1 NAME OF THE MEDICINAL PRODUCT

PENTAXIM, powder and suspension for suspension for injection in prefilled syringe
Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine and *Haemophilus* type b conjugate vaccine, adsorbed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution one dose (0.5 ml) contains:
Diphtheria toxoid [(1)].....≥ 30 IU
Tetanus toxoid [(1)]
.....≥ 40 IU
*Bordetella pertussi*s 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)]

Polysaccharide of *Haemophilus influenzae* type b..... 10 micrograms
conjugated to the tetanus protein ..... 18 - 30 micrograms
[(1)]adsorbed on aluminium hydroxide, hydrated.....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

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

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

PENTAXIM is made up of a syringe prefilled with a cloudy, whitish, sterile suspension and a vial of white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This vaccine is indicated in the joint prevention of diphtheria, tetanus, pertussis, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b (such as meningitis, septicaemia, cellulitis, arthritis, epiglottitis, etc.,),

- 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 does not protect against infections caused by the other types of *Haemophilus influenzae* or against meningitis due to other micro-organisms.

4.2 Posology and Method of Administration

PENTAXIM must be administered according to the official recommendations in effect.

Posology

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

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

Method of Administration

Administer via the intramuscular route (IM).

Administration should preferably be performed in the anterolateral side of the thigh (middle third) in infants and in the deltoid area in children.

For instructions on reconstitution, see Section 6.6.

Once reconstituted, the suspension is cloudy and whitish.

4.3 Contraindications

- Hypersensitivity:
    - to any of the active substances of PENTAXIM,
    - to any of the excipients,
    - 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 injection of the vaccine or a vaccine containing the same substances.
- Vaccination must be postponed in case of fever 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 PENTAXIM 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 via 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, PENTAXIM 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 the 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.

PENTAXIM does not protect against invasive diseases caused by serotypes other than *Haemophilus influenzae* type b, nor against meningitis from other origins.

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.

Interference with laboratory tests: see Section 4.5.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

This vaccine may be administered simultaneously with the measles-mumps-rubella vaccine or with any recombinant Hepatitis B surface antigen vaccines, but in two separate sites.

Interference with laboratory tests

Since the Hib capsular polysaccharide antigen is excreted in the urine, a positive urine test can be observed within 1 to 2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

4.6 Pregnancy and Lactation

Not applicable.

PENTAXIM is intended for paediatric use only.

4.7 Effects on Ability to Drive and Use Machines

Not applicable.

PENTAXIM 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: ≥10%
Common: ≥ 1% and <10%
Uncommon: ≥ 0,1% and < 1%

Rare: ≥ 0,01% and < 0,1%
Very Rare: < 0,01%
Not known: cannot be estimated from the available data.

Based on spontaneous reports, certain undesirable events were very rarely reported following the 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. This is why these undesirable events are ranked under the « Not known » frequency.

In clinical studies in children who received PENTAXIM as a primary series, the most frequently reported reactions are local injection-site reactions, abnormal crying, irritability and fever.

These signs and symptoms usually occur within 48 hours following the vaccination and may continue for 48-72 hours. They resolve spontaneously without specific treatment.

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

Immune system disorders

Reactions with a Not Known frequency
- Immediate hypersensitivity reactions such as face oedema, angioedema, Quincke's oedema, anaphylactic reactions and shocks.

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.

Reactions with a Not Known frequency
- Convulsions with or without fever.

- Hypotonic-hyporesponsive episodes.

Gastro-intestinal disorders

Very common reactions
- Vomiting.

Common reactions
- Diarrhoea.

Skin and subcutaneous tissue disorders

Reactions with a Not Known frequency
- Rash, erythema, urticaria.

General disorders and administration site conditions

Very common reactions
- Injection-site erythema.
- Fever ≥38°C.
- Injection-site oedema.
- Injection-site pain.

Common reactions
- Injection-site induration.

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

Rare reactions
- Fever >40°C.

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.

Reactions with a Not Known frequency
- Large injection site reactions (> 50 mm), including extensive limb swelling that may spread from the injection site to one or both adjacent 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.

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

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

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

4.9 Overdose

Not documented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

VACCINE AGAINST DIPHTHERIA, TETANUS, PERTUSSIS AND POLIOMYELITIS AND INFECTIONS CAUSED BY HAEMOPHILUS INFLUENZAE TYPE b.

Pharmacotherapeutic group: BACTERIAL AND VIRAL VACCINES, COMBINED, ATC code: J07CA06

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 by 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.

The PRP capsular polysaccharide (polyribosyl ribitol phosphate: PRP) is extracted from the culture of *Haemophilus influenzae* type b and conjugated to the tetanus protein (T) to give the PRP-T conjugate vaccine.

The PRP capsular polysaccharide (polyribosyl ribitol phosphate: PRP) induces an anti-PRP serological response in humans. However, as for all polysaccharide antigens, the immune response is thymoindependent, characterised by a low immunogenicity in infants and by the absence of a booster effect before the age of 15 months. The covalent bond of the *Haemophilus*

influenzae type b capsular polysaccharide to a carrier protein, the tetanus protein, enables the conjugate vaccine to behave like a thymo-dependent antigen inducing a specific anti-PRP serological response in infants and to obtain a booster effect.

Immune response after primary vaccination:

Immunogenicity studies in infants have shown that, one month after the third dose of the primary vaccination, all (100%) developed a seroprotective antibody level (> 0.01 IU/ml) to both diphtheria and tetanus antigens.

As for pertussis, one month after the third dose of the primary vaccination, 93% of infants achieved a fourfold rise in PT antibodies and more than 88% in FHA antibodies.

At least 99% of children had seroprotective antibody titres to poliomyelitis virus types 1, 2 and 3 (≥ 5 as expressed by reciprocal of dilution in seroneutralisation).

At least 97.2% of infants achieved anti PRP titres above 0.15 µg/ml one month after the third dose of the primary vaccination.

Immune response after the booster:

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), 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 titers) is at least 98% for PT (EIA) and 99% for FHA (EIA).

An antibody titre anti-PRP ≥ 1.0 µg/ml was reached in all toddlers.

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.

Suspension for injection:

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

Powder:
- Saccharose
- Tromethamol

6.2 Incompatibilities

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

6.3 Shelf Life

3 years.

The vaccine must be administered immediately after reconstitution.

6.4 Special Precautions for Storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For storage conditions of the reconstituted medicinal product, see Sections 6.3.

6.5 Nature and Contents of Container

Powder in vial (type I glass) equipped with a stopper (chlorobutyl) + 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.

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

Powder in vial (type I glass) equipped with a stopper (chlorobutyl) + 0.5 mL of suspension in prefilled syringe (type I glass) equipped with a plunger-stopper (bromobutyl or chlorobutyl or bromochlorobutyl) 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 needle must be fitted firmly to the syringe, rotating it by a one quarter turn.

Reconstitute the solution by injecting the suspension of the combined diphtheria, tetanus, acellular pertussis and poliomyelitis vaccine into the vial with the powder of the Haemophilus type b conjugate vaccine. Shake until complete dissolution of the powder. After reconstitution, the whitish-turbid appearance of the suspension is normal.

The vaccine must be used immediately after reconstitution.

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

7 PRODUCT OWNER

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8 DATE OF REVISION OF THE TEXT

25 January 2018