1. NAME OF THE MEDICINAL PRODUCT

PENTAXIM

Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 ml dose of reconstituted 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 µg
Purified filamentous haemagglutinin (FHA)[1]	25 µg
Inactivated type 1 poliovirus[5]	D antigen[6]: 40 units
Inactivated type 2 poliovirus[5]	D antigen[6]: 8 units
Inactivated type 3 poliovirus[5]	D antigen[6]: 32 units
Haemophilus influenzae type b polysaccharide conjugated to tetanus protein	10 µg

[1] Adsorbed on aluminium hydroxide, hydrated (0.3 mg Al^{3+})
[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

Pentaxim solution for injection is obtained by reconstitution of the powder of conjugate Haemophilus influenzae type b vaccine (vial) with the suspension of combined diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine, adsorbed (pre-filled syringe).

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

Powder and suspension for injection.
Pentaxim is composed of a sterile and whitish turbid suspension and a white and homogenous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against diphtheria, tetanus, pertussis, poliomyelitis and invasive infections caused by Haemophilus influenzae type b (meningitis, septicaemia, cellulitis,

arthritis, epiglottitis, ...)
- for primary vaccination in infants,
- for booster in children who have previously received a primary vaccination with this vaccine or a diphtheria-tetanus-whole-cell or acellular pertussis-poliomyelitis vaccine, whether mixed or not with freeze-dried conjugate *Haemophilus influenzae* type b vaccine.

4.2 Posology and method of administration

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 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.

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

More data (e.g. epidemiological, clinical trial follow up) are required to establish the need for additional doses of acellular pertussis vaccines.

In a study involving 136 children, it was shown that Pentaxim can be administered simultaneously with measles-mumps-rubella vaccine (MMR II) at two separate injection sites.

Method of administration
Pentaxim 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.
Pentaxim must be injected immediately after reconstitution of the freeze-dried powder by the suspension.

For instructions on the reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

As with other vaccines, the vaccination with Pentaxim should be postponed in the case of
- fever or an acute severe 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 special 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 disease or treatment. 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 immunization schedule has been completed. Vaccination is usually justified for infants whose primary immunization schedules are incomplete (i.e., fewer than three does 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.

Pentaxim does not protect against infectious diseases caused by other types of Haemophilus influenzae or against meningitis of other origins.

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 Pentaxim, the parent or guardian of the recipient must be asked about the personal history of the recipient, family history and recent health status, including immunization history, current health status and any adverse event after previous immunizations.
- 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 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.

Pentaxim contains phenylalanine, ethanol and sodium

Pentaxim 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.

Pentaxim 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.

Pentaxim 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 interaction

Except in the case of 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 with MMR II.

Antigenuria has been detected in some instances following receipt of Pentaxim. Therefore, urine antigen detection may not have definite diagnostic value in suspected Haemophilus influenzae type b disease within two weeks of immunization.

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 to <1/10)
- Uncommon (≥1/1000 to <1/100)
- Rare (≥1/10 000 to 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 Pentaxim. 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 in infants who received Pentaxim as a primary series the most frequently reported reactions are local reactions at the injection site, abnormal crying, irritability and fever.
These signs and symptoms usually occurred within 48 hours after vaccination. They resolved spontaneously without requiring specific treatment.
After the primary series, the frequencies of injection site reactions tend to increase with the booster dose.

Immune system disorders

- *Not Known:*
  - Anaphylactic reactions such as face oedema, Quincke's oedema or shock.

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)
- *Not Known:*
  - Convulsions with or without fever
  - Hypotonic reaction or hypotonic-hyporesponsive episodes (HHE)

Gastro-intestinal disorders

- *Very common:*
  - Vomiting
- *Common:*
  - Diarrhoea

Skin and subcutaneous tissue disorders

- *Not Known:*
  - Rash
  - Urticaria

General disorders and administration site conditions

- *Very common:*
  - Redness at the injection site
  - Pyrexia, (fever) ≥38°C
  - Injection site swelling
  - Injection site pain

- *Common:*
  - Induration at the injection site

- *Uncommon:*
  - Pyrexia, (fever) ≥39°C
  - Redness and swelling ≥5cm at the injection site

- *Rare:*
  - Pyrexia >40°C (high fever)
  - 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.

- *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.

    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.

Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combined bacterial and viral vaccines (diphtheria-Haemophilus influenzae b-pertussis-poliomyelitis-tetanus),

ATC code: J07C A06

When administered alone PRP induces a serological response but it is weak in infants. The covalent binding of PRP to tetanus protein makes it a T-cell dependent antigen which induces a specific IgG anti-PRP response in infants and which can activate an immunological memory.

Immune response after primary vaccination:
Immunogenicity studies in infants given three doses of Pentaxim starting at 2 months of age have shown that, one month after the third dose, all developed a seroprotective antibody level (≥ 0.01 IU/mL) to both diphtheria and tetanus antigens and more than 88% of infants achieved a four-fold rise in PT and FHA antibodies. At least 99% of children had seroprotective antibody titres to poliomyelitis virus types 1, 2 and 3. At least 92% of children achieved anti PRP titres above 0.15 µg/ml.

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.

An immunogenicity study in Sweden given 3 doses of Pentaxim starting at 3 months of age has shown results of the same order of magnitude in terms of seroprotection and seroconversion.

In these clinical studies anti-PRP antibody titres after completion of the primary series with Pentaxim are lower than those obtained when a diphtheria-tetanus-acellular pertussis- poliomyelitis vaccine (TETRAVAC) is administered simultaneously with conjugate Haemophilus influenzae type b vaccine at two separate injection sites. However, the clinical impact of this interaction is not significant after the third dose, whatever the vaccination schedule used.

Immune response after booster injection:
Immunogenicity studies in toddlers who had received a 3-dose primary vaccination series with Pentaxim and a booster dose at 15-18 months of age have shown high antibody responses to all components including over 99% of children with anti-PRP titres above 1.0µg/mL.

5.2 Pharmacokinetic properties
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5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suspension for injection:
- 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

Freeze-dried substance:
- Trometamol
- Sucrose
- Concentrated hydrochloric acid for pH adjustment

For adsorbent: see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

The vaccine must be injected immediately after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and content of container

Freeze-dried substance:
Single dose vial (glass) with stopper (chlorobutyl elastomer) and detachable cap (aluminium).

Suspension for injection
Single dose prefilled syringe (glass) with plunger (bromobutyl or chlorobutyl), attached needle and needle shield (elastomer).

Single dose prefilled syringe (glass) with plunger (bromobutyl or chlorobutyl) and tip cap (elastomer), without needle.

Single dose prefilled syringe (glass) with plunger (bromobutyl or chlorobutyl) and tip cap (elastomer), with 1 separate needle (for each syringe).

Single dose prefilled syringe (glass) with plunger (bromobutyl or chlorobutyl) and tip cap (elastomer), with 2 separate needles (for each syringe).

Packs of 1 or 10 or 20.

Not all pack sizes and presentations may be marketed.

6.6 Special precautions for disposal and other handling

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

- Shake the pre-filled syringe containing the suspension until the contents become homogeneous.
- Inject this suspension into the vial with the powder
- Gently shake the vial until complete dissolution of the powder, achieving a whitish-turbid appearance
- Withdraw immediately the reconstituted vaccine into the syringe
- Gently shake the loaded syringe and promptly deliver the injection.
- Should the reconstituted vaccine separate into a transparent phase and gel-like phase, then remix by shaking the syringe vigorously before administration.

The whitish cloudy aspect of the reconstituted vaccine is normal.

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

7. MARKETING AUTHORISATION HOLDER

Medici Medical Ltd, 3 Hamachshev St. Netanya 4250713, Israel

8. MANUFACTURER:

Sanofi Pasteur 14 Espace Henry Vallée 69007 Lyon FRANCE

9. MARKETING AUTHORISATION NUMBER(S)

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