or whole cell vaccine. Booster doses in 5 through 12 years old individuals should be given in accordance with the official national vaccination policies.

Method of administration:

Before injection, shake to obtain a homogenous whitish-turbid suspension.

This vaccine must be administered intramuscularly. The intradermal or intravenous routes must not be used. The recommended injection sites are the antero-lateral aspect of the upper thigh in infants and the deltoid muscle in older children.

The vaccine must neither be mixed with other medical products, except Act-HIB vaccine, nor with other substances for parenteral use.

4.3 Contraindications

- Known systemic hypersensitivity to any component of TETRAXIM or to pertussis vaccines (acellular or whole cell pertussis), or a life- threatening reaction after previous administration of the 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

- 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 the 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 hours 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.
- Do not administer by the intravascular route – ensure that the needle does not enter 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 the administration of any dose of TETRAXIM, the parent or guardian of the recipient or the adult recipient her/himself must be asked about their personal history, family history and recent health status, including immunisation history, current health status and any adverse event after previous immunisations.

- 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 following a previous pertussis-containing vaccine injection, the decision to give further doses of pertussis-containing vaccine should be carefully considered:
    - fever greater than or equal to 40 °C within 48 hours of vaccination not due to another identifiable cause
    - collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination
    - persistent, inconsolable crying lasting for three hours or longer and occurring within 48 hours of vaccination
    - febrile or non-febrile convulsions 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 be readily available for immediate use in case of a rare anaphylactic reaction following administration of vaccine.

Excipient(s) with known effect

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.

4.5 Interactions with other medicines and other forms of interaction

- Except in the case of immunosuppressive therapy, no significant clinical interaction with other treatments or biological products has been documented.
- TETRAXIM may be administered concomitantly with measles-mumps-rubella (MMR) and varicella-containing vaccines at separate injection sites.
- If the vaccine is used in persons deficient in producing antibodies, whether due to genetic defects, immunodeficiency disease or immunosuppressive therapy, the expected immune response may not be obtained.

4.6 Fertility, pregnancy and lactation

Pregnancy

As TETRAXIM is not intended for administration to adults, data on the use of this vaccine in pregnant women are not available. Therefore, TETRAXIM is not recommended for pregnant women.

Breastfeeding

As TETRAXIM is not intended for adults, it is not known whether this vaccine is excreted in human milk. Caution must be exercised when TETRAXIM is administered to a nursing mother.

4.7 Effects on the ability to drive and use machines

Not applicable.

TETRAXIM is intended for paediatric use only.

4.8 Undesirable effects

The adverse events are ranked under headings of frequency using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

Data from clinical studies

Three studies included over 2 800 infants who received TETRAXIM administered simultaneously with Act-HIB at one or two injection sites.

Over 8 400 doses were administered as a primary series and the most frequently reported reactions include 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.

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

Gastro-intestinal disorders:

Very common: vomiting

Common: diarrhoea

Musculoskeletal and connective tissue disorders:

Very common: myalgia (muscle pain)

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 (feeling of discomfort or uneasiness)

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).

Hypotonic-hyporesponsive episodes (HHE) have not been reported following the use of TETRAXIM during clinical studies but have been reported for other pertussis-containing 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 the diphtheria-tetanus-acellular pertussis-poliomyelitis vaccine TETRAXIM administered simultaneously with the conjugate *Haemophilus influenzae* type b vaccine at two separate injection sites.

TETRAXIM is indicated for administration to children aged from 5 to 12 years as a late booster.

Reactions to TETRAXIM in children in this age group are equally or less frequently reported than after administration of DTP-IPV (whole cell pertussis) or DT-IPV, respectively, at the same age.

Data from post-marketing surveillance:

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of TETRAXIM.

These events have been very rarely (< 0,01 %) reported; however, exact incidence rates cannot be precisely calculated and their frequency is qualified as “Not known”.

Blood and lymphatic disorders:

Lymphadenopathy.

Immune system disorders:

Anaphylactic reactions such as facial oedema, Quincke’s oedema.

Nervous system disorders:

Convulsions with or without fever, syncope.

Skin and subcutaneous tissue disorders:

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

General disorders and administration site conditions:

Large injection site reactions (> 50 mm), including extensive limb swelling from the injection site beyond one or both joints 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.

Potential adverse events

(i.e. adverse events which have been reported with other vaccines containing one or more of the antigenic constituents of TETRAXIM and not directly with TETRAXIM.) Brachial neuritis and Guillain-Barré syndrome have been reported after administration of a tetanus toxoid-containing vaccine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: email: za.drugsafety@sanofi.com or Tel: 011 256 3700, or
- SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Not documented.

5. PHARMACOLOGICAL PROPERTIES

A.30.2 Antigens.

Pharmacotherapeutic group: Combined bacterial and viral vaccines (diphtheria-pertussis-poliomyelitis-tetanus).

ATC code: J07C A02.

5.1 Pharmacodynamic properties

Immune response after primary vaccination:

Immunogenicity studies in infants given three doses of TETRAXIM 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, approximately 90 % of infants achieved a four-fold rise in PT and FHA antibody titres one to two months after completion of the primary vaccination. In the absence of a serological correlate of protection, a four-fold increase in post-immunisation titres is considered as a seroconversion.

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.

Immune response after booster injection:

Immunogenicity studies in toddlers in the second year of life who have received a 3-dose primary vaccination series with TETRAXIM have shown high antibody responses to all the 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 or DTP-IPV-ACT- HIB, have shown that a booster dose with TETRAXIM is safe and immunogenic for all components of the vaccine.

Studies in children 5 to 12 years of age who were given 4 doses of whole-cell pertussis vaccines, DTP-IPV (or DTP-IPV-Act-HIB) have shown that a booster dose with TETRAXIM is immunogenic for all components and is well tolerated.

5.2 Pharmacokinetic properties

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Aluminium hydroxide (expressed as Al^{3+})

Ethanol anhydrous (as preservative)

Formaldehyde (as preservative)

Medium 199 Hanks' 10 x C without phenol red

Phenoxyethanol (as preservative)

Acetic acid glacial and/or sodium hydroxide (for pH adjustment)

Water for injection.

The 10 x C Medium 199 Hanks' (without phenol red) is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other components (such as glucose) diluted in water for injections.

See section 2 for detail on the adsorbent.

During manufacture of the poliomyelitis valence, polymyxin B, glutaraldehyde, streptomycin and neomycin are used and traces may remain in the final vaccine.

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

36 months.

6.4 Special precautions for storage

Store at a temperature between +2 °C and +8 °C (in a refrigerator).

DO NOT FREEZE. Discard the vaccine if it has been frozen.

Protect from light. Keep the syringe in the blister pack until required for use.

6.5 Nature and contents of container

0,5 mL of suspension in pre-filled syringe (type 1 clear glass) with a black plunger stopper (bromobutyl or chlorobutyl) with or without a needle. The syringe is a blister pack and packed in a carton. Pack of 1.

6.6 Special precautions for disposal and other handling

For needle free syringes, the needle should be pushed firmly to the end of the pre-filled syringe and rotated through 90 degrees. Shake before using to obtain a homogeneous white turbid suspension.

TETRAXIM 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. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

A38/30.1/0526

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 March 2007

10. DATE OF REVISION OF THE TEXT

30 November 2023