1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution one dose (0.5 mL) contains:
Diphtheria toxoid[1].....≥ 20 IU[2,3] (30Lf)
Tetanus toxoid[1] .....≥ 40 IU[3,4] (10Lf)
*Bordetella pertussi*s antigens:
Pertussis toxoid[1] ..... 25 micrograms
Filamentous haemagglutinin[1] ..... 25 micrograms
Poliomyelitis virus (inactivated)[5]
- Type 1 (Mahoney)….....40 D antigen units[6]
- Type 2 (MEF-1).....8 D antigen units[6]
- Type 3 (Saukett) .....32 D antigen units[6]

Haemophilus influenzae type b polysaccharide.....10 micrograms
conjugated with tetanus protein ..... 18 - 30 micrograms
[1] Adsorbed on hydrated aluminium hydroxide.....0.3 mg Al^{3+}
[2] As lower confidence limit (p=0.95), and not less than 30 IU in mean value
[3] Or equivalent potency determined by immunogenicity assessment
[4] As a lower confidence limit (p=0.95)
[5] Produced on VERO cells.
[6] Or equivalent antigen quantity determined using an appropriate immunochemical method.

PENTAXIM may contain traces of glutaraldehyde, neomycin, streptomycin and polymyxin B (see Section 4.3).
Excipient(s) 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 suspension for injection.

PENTAXIM consists of a syringe pre-filled with a cloudy, whitish, sterile suspension and a vial of white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

PENTAXIM (DTaP-IPV-Hib) is indicated for the joint prevention of diphtheria, tetanus, pertussis, poliomyelitis and invasive *Haemophilus influenzae* type b infections (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* nor against meningitis caused by other micro-organisms.

4.2 Posology and Method of Administration

PENTAXIM should be administered according to current official recommendations.

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 intramuscularly (IM).

Administration will preferably be in the anterolateral aspect of the thigh (middle third) in infants and in the deltoid region in children.

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

After reconstitution, the suspension is cloudy and whitish.

4.3 Contraindications

- Hypersensitivity:
    - to one of the active substances of PENTAXIM,
    - to any of the excipients listed in section 6.1,
    - glutaraldehyde, neomycin, streptomycin, or polymyxin B (used during manufacturing, and which may be present in trace amounts),
    - pertussis vaccine (acellular or "whole cell").
- Severe reaction after a previous injection of the vaccine or a vaccine containing the same substances.
- Vaccination should be postponed in case of fever or acute illness.
- Progressive encephalopathies.

- Encephalopathy within 7 days of a previous dose of any vaccine containing pertussis antigens ("whole cell" or acellular pertussis vaccine).

4.4 Special Warnings and Precautions for Use

The immunogenicity of PENTAXIM may be reduced by immunosuppressive therapy or an immunodeficiency state. It is then recommended to wait until the end of the treatment or the disease to vaccinate. Nevertheless, vaccination of subjects with chronic immunosuppresion such as HIV infection is recommended even if the immune response may be limited.

In subjects who have had Guillain-Barré syndrome or brachial plexus neuropathy during previous administration of a vaccine containing tetanus toxoid, the decision to vaccinate with a vaccine containing tetanus toxoid should be based on careful evaluation of the potential benefits and risks of continuing this vaccination. Vaccination is usually warranted in young children for whom the primary vaccination schedule is not complete (i.e., less than three doses administered).

Do not inject intravascularly; ensure that the needle does not enter a blood vessel. Do not inject intradermally.

As with any injectable vaccine, PENTAXIM should be administered with caution in case of thrombocytopenia or coagulation disorders, because intramuscular injection may cause bleeding in these subjects.

Vaccination must be preceded by a search of the medical history (especially for previous vaccinations and adverse events that may have occurred), and a physical examination.

If the occurrence of any of the following events is chronologically linked to the administration of the vaccine, the decision to administer further doses of vaccine containing a pertussis component should be carefully considered:
- Fever ≥ 40°C within 48 hours, with no other identifiable cause.
- Collapse or shock-like state with episode of hypotonia-hyporesponsiveness within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours after vaccination.
- Seizures with or without fever, occurring within 3 days after vaccination.

A history of febrile convulsions unrelated to a previous vaccine injection does not in itself constitute a contraindication to vaccination.

It is particularly important in this field to monitor the temperature within 48 hours of vaccination and to give regular antipyretic treatment for 48 hours.

A history of non-febrile seizures unrelated to a previous vaccine injection must be the subject of specialist advice before any decision to vaccinate.

In the event of oedematous reactions of the lower limbs occurring following an injection of a vaccine containing the *Haemophilus influenzae* type b valence, the administration of the two

vaccines, diphtheria-tetanus-pertussis-poliomyelitis vaccine and the *Haemophilus influenzae* type b conjugate vaccine must be carried out at two separate injection sites, and on different days.

As with any injectable vaccine, appropriate medical treatment should be immediately available, and monitoring should be carried out for the rare event that an anaphylactic reaction occurs after vaccine administration .

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

The potential risk of apnoea and the need for respiratory monitoring for 48 - 72 hours should be carefully considered when administering the primary vaccination doses in very premature infants (born at ≤ 28 weeks of pregnancy) and particularly for those with a history of respiratory immaturity. Due to the high benefit of vaccination in these infants, administration should not be suspended or postponed.

Interference with laboratory tests: see Section 4.5.

PENTAXIM contains phenylalanine, ethanol and sodium

PENTAXIM contains 12.5 micrograms of phenylalanine per 0.5 mL dose. Phenylalanine may be dangerous for people with phenylketonuria (PKU), a rare genetic condition where phenylalanine builds up and cannot be eliminated properly.

PENTAXIM contains 2 mg of alcohol (ethanol) per 0.5 mL dose. The low quantity of alcohol in this medicinal product is unlikely to cause a notable effect.

PENTAXIM contains less than 1 mmol (23 mg) sodium per dose, i.e. it is 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 Interactions with Other Medicinal Products and Other Forms of Interaction

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

Interference with laboratory testing

Due to the urinary elimination of the Hib polysaccharide capsular antigen, a positive result may be observed in a urine test for 1 to 2 weeks after vaccination. Other tests should be done to confirm Hib infection during this time.

4.6 Fertility, 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

Adverse reactions are ranked in terms 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.

According to spontaneous reports, some adverse events have been reported very rarely following the use of PENTAXIM. As 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.

During clinical studies in children who received PENTAXIM as a primary vaccination series, the most frequently reported reactions were local reactions at the injection site, abnormal crying, irritability and fever.

These signs and symptoms usually appear within 48 hours of vaccination and may last between 48 and 72 hours. They disappear spontaneously without specific treatment.

The frequency of reactions at the injection site tends to increase during the booster compared to the frequency observed in the primary vaccination series.

Immune system disorders

Reactions of unknown frequency
- Immediate hypersensitivity reactions such as face oedema, angioedema, Quincke's oedema, anaphylactic reactions and shock.

Metabolism and nutrition disorders

Very common reactions
- Loss of appetite.

Psychiatric disorders

Very common reactions
- Nervousness, irritability.
- Abnormal crying and screaming.

Common reactions
- Insomnia, sleep disorders.

Uncommon reactions
- Inconsolable and prolonged crying and screaming

Nervous system disorders

Very common reactions
- Somnolence.

Reactions of unknown frequency
- Seizures with or without fever.
- Episodes of hypotonia-hyporesponsiveness.

Gastro-intestinal disorders

Very common reactions
- Vomiting.

Common reactions
- Diarrhoea.

Skin and subcutaneous tissue disorders

Reactions of unknown frequency
- Skin rashes, erythema, urticaria.

General disorders and administration site conditions

Very common reactions
- Erythema at the injection site.
- Fever ≥38°C.
- Oedema at the injection site.
- Pain at the injection site.

Common reactions
- Induration at the injection-site.

Uncommon reactions
- Fever ≥39°C.
- Redness and oedema ≥5 cm at the injection site.

Rare reactions
- Fever >40°C.

Oedematous reactions of one or both lower limbs may occur after vaccination with a vaccine containing the *Haemophilus influenzae* type b conjugate valence. These reactions occur mainly after the primary vaccination, in the first hours following vaccination, and disappear spontaneously and without sequelae within 24 hours. These reactions may be accompanied by cyanosis, erythema, transient purpura and severe crying.

Reactions of unknown frequency
- Large reactions at the injection site (> 50 mm), including limb oedema, which may extend from the injection site to either of the adjacent joints. These reactions appear 24 to 72 hours after vaccination and may be associated with symptoms such as erythema, warmth, tenderness or pain at the injection site. They disappear spontaneously in 3 to 5 days. The risk appears to be related to the number of previous doses of vaccine containing the acellular pertussis component, with an increased risk after the 4^{th} and 5^{th} dose.

Potential adverse reactions (i.e., which 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 plexus neuropathy after administration of a vaccine containing tetanus toxoid.

Additional information concerning particular populations

Apnoea in very premature infants (born at ≤ 28 weeks of pregnancy) (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

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

The diphtheria and tetanus toxins are detoxified by formaldehyde, and then purified.

The poliomyelitis vaccine is obtained by culture of polio virus types 1, 2 and 3 on Vero cells, purified, and then inactivated by formaldehyde.

The acellular pertussis components (PT and FHA) are extracted from cultures of Bordetella pertussis, then purified. The pertussis toxin (PT) is detoxified by glutaraldehyde and corresponds to pertussis toxoid (PTxd). The FHA is native. PTxd and FHA have been shown to play a major role in protection as regards pertussis.

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

Capsular polysaccharide (polyribosyl ribitol phosphate: PRP) induces a serological anti-PRP response in humans. However, as with all polysaccharide antigens, the immune response is thymus-independent, characterised by low immunogenicity in infants, and by the absence of a booster effect before the age of 15 months. The covalent bond of the capsular polysaccharide of *Haemophilus influenzae* type b to a carrier protein, tetanus protein, allows the conjugate vaccine to behave as a thymus-dependent antigen leading to a specific anti-PRP serological response in the infant, and to achieve a booster effect.

Immune response after primary vaccination:

Immunogenicity studies performed in infants one month after primary vaccination showed that all infants (100%) developed a protective antibody titre (> 0.01 IU/mL) against diphtheria and tetanus antigens.

For pertussis, one month after receiving the three primary doses, anti-PT and anti-FHA antibody titres increased fourfold in 93%, and more than 88% of infants, respectively.

At least 99% of primary vaccinated children had protective titres of antibodies directed against poliomyelitis virus types 1, 2, and 3 (≥ 5 reciprocal of dilution in seroneutralisation).

Finally, one month after the third dose of primary vaccination, at least 97.2% of vaccinated infants have an anti-PRP antibody titre greater than 0.15 µg/mL.

Immune response after booster:

After the first booster dose (16 - 18 months), all the children developed protective antibody titres against diphtheria (> 0.1 IU/mL) and tetanus (> 0.1 IU/mL), and against poliomyelitis viruses (≥ 5 reciprocal of dilution in seroneutralisation).

The rate of seroconversion to pertussis antibodies (titres greater than 4 times the pre-vaccination titres) is at least 98% for PT (EIA) and 99% for FHA (EIA).

An anti-PRP antibody titre of ≥ 1.0 µg/mL was obtained in all children.

A follow-up study of pertussis immunogenicity in children aged 5-6 years showed that the anti-PT and anti-FHA antibody titres of children who received primary and booster vaccinations with combined acellular vaccines were at least equivalent to those observed in children of the same age who had been vaccinated with combined whole-cell pertussis vaccines.

5.2 Pharmacokinetic Properties

Not applicable.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute toxicity, repeated dose toxicity and local tolerability.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Concerning the adsorbent, see Section 2.

Suspension for injection:
- Hanks' Medium 199 without phenol red
- Glacial acetic acid and/or sodium hydroxide (for pH adjustment)
- Formaldehyde
- Phenoxyethanol
- Ethanol, anhydrous
- 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.

Powder:
- Sucrose
- Trometamol
- Concentrated hydrochloric acid for pH adjustment.

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 should 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 after reconstitution of the medicinal product, see Sections 6.3.

6.5 Nature and Contents of Container

Powder in vial (type I glass) fitted with a stopper (chlorobutyl) + 0.5 mL of suspension in pre-filled syringe (type I glass) fitted with a plunger stopper (bromobutyl or chlorobutyl). Box of 1, 10 or 20.

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

Powder in a vial (type I glass) fitted with a stopper (chlorobutyl) + 0.5 mL of suspension in a pre-filled syringe (type I glass) fitted with a plunger stopper (bromobutyl or chlorobutyl), 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 a needle attached, the needle should be fitted firmly onto the syringe by rotating it a quarter turn.

Reconstitute the solution by injecting the combined diphtheria, tetanus, acellular pertussis and poliomyelitis vaccine suspension into the Haemophilus type b conjugate vaccine powder vial. Shake until the powder is completely dissolved. The cloudy whitish appearance of the suspension after reconstitution is normal.

The vaccine should be administered immediately after reconstitution.

Any unused medicinal 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

Nov 2023(CCDS V14 Part 1)