## 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

Tetanus toxoid[(1)] ..... ≥ 40 IU

*Bordetella pertussis* antigens:

Pertussis toxoid[(1)] ..... 25 micrograms

Filamentous haemagglutinin[(1)] ..... 25 micrograms

Poliomyelitis virus (inactivated)

-type 1 (Mahoney strain)…… 40 DU[(2) (3)(4)]

-type 2 (MEF-1 strain)…… 8 DU[(2) (3)(4)]

-type 3 (Saukett strain)…… 32 DU[(2) (3)(4)]

[(1)] adsorbed on aluminium hydroxide, dihydrate ..... 0.3 mg $Al^{3+}$

[(2)] DU: D antigen unit.

[(3)] or equivalent antigenic quantity determined by a suitable immunochemical method.

[(4)] produced on VERO cells.

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

For a 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:

- for primary vaccination in infants from the age of 2 months,
- for booster vaccination, one year after primary vaccination during the second year of life,

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

- for booster vaccination between 5 and 7 years of age, according to official recommendations.

## 4.2 Posology and method of administration

**Posology**

Primary vaccination: 3 injections given at an interval of one month, i.e. according to the official schedule, at the age of 2, 3, 4 months.

Booster vaccination: 1 injection one year after primary vaccination, i.e. usually, between 16 and 18 months.

Late booster vaccination between 5 and 7 years of age: 1 injection.

For primary vaccination, first booster dose and late booster at 5-7 years, 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 5 and 7 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 as traces)
  - 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 immunization schedules are incomplete (i.e. fewer than three doses administered).

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

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 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.

## 4.5 Interaction with other medicinal products and other forms of interaction

This vaccine can be administered simultaneously with the M-M-RVAXPRO vaccine or with the HBVAXPRO vaccine, but in two separate sites.

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

## 4.6 Pregnancy and lactation

Not applicable.

## 4.7 Effects on ability to drive and use machines

Not applicable.

TETRAXIM is intended for paediatric use only.

## 4.8 Undesirable effects

**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 accordingly 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: ≥1/10
Common: ≥1/100 and <1/10
Uncommon: ≥1/1000 and <1/100
Rare: ≥1/10000 and <1/1000
Very rare: <1/10000
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 with a Not Known frequency

Lymphadenopathy.

**Immune system disorders**

Reactions with a Not Known frequency

- 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 with a Not Known frequency**

- Convulsions with or without fever.
- Syncope.

**Gastro-intestinal disorders**

Very common reactions

- Vomiting.

Common reactions

- Diarrhoea.

**Skin and subcutaneous tissue disorders**
Reactions with a Not Known frequency
- 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 ≥38°C.
- Malaise.

Common reactions
- Injection-site induration.

Uncommon reactions
- Injection-site redness and oedema ≥5 cm.
- Fever ≥39°C.

Rare reactions
- Fever >40°C.

Reactions with a Not Known frequency
- 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.

**Complementary information concerning particular 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## 4.9 Overdose

Not applicable.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**VACCINE AGAINST DIPHTHERIA, TETANUS, PERTUSSIS AND POLIOMYELITIS**

**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 viruses 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.

After booster vaccination between 5 to 13 years of age, all children developed protective antibody titres against tetanus (> 0.1 IU/ml) and poliomyelitis viruses. Protective antibody titres against diphtheria (> 0.1 IU/ml) were achieved in at least 99.6% of them. Seroconversion rates in pertussis antibodies (titres higher than four-fold the pre-vaccinal titres) are from 89.1% to 98% for PT (EIA) and from 78.7% to 91% for FHA (EIA).

## 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

Concerning the adsorbent, see section 2.

- Hanks' medium (without phenol red)
- Acetic acid and/or sodium hydroxide (for pH adjustment)
- Formaldehyde,
- Phenoxyethanol
- Ethanol
- Water for injections.

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

## 6.2 Incompatibilities

In the absence of compatibility 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 or bromochlorobutyl). 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 or bromochlorobutyl) 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 or bromochlorobutyl) 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 or bromochlorobutyl) and a tip-cap, with two separate needles. Box of 1 or 10.

Not all pack sizes may be marketed.

## 6.6 Instructions for use, handling and disposal

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 Influenza* type b conjugate vaccine (Act-HIB).

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

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

## 7 MARKETING AUTHORISATION HOLDER

**SANOFI PASTEUR**
14 ESPACE HENRY VALLÉE
69007 LYON FRANCE

Reference: MYTetraxim0418/SPC0115