

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Hexacima suspension for injection in pre-filled syringe
Hexacima suspension for injection

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose¹ (0.5 ml) contains:

| | |
|--|-----------------------------------|
| Diphtheria Toxoid | not less than 20 IU ² |
| Tetanus Toxoid | not less than 40 IU ² |
| <i>Bordetella pertussis</i> antigens | |
| Pertussis Toxoid | 25 micrograms |
| Filamentous Haemagglutinin | 25 micrograms |
| Poliovirus (Inactivated) ³ | |
| Type 1 (Mahoney) | 40 D antigen units ⁴ |
| Type 2 (MEF-1) | 8 D antigen units ⁴ |
| Type 3 (Saukett) | 32 D antigen units ⁴ |
| Hepatitis B surface antigen ⁵ | 10 micrograms |
| <i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein | 12 micrograms 22-36 micrograms |

¹ Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al³⁺)

² As lower confidence limit (p= 0.95)

³ Produced on Vero cells

⁴ Or equivalent antigenic quantity determined by a suitable immunochemical method

⁵ Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Hexacima is a whitish, cloudy suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hexacima (DTaP-IPV-HB-Hib) is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b (Hib).

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination:

The primary vaccination consists of two doses (with an interval of at least 8 weeks) or three doses (with an interval of at least 4 weeks) in accordance with the official recommendations.

All vaccination schedules including the WHO Expanded Program on Immunisation (EPI) at 6, 10, 14 weeks of age can be used whether or not a dose of hepatitis B vaccine has been given at birth.

Where a dose of hepatitis B vaccine is given at birth, Hexacima can be used for supplementary doses of hepatitis B vaccine from the age of six weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

When a dose of hepatitis B vaccine is given at birth, the sequential infant primary vaccination hexavalent/pentavalent/hexavalent schedule with Hexacima and a pentavalent DTaP-IPV/Hib vaccine can be used in accordance with official recommendations.

Booster vaccination:

After a 2-dose primary vaccination with Hexacima, a booster dose must be given.

After a 3-dose primary vaccination with Hexacima, a booster dose should be given.

Booster doses should be given at least 6 months after the last priming dose and in accordance with the official recommendations. At the very least, a dose of Hib vaccine must be administered.

In addition:

In the absence of hepatitis B vaccination at birth, it is necessary to give a hepatitis B vaccine booster dose. Hexacima can be considered for the booster.

After a 3-dose WHO EPI schedule with Hexacima (6, 10, 14 weeks) and in the absence of hepatitis B vaccination at birth, a hepatitis B vaccine booster must be given. At the very least, a booster dose of polio vaccine should be given. Hexacima can be considered for the booster.

When a hepatitis B vaccine is given at birth, after a 3-dose primary vaccination, Hexacima or a pentavalent DTaP-IPV/Hib vaccine can be administered for the booster.

Hexacima may be used as a booster in individuals who have previously been vaccinated with another hexavalent vaccine or a pentavalent DTaP-IPV/Hib vaccine associated with a monovalent hepatitis B vaccine.

Other paediatric population

The safety and efficacy of Hexacima in infants less than 6 weeks of age have not been established. No data are available.

No data are available in older children (see sections 4.8 and 5.1).

Method of administration

Immunisation must be carried out by intramuscular (IM) injection. The recommended injection site is preferably the antero-lateral area of the upper thigh and the deltoid muscle in older children (possibly from 15 months of age).

For instructions on handling see section 6.6.

4.3 Contraindications

History of an anaphylactic reaction after a previous administration of Hexacima.

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, to trace residuals (glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B), to any pertussis vaccine, or after previous administration of Hexacima or a vaccine containing the same components or constituents.

Vaccination with Hexacima is contraindicated if the individual has experienced an encephalopathy of unknown aetiology, occurring within 7 days following prior vaccination with a pertussis containing vaccine (whole cell or acellular pertussis vaccines).

In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria, tetanus, hepatitis B, poliomyelitis and Hib vaccines.

Pertussis vaccine should not be administered to individuals with uncontrolled neurologic disorder or uncontrolled epilepsy until treatment for the condition has been established, the condition has stabilised and the benefit clearly outweighs the risk.

4.4 Special warnings and precautions for use

Hexacima will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Hexacima will not protect against hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E or by other liver pathogens.

Because of the long incubation period of hepatitis B, it is possible for unrecognised hepatitis B infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B infection in such cases.

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

Prior to immunisation

Immunisation should be postponed in individuals suffering from moderate to severe acute febrile illness or infection. The presence of a minor infection and/or low-grade fever should not result in the deferral of vaccination.

Vaccination should be preceded by a review of the person's medical history (in particular previous vaccinations and possible adverse reactions). The administration of Hexacima must be carefully considered in individuals who have a history of serious or severe reactions within 48 hours following administration of a vaccine containing similar components.

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 an anaphylactic reaction following administration of the vaccine.

If any of the following events are known to have occurred after receiving any pertussis containing vaccine, the decision to give further doses of pertussis containing vaccine should be carefully considered:

- Temperature of $\geq 40^{\circ}\text{C}$ 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.

There may be some circumstances, such as high incidence of pertussis, when the potential benefits outweigh possible risks.

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute a contraindication for the use of Hexacima. Individuals with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

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 vaccination has been completed. Vaccination is usually justified for individuals whose primary vaccination is incomplete (i.e. fewer than three doses have been received).

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 individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.

Special populations

No data are available for premature infants. However, a lower immune response may be observed and the level of clinical protection is unknown.

Immune responses to the vaccine have not been studied in the context of genetic polymorphism.

In individuals with chronic renal failure, an impaired hepatitis B response is observed and administration of additional doses of hepatitis B vaccine should be considered according to the antibody level against hepatitis B virus surface antigen (anti-HBsAg).

Precautions for use

Do not administer by intravascular, intradermal or subcutaneous injection.

As with all injectable vaccines, the vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

The potential risk of apnoea and the need for respiratory monitoring for 48 to 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.

Interference with laboratory testing

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.

4.5 Interaction with other medicinal products and other forms of interaction

Data on concomitant administration of Hexacima with a pneumococcal polysaccharide conjugate vaccine have shown no clinically relevant interference in the antibody response to each of the antigens.

Data on concomitant administration of a booster dose of Hexacima with measles-mumps-rubella vaccines have shown no clinically relevant interference in the antibody response to each of the antigens. There may be a clinically relevant interference in the antibody response of Hexacima and a varicella vaccine and these vaccines should not be administered at the same time.

Data on concomitant administration of rotavirus vaccines have shown no clinically relevant interference in the antibody response to each of the antigens.

Data on concomitant administration of Hexacima with a meningococcal C conjugate vaccine or a meningococcal group A, C, W-135 and Y conjugate vaccine have shown no clinically relevant interference in the antibody response to each of the antigens.

If co-administration with another vaccine is considered, immunisation should be carried out on separate injection sites.

Hexacima must not be mixed with any other vaccines or other parenterally administered medicinal products.

No significant clinical interaction with other treatments or biological products has been reported except in the case of immunosuppressive therapy (see section 4.4).

Interference with laboratory testing: see section 4.4.

4.6 Fertility, pregnancy and lactation

Not applicable. This vaccine is not intended for administration to women of child-bearing age.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

a- Summary of the safety profile

In clinical studies in individuals who received Hexacima, the most frequently reported reactions include injection-site pain, irritability, crying, and injection-site erythema. Slightly higher solicited reactogenicity was observed after the first dose compared to subsequent doses.

The safety of Hexacima in children over 24 months of age has not been studied in clinical trials.

b- Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions;
Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)
 Uncommon ($\geq 1/1,000$ to $< 1/100$)
 Rare ($\geq 1/10,000$ to $< 1/1,000$)
 Very rare ($< 1/10,000$)
 Not known (cannot be estimated from available data)

Table 1: Adverse Reactions from clinical trials and reported during commercial use

| System Organ Class | Frequency | Adverse Events |
|--|-------------|--|
| Immune system disorders | Uncommon | Hypersensitivity reaction |
| | Rare | Anaphylactic reaction* |
| Metabolism and nutrition disorders | Very common | Anorexia (decreased appetite) |
| Nervous system disorders | Very common | Crying, somnolence |
| | Common | Abnormal crying (prolonged crying) |
| | Rare | Convulsions with or without fever* |
| | Very rare | Hypotonic reactions or hypotonic-hyporesponsive episodes (HHE) |
| Gastrointestinal disorders | Very common | Vomiting |
| | Common | Diarrhoea |
| Skin and subcutaneous tissue disorders | Rare | Rash |
| General disorders and administration site conditions | Very common | Injection-site pain, injection-site erythema, injection-site swelling Irritability Pyrexia (body temperature $\geq 38.0^{\circ}\text{C}$) |
| | Common | Injection-site induration |
| | Uncommon | Injection-site nodule Pyrexia (body temperature $\geq 39.6^{\circ}\text{C}$) |
| | Rare | Extensive limb swelling† |

* Adverse reactions from spontaneous reporting.

† See section c.

c- Description of selected adverse reactions

Extensive limb swelling: 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.

d- Potential adverse events (i.e. adverse events which have been reported with other vaccines containing one or more of the components or constituents of Hexacima and not directly with Hexacima)

Nervous system disorders

- Brachial neuritis and Guillain-Barré Syndrome have been reported after administration of a tetanus toxoid containing vaccine
- Peripheral neuropathy (polyradiculoneuritis, facial paralysis), optic neuritis, central nervous system demyelination (multiple sclerosis) have been reported after administration of a hepatitis B antigen containing vaccine
- Encephalopathy/encephalitis

Respiratory, thoracic and mediastinal disorders

Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

General disorders and administration site conditions

Oedematous reaction affecting one or both lower limbs may occur following vaccination with *Haemophilus influenzae* type b containing vaccines. If this reaction occurs, it is mainly after primary injections and within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events should resolve spontaneously without sequel within 24 hours.

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 listed in [Appendix V](#).

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Vaccines, Bacterial and viral vaccines combined, ATC code: J07CA09

The immunogenicity of Hexacima in children over 24 months of age has not been studied in clinical trials.

Results obtained for each of the components are summarised in the tables below:

Table 1: Seroprotection/Seroconversion rates* one month after primary vaccination with 2 or 3 doses of Hexacima

| Antibody Thresholds | | Two doses | Three doses | | |
|--|--|--------------|---------------|--------------|----------------|
| | | 3-5 Months | 6-10-14 Weeks | 2-3-4 Months | 2-4-6 Months |
| | | N=249** | N=123 to 220† | N=322†† | N=934 to 1270‡ |
| | | % | % | % | % |
| Anti-diphtheria (≥ 0.01 IU/ml) | | 99.6 | 97.6 | 99.7 | 97.1 |
| Anti-tetanus (≥ 0.01 IU/ml) | | 100.0 | 100.0 | 100.0 | 100.0 |
| Anti-PT (Seroconversion ‡‡) (Vaccine response§) | | 93.4 98.4 | 93.6 100.0 | 88.3 99.4 | 96.0 99.7 |
| Anti-FHA (Seroconversion ‡‡) (Vaccine response§) | | 92.5 99.6 | 93.1 100.0 | 90.6 99.7 | 97.0 99.9 |
| Anti-HBs (≥ 10 mIU/ml) | With hepatitis B vaccination at birth | / | 99.0 | / | 99.7 |
| | Without hepatitis B vaccination at birth | 97.2 | 95.7 | 96.8 | 98.8 |
| Anti-Polio type 1 (≥ 8 (1/dilution)) | | 90.8 | 100.0 | 99.4 | 99.9 |
| Anti-Polio type 2 (≥ 8 (1/dilution)) | | 95.0 | 98.5 | 100.0 | 100.0 |
| Anti-Polio type 3 (≥ 8 (1/dilution)) | | 96.7 | 100.0 | 99.7 | 99.9 |
| Anti-PRP (≥ 0.15 µg/ml) | | 71.5 | 95.4 | 96.2 | 98.0 |

* Generally accepted surrogates (PT, FHA) or correlates of protection (other components)

N = Number of individuals analysed (per protocol set)

** 3, 5 months without hepatitis B vaccination at birth (Finland, Sweden)

† 6, 10, 14 weeks with and without hepatitis B vaccination at birth (Republic of South Africa)

†† 2, 3, 4 months without hepatitis B vaccination at birth (Finland)

‡ 2, 4, 6 months without hepatitis B vaccination at birth (Argentina, Mexico, Peru) and with hepatitis B vaccination at birth (Costa Rica and Colombia)

‡‡ Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)

§ Vaccine response: If pre-vaccination antibody concentration <8 EU/ml, then the post-vaccination antibody concentration should be ≥8 EU/ml. Otherwise, post-vaccination antibody concentration should be ≥ pre-immunisation level

Table 2: Seroprotection/Seroconversion rates* one month after booster vaccination with Hexacima

| Antibody Thresholds | | Booster vaccination at 11-12 months of age after a two doses primary course | Booster vaccination during the second year of life following a three dose primary course | | |
|---|--|---|--|---------------|---------------|
| | | 3-5 Months | 6-10-14 Weeks | 2-3-4 Months | 2-4-6 Months |
| | | N=249** | N=204† | N=178†† | N=177 to 396‡ |
| | | % | % | % | % |
| Anti-diphtheria (≥ 0.1 IU/ml) | | 100.0 | 100.0 | 100.0 | 97.2 |
| Anti-tetanus (≥ 0.1 IU/ml) | | 100.0 | 100.0 | 100.0 | 100.0 |
| Anti-PT (Seroconversion‡‡) (Vaccine response§) | | 94.3 98.0 | 94.4 100.0 | 86.0 98.8 | 96.2 100.0 |
| Anti-FHA (Seroconversion‡‡) (Vaccine response§) | | 97.6 100.0 | 99.4 100.0 | 94.3 100.0 | 98.4 100.0 |
| Anti-HBs (≥ 10 mIU/ml) | With hepatitis B vaccination at birth | / | 100.0 | / | 99.7 |
| | Without hepatitis B vaccination at birth | 96.4 | 98.5 | 98.9 | 99.4 |
| Anti-Polio type 1 (≥ 8 (1/dilution)) | | 100.0 | 100.0 | 98.9 | 100.0 |
| Anti-Polio type 2 (≥ 8 (1/dilution)) | | 100.0 | 100.0 | 100.0 | 100.0 |
| Anti-Polio type 3 (≥ 8 (1/dilution)) | | 99.6 | 100.0 | 100.0 | 100.0 |
| Anti-PRP (≥ 1.0 µg/ml) | | 93.5 | 98.5 | 98.9 | 98.3 |

* Generally accepted surrogates (PT, FHA) or correlates of protection (other components)

N = Number of individuals analysed (per protocol set)

** 3, 5 months without hepatitis B vaccination at birth (Finland, Sweden)

† 6, 10, 14 weeks with and without hepatitis B vaccination at birth (Republic of South Africa)

†† 2, 3, 4 months without hepatitis B vaccination at birth (Finland)

‡ 2, 4, 6 months without hepatitis B vaccination at birth (Mexico) and with hepatitis B vaccination at birth (Costa Rica and Colombia)

‡‡ Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)

§ Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be ≥8 EU/ml. Otherwise, post-booster antibody concentration should be ≥ pre-immunisation level (pre-dose 1)

Immune responses to Hib and pertussis antigens after 2 doses at 2 and 4 months of age

The immune responses to Hib (PRP) and pertussis antigens (PT and FHA) were evaluated after 2 doses in a subset of subjects receiving Hexacima (N=148) at 2, 4, 6 months of age. The immune responses to PRP, PT and FHA antigens one month after 2 doses given at 2 and 4 months of age were similar to those observed one month after a 2-dose priming given at 3 and 5 months of age: anti-PRP titers ≥ 0.15 $\mu\text{g/ml}$ were observed in 73.0% of individuals, anti-PT vaccine response in 97.9% of individuals and anti-FHA vaccine response in 98.6% of individuals.

Persistence of immune response

Studies on long-term persistence of vaccine induced antibodies following varying infant / toddler primary series and following Hepatitis B vaccine given at birth or not have shown maintenance of levels above the recognized protective levels or antibody thresholds for the vaccine antigens (see Table 3).

In addition, immunity against the hepatitis B component of the vaccine has been shown to persist up to 9 years of age after a primary series consisting of one dose of Hepatitis B vaccine given at birth followed by a 3-dose infant series at 2, 4, and 6 months of age without a toddler booster where 49.3% of vaccinees had antibodies ≥ 10 mIU/ml with geometric mean concentrations at 13.3 (95% CI: 8.82 – 20.0) mIU/ml. Immune memory against Hepatitis B had been demonstrated by the presence of an anamnestic response to a challenge Hepatitis B vaccination at the age of 9 years in 93% of vaccinees with development of geometric mean concentrations at 3692 (95% CI: 1886 – 7225) mIU/ml after vaccination.

Table 3: Seroprotection rates^a at the age of 4.5 years old after vaccination with Hexacima

| Antibody Thresholds | Primary 6-10-14 weeks and booster at 15-18 months | | Primary 2-4-6 months and booster at 12–24 months |
|---|---|---------------------------|--|
| | Without hepatitis B at birth | With hepatitis B at birth | With hepatitis B at birth |
| | N=173 ^b | N=103 ^b | N=220 ^c |
| | % | % | % |
| Anti-diphtheria (≥ 0.01 IU/ml) | 98.2 | 97 | 100 |
| (≥ 0.1 IU/ml) | 75.3 | 64.4 | 57.2 |
| Anti-tetanus (≥ 0.01 IU/ml) | 100 | 100 | 100 |
| (≥ 0.1 IU/ml) | 89.5 | 82.8 | 80.8 |
| Anti-PT ^e (≥ 8 EU/ml) | 42.5 | 23.7 | 22.2 |
| Anti-FHA ^e (≥ 8 EU/ml) | 93.8 | 89.0 | 85.6 |
| Anti-HBs (≥ 10 mIU/ml) | 73.3 | 96.1 | 92.3 |
| Anti-Polio type 1 (≥ 8 (1/dilution)) | NA ^d | NA ^d | 99.5 |
| Anti-Polio type 2 (≥ 8 (1/dilution)) | NA ^d | NA ^d | 100 |
| Anti-Polio type 3 (≥ 8 (1/dilution)) | NA ^d | NA ^d | 100 |
| Anti-PRP (≥ 0.15 µg/ml) | 98.8 | 100 | 100 |

N = Number of individuals analysed (per protocol set)

a: Generally accepted surrogates (PT, FHA) or correlates of protection (other components)

b: 6, 10, 14 weeks with and without hepatitis B vaccination at birth (Republic of South Africa)

c: 2, 4, 6 months with hepatitis B vaccination at birth (Colombia)

d: Due to an OPV National Immunisation Days in the country, Polio results have not have been analysed

e: 8 EU/ml corresponds to 4 LLOQ (Lower Limit Of Quantification in enzyme-linked immunosorbent assay ELISA).

LLOQ value for anti-PT and anti-FHA is 2 EU/ml

Efficacy and effectiveness in protecting against pertussis

Vaccine efficacy of the acellular pertussis (aP) antigens contained in Hexacima against the most severe WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) is documented in a randomised double-blind study among infants with a 3 dose primary series using a DTaP vaccine in a highly endemic country (Senegal). The need for a toddler booster dose was seen in this study.

The long term capability of the acellular pertussis (aP) antigens contained in Hexacima to reduce pertussis incidence and control pertussis disease in the childhood has been demonstrated in a 10-year national pertussis surveillance on pertussis disease in Sweden with the pentavalent DTaP-IPV/Hib vaccine using a 3, 5, 12 months schedule. Results of long term follow-up demonstrated a dramatic reduction of the pertussis incidence following the second dose regardless of the vaccine used.

Effectiveness in protecting against Hib invasive disease

The vaccine effectiveness against Hib invasive disease of DTaP and Hib combination vaccines (pentavalent and hexavalent including vaccines containing the Hib antigen from Hexacima) has been demonstrated in Germany via an extensive (over five years follow-up period) post-marketing surveillance study. The vaccine effectiveness was of 96.7% for the full primary series, and 98.5% for booster dose (irrespective of priming).

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional repeat dose toxicity and local tolerance studies.

At the injection sites, chronic histological inflammatory changes were observed, that are expected to have a slow recovery.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Trometamol
Saccharose
Essential amino acids including L-phenylalanine
Water for injections.

For adsorbent: see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the container in the outer carton in order to protect from light.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period, Hexacima should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

Hexacima in pre-filled syringes

0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), without needle.

0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), with 1 separate needle.

0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), with 2 separate needles.

Pack size of 1 or 10.

Hexacima in vials

0.5 ml suspension in vial (type I glass) with a stopper (halobutyl).

Pack size of 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hexacima in pre-filled syringes

Prior to administration, the pre-filled syringe should be shaken in order to obtain a homogeneous, whitish, cloudy suspension.

The suspension should be visually inspected prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the pre-filled syringe.

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

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

Hexacima in vials

Prior to administration, the vial should be shaken in order to obtain a homogeneous, whitish, cloudy suspension.

The suspension should be visually inspected prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the vial.

A dose of 0.5 ml is withdrawn using a syringe for injection.

Any unused medicinal 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

8. MARKETING AUTHORISATION NUMBER(S)

Hexacima in pre-filled syringes

EU/1/13/828/002

EU/1/13/828/003

EU/1/13/828/004

EU/1/13/828/005

EU/1/13/828/006
EU/1/13/828/007

Hexacima in vials
EU/1/13/828/001

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2013

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Sanofi Pasteur
1541 avenue Marcel Mérieux
69280 Marcy L'Etoile
France

Sanofi Pasteur
Calle 8, N° 703 (esquina 5)
Parque Industrial Pilar - (1629)
Provincia de Buenos Aires
Argentina

Sanofi Pasteur
Parc Industriel d'Incarville
27100 Val de Reuil
France

Name and address of the manufacturer(s) responsible for batch release

Sanofi Pasteur
Parc Industriel d'Incarville
27100 Val de Reuil
France

Sanofi Pasteur
1541 avenue Marcel Mérieux
69280 Marcy L'Etoile
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Hexacima – Carton for pre-filled syringe without needle, with one separate needle, with two separate needles. Pack of 1 or 10.

1. NAME OF THE MEDICINAL PRODUCT

Hexacima suspension for injection in pre-filled syringe

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

DTaP-IPV-HB-Hib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains:

| | |
|---|-------------------|
| • Diphtheria Toxoid | ≥ 20 IU |
| • Tetanus Toxoid | ≥ 40 IU |
| • Bordetella pertussis antigens : Pertussis Toxoid/Filamentous Haemagglutinin | 25/25 µg |
| • Poliovirus (Inactivated) Types 1/2/3 | 40/8/32 DU |
| • Hepatitis B surface antigen | 10 µg |
| • <i>Haemophilus influenzae</i> type b polysaccharide conjugated to Tetanus protein | 12 µg 22-36 µg |

3. LIST OF EXCIPIENTS

Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Trometamol
Saccharose
Essential amino acids including L-phenylalanine
Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in pre-filled syringe.
1 pre-filled syringe (0.5 ml) without needle
10 pre-filled syringes (0.5 ml) without needle
1 pre-filled syringe (0.5 ml) with 1 needle
10 pre-filled syringes (0.5 ml) with 10 needles
1 pre-filled syringe (0.5 ml) with 2 needles
10 pre-filled syringes (0.5 ml) with 20 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Shake before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vaccine in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Pasteur, 14 Espace Henry Vallée, 69007 Lyon, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/828/002
EU/1/13/828/003
EU/1/13/828/004
EU/1/13/828/005
EU/1/13/828/006
EU/1/13/828/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Hexacima – Carton for vial. Pack of 10.

1. NAME OF THE MEDICINAL PRODUCT

Hexacima suspension for injection

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

DTaP-IPV-HB-Hib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 ml) contains:

- | | |
|---|-------------------|
| • Diphtheria Toxoid | ≥ 20 IU |
| • Tetanus Toxoid | ≥ 40 IU |
| • Bordetella pertussis antigens : Pertussis Toxoid/Filamentous Haemagglutinin | 25/25 µg |
| • Poliovirus (Inactivated) Types 1/2/3 | 40/8/32 DU |
| • Hepatitis B surface antigen | 10 µg |
| • <i>Haemophilus influenzae</i> type b polysaccharide conjugated to Tetanus protein | 12 µg 22-36 µg |

3. LIST OF EXCIPIENTS

Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Trometamol
Saccharose
Essential amino acids including L-phenylalanine
Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

10 vials (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Shake before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the vaccine in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Pasteur, 14 Espace Henry Vallée, 69007 Lyon, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/828/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label – Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hexacima suspension for injection
DTaP-IPV-HB-Hib
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

Sanofi Pasteur

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label – Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hexacima suspension for injection
DTaP-IPV-HB-Hib
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

Sanofi Pasteur

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hexacima suspension for injection in pre-filled syringe

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is vaccinated because it contains important information for him/her.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hexacima is and what it is used for
2. What you need to know before Hexacima is given to your child
3. How to use Hexacima
4. Possible side effects
5. How to store Hexacima
6. Contents of the pack and other information

1. What Hexacima is and what it is used for

Hexacima (DTaP-IPV-HB-Hib) is a vaccine used to protect against infectious diseases.

Hexacima helps to protect against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and serious diseases caused by *Haemophilus influenzae* type b. Hexacima is given to children from six weeks of age.

The vaccine works by causing the body to produce its own protection (antibodies) against the bacteria and viruses that cause these different infections:

- Diphtheria is an infectious disease that usually first affects the throat. In the throat, the infection causes pain and swelling which can lead to suffocation. The bacteria that cause the disease also make a toxin (poison) that can damage the heart, kidneys and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacteria entering a deep wound. The bacteria make a toxin (poison) that causes spasms of the muscles, leading to inability to breathe and the possibility of suffocation.
- Pertussis (often called whooping cough) is a highly infectious illness that affects the airways. It causes severe coughing that may lead to problems with breathing. The coughing often has a “whooping” sound. The cough may last for one to two months or longer. Whooping cough can also cause ear infections, chest infections (bronchitis) which may last a long time, lung infections (pneumonia), fits, brain damage and even death.
- Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). In some people, the virus can stay in the body for a long time, and can eventually lead to serious liver problems, including liver cancer.
- Poliomyelitis (often just called polio) is caused by viruses that affect the nerves. It can lead to paralysis or muscle weakness most commonly of the legs. Paralysis of the muscles that control breathing and swallowing can be fatal.

- *Haemophilus influenzae* type b infections (often just called Hib) are serious bacterial infections and can cause meningitis (inflammation of the outer covering of the brain), which can lead to brain damage, deafness, epilepsy, or partial blindness. Infection can also cause inflammation and swelling of the throat, leading to difficulties in swallowing and breathing, and infection can affect other parts of the body such as the blood, lungs, skin, bones, and joints.

Important information about the protection provided

- Hexacima will only help to prevent these diseases if they are caused by the bacteria or viruses targeted by the vaccine. Your child could get diseases with similar symptoms if they are caused by other bacteria or viruses.
- The vaccine does not contain any live bacteria or viruses and it cannot cause any of the infectious diseases against which it protects.
- This vaccine does not protect against infections caused by other types of *Haemophilus influenzae* nor against meningitis due to other micro-organisms.
- Hexacima will not protect against hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E.
- Because symptoms of hepatitis B take a long time to develop, it is possible for unrecognised hepatitis B infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B infection in such cases.
- As with any vaccine, Hexacima may not protect 100% of children who receive the vaccine.

2. What you need to know before Hexacima is given to your child

To make sure that Hexacima is suitable for your child, it is important to talk to your doctor or nurse if any of the points below apply to your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not use Hexacima if your child:

- has had respiratory disorder or swelling of the face (anaphylactic reaction) after administration of Hexacima.
- has had an allergic reaction
 - to the active substances,
 - to any of the excipients listed in section 6,
 - to glutaraldehyde, formaldehyde, neomycin, streptomycin or polymyxin B, as these substances are used during the manufacturing process.
 - after previous administration of Hexacima or any other diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines.
- suffered from a severe reaction affecting the brain (encephalopathy) within 7 days of a prior dose of a pertussis vaccine (acellular or whole cell pertussis).
- has an uncontrolled condition or severe illness affecting the brain and nervous system (uncontrolled neurologic disorder) or uncontrolled epilepsy.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before vaccination if your child:

- has a moderate or high temperature or an acute illness (e.g. fever, sore throat, cough, cold or flu). Vaccination with Hexacima may need to be delayed until your child is better.
- has had any of the following events after receiving a pertussis vaccine, as the decision to give further doses of pertussis containing vaccine will need to be carefully considered:
 - fever of 40°C or above within 48 hours not due to another identifiable cause.
 - collapse or shock-like state with hypotonic-hyporesponsive episode (drop in energy) within 48 hours of vaccination.

- persistent, inconsolable crying lasting 3 hours or more, occurring within 48 hours of vaccination.
- fits (convulsions) with or without fever, occurring within 3 days of vaccination.
- previously had Guillain-Barré syndrome (temporary inflammation of nerves causing pain, paralysis and sensitivity disorders) or brachial neuritis (severe pain and decreased mobility of arm and shoulder) after being given a vaccine containing tetanus toxoid (an inactivated form of tetanus toxin). In this case, the decision to give any further vaccine containing tetanus toxoid should be evaluated by your doctor.
- is having a treatment that suppresses her/his immune system (the body's natural defenses) or has any disease that causes the weakness of the immune system. In these cases the immune response to the vaccine may be decreased. It is normally recommended to wait until the end of the treatment or disease before vaccinating. However children with long standing problems with their immune system such as HIV infection (AIDS) may still be given Hexacima but the protection may not be as good as in children whose immune system is healthy.
- suffers from an acute or chronic illness including chronic renal insufficiency or failure (inability of the kidneys to work properly).
- suffers from any undiagnosed illness of the brain or epilepsy which is not controlled. Your doctor will assess the potential benefit offered by vaccination.
- has any problems with the blood that cause easy bruising or bleeding for a long time after minor cuts. Your doctor will advise you whether your child should have Hexacima.

Other medicines or vaccines and Hexacima

Tell your doctor or nurse if your child is taking, has recently taken or might take any other medicines or vaccines.

Hexacima can be given at the same time as other vaccines such as pneumococcal vaccines, measles-mumps-rubella vaccines, rotavirus vaccines or meningococcal vaccines.

When given at the same time with other vaccines, Hexacima will be given at different injection sites.

3. How to use Hexacima

Hexacima will be given to your child by a doctor or nurse trained in the use of vaccines and who are equipped to deal with any uncommon severe allergic reaction to the injection (see section 4 Possible side effects).

Hexacima is given as an injection into a muscle (intramuscular route IM) in the upper part of your child's leg or upper arm. The vaccine will never be given into a blood vessel or into or under the skin.

The recommended dose is as follows:

First course of vaccination (primary vaccination)

Your child will receive either two injections given at an interval of two months or three injections given at an interval of one to two months (at least four weeks apart). This vaccine should be used according to the local vaccination programme.

Additional injections (booster)

After the first course of injections, your child will receive a booster dose, in accordance with local recommendations, at least 6 months after the last dose of the first course. Your doctor will tell you when this dose should be given.

If you forget one dose of Hexacima

If your child misses a scheduled injection, it is important that you discuss with your doctor or nurse who will decide when to give the missed dose.

It is important to follow the instructions from the doctor or nurse so that your child completes the course of injections. If not, your child may not be fully protected against the diseases.

If you have any further questions on the use of this vaccine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Serious allergic reactions (anaphylactic reaction)

If any of these symptoms occur after leaving the place where your child received his/her injection, you must consult a doctor IMMEDIATELY:

- difficulty in breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- sudden and serious malaise with drop in blood pressure causing dizziness and loss of consciousness, accelerated heart rate associated with respiratory disorders.

When these signs or symptoms (signs or symptoms of anaphylactic reaction) occur they usually develop quickly after the injection is given and while the child is still in the clinic or doctor's surgery.

Serious allergic reactions are a rare possibility (may affect up to 1 in 1,000 people) after receiving this vaccine.

Other side effects

If your child experiences any of the following side effects, please tell your doctor, nurse or pharmacist.

- Very common side effects (may affect more than 1 in 10 people) are:
 - loss of appetite (anorexia)
 - crying
 - sleepiness (somnolence)
 - vomiting
 - pain, redness or swelling at the injection site
 - irritability
 - fever (temperature 38°C or higher)
- Common side effects (may affect up to 1 in 10 people) are:
 - abnormal crying (prolonged crying)
 - diarrhoea
 - injection site hardness (induration)
- Uncommon side effects (may affect up to 1 in 100 people) are:
 - allergic reaction
 - lump (nodule) at the injection site
 - high fever (temperature 39.6°C or higher)
- Rare side effects (may affect up to 1 in 1,000 people) are:
 - rash
 - large reactions at the injection site (larger than 5 cm), including extensive limb swelling from the injection site beyond one or both joints. These reactions start within 24-72 hours after vaccination, may be associated with redness, warmth, tenderness or pain at the injection site, and get better within 3-5 days without the need for treatment.
 - fits (convulsions) with or without fever.
- Very rare side effects (may affect up to 1 in 10,000 people) are:

- episodes when your child goes into a shock-like state or is pale, floppy and unresponsive for a period of time (hypotonic reactions or hypotonic hyporesponsive episodes HHE).

Potential side effects

Other side effects not listed above have been reported occasionally with other diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines and not directly with Hexacima:

- Temporary inflammation of nerves causing pain, paralysis and sensitivity disorders (Guillain-Barré syndrome) and severe pain and decreased mobility of arm and shoulder (brachial neuritis) have been reported after administration of a tetanus containing vaccine.
- Inflammation of several nerves causing sensory disorders or weakness of limbs (polyradiculoneuritis), facial paralysis, visual disturbances, sudden dimming or loss of vision (optic neuritis), inflammatory disease of brain and spinal cord (central nervous system demyelination, multiple sclerosis) have been reported after administration of a hepatitis B antigen containing vaccine.
- Swelling or inflammation of the brain (encephalopathy/encephalitis).
- In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2 - 3 days after vaccination.
- Swelling of one or both feet and lower limbs which may occur along with bluish discoloration of the skin (cyanosis), redness, small areas of bleeding under the skin (transient purpura) and severe crying following vaccination with *Haemophilus influenzae* type b containing vaccines. If this reaction occurs, it is mainly after first injections and within the first few hours following vaccination. All symptoms should disappear completely within 24 hours without need for treatment.

Reporting of side effects

If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hexacima

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the vaccine in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Hexacima contains

The active substances are per dose (0.5 ml)¹:

Diphtheria Toxoid

not less than 20 IU²

Tetanus Toxoid

not less than 40 IU²

Bordetella pertussis antigens

| | |
|--|---------------------------------------|
| Pertussis Toxoid | 25 micrograms |
| Filamentous Haemagglutinin | 25 micrograms |
| Poliovirus (Inactivated) ³ | |
| Type 1 (Mahoney) | 40 D antigen units ⁴ |
| Type 2 (MEF-1) | 8 D antigen units ⁴ |
| Type 3 (Saukett) | 32 D antigen units ⁴ |
| Hepatitis B surface antigen ⁵ | 10 micrograms |
| <i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein | 12 micrograms 22-36 micrograms |

¹ Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al³⁺)

² IU International Unit

³ Produced on Vero cells

⁴ Equivalent antigenic quantity in the vaccine

⁵ Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The other ingredients are:

Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine and water for injections.

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.

What Hexacima looks like and contents of the pack

Hexacima is provided as a suspension for injection in pre-filled syringe (0.5 ml).

Hexacima is available in pack containing 1 or 10 pre-filled syringes without attached needle.

Hexacima is available in pack containing 1 or 10 pre-filled syringes with 1 separate needle.

Hexacima is available in pack containing 1 or 10 pre-filled syringes with 2 separate needles.

Not all pack sizes may be marketed.

After shaking, the normal appearance of the vaccine is a whitish cloudy suspension.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Sanofi Pasteur, 14 Espace Henry Vallée, 69007 Lyon , France

Manufacturer:

Sanofi Pasteur, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France

Sanofi Pasteur, Parc Industriel d'Incarville, 27100 Val de Reuil, France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

| | |
|---|---|
| België/ Belgique /Belgien Sanofi Belgium tel.: +32 2 710.54.00 | Lietuva Sanofi – Aventis Lietuva, UAB Tel.: +370 5 2730967 |
| България Sanofi Bulgaria EOOD Тел.: +359 2 970 53 00 | Luxembourg/Luxemburg Sanofi Belgium tel.: +32 2 710.54.00 |

| | |
|--|---|
| Česká republika Sanofi Pasteur divize. vakcín sanofi-aventis, s.r.o. Tel: +420 233 086 111 | Magyarország sanofi-aventis zrt Tel.: +36 1 505 0055 |
| Danmark sanofi-aventis Denmark A/S Tel: +45 4516 7000 | Malta Cherubino Ltd Tel.: +356 21 343270 |
| Deutschland Sanofi-Aventis Deutschland GmbH Tel.: 0800 54 54 010 Tel. aus dem Ausland: +49 69 305 21 130 | Nederland sanofi-aventis Netherlands B.V. Tel: +31 182 557 755 |
| Eesti Sanofi-Aventis Estonia OÜ Tel.: +372 627 3488 | Norge Sanofi-aventis Norge AS Tel: + 47 67 10 71 00 |
| Ελλάδα BIANEE A.E. Τηλ: +30.210.8009111 | Österreich Sanofi-Aventis GmbH Tel: +43 (1) 80185-0. |
| España sanofi-aventis, S.A. Tel: +34 93 485 94 00 | Polska Sanofi Pasteur Sp. z o.o. Tel.: +48 22 280 05 00 |
| France Sanofi Pasteur Europe Tél: 0800 42 43 46 Appel depuis l'étranger : +33 1 57 63 23 23 | Portugal Sanofi – Produtos Farmacêuticos, Lda. Tel: + 351 21 35 89 400 |
| Hrvatska sanofi-aventis Croatia d.o.o Tel.: +385 1 6003 400 | România Sanofi Romania SRL Tel.: +40(21) 317 31 36 |
| Ireland sanofi-aventis Ireland T/A SANOFI Tel: + 353 (0) 1 4035 600 | Slovenija ALPE s.p. Tel.: +386 (0)1 432 62 38 |
| Ísland Vistor Tel : +354 535 7000 | Slovenská republika sanofi-aventis Pharma Slovakia s.r.o. divízia vakcín Sanofi Pasteur Tel.: +421 2 33 100 100 |
| Italia Sanofi S.p.A. Tel: 800536389 Tel dall'estero: +39 02 39394983 | Suomi/Finland Sanofi Oy Tel: +358 (0) 201 200 300 |
| Κύπρος Γ. Α. Σταμάτης & Σια Λτδ. Τηλ.: +357 – 22 76 62 76 | Sverige Sanofi AB Tel: +46 8-634 50 00 |

| | |
|---|--|
| Latvija Sanofi Aventis Latvia SIA Vakcīnu nodaļa Tel.: +371 67114978 | United Kingdom Sanofi Tel: +44 845 372 7101 |
|---|--|

This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

- For syringes without attached needle, the needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.
- Shake the pre-filled syringe so that the contents become homogeneous.
- Hexacima should not be mixed with other medicinal products.
- Hexacima must be administered intramuscularly. The recommended injection site is preferably the antero-lateral area of the upper thigh and the deltoid muscle in older children (possibly from 15 months of age).
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.

Package leaflet: Information for the user

Hexacima suspension for injection

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is vaccinated because it contains important information for him/her.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hexacima is and what it is used for
2. What you need to know before Hexacima is given to your child
3. How to use Hexacima
4. Possible side effects
5. How to store Hexacima
6. Contents of the pack and other information

1. What Hexacima is and what it is used for

Hexacima (DTaP-IPV-HB-Hib) is a vaccine used to protect against infectious diseases.

Hexacima helps to protect against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and serious diseases caused by *Haemophilus influenzae* type b. Hexacima is given to children from six weeks of age.

The vaccine works by causing the body to produce its own protection (antibodies) against the bacteria and viruses that cause these different infections:

- Diphtheria is an infectious disease that usually first affects the throat. In the throat, the infection causes pain and swelling which can lead to suffocation. The bacteria that cause the disease also make a toxin (poison) that can damage the heart, kidneys and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacteria entering a deep wound. The bacteria make a toxin (poison) that causes spasms of the muscles, leading to inability to breathe and the possibility of suffocation.
- Pertussis (often called whooping cough) is a highly infectious illness that affects the airways. It causes severe coughing that may lead to problems with breathing. The coughing often has a “whooping” sound. The cough may last for one to two months or longer. Whooping cough can also cause ear infections, chest infections (bronchitis) which may last a long time, lung infections (pneumonia), fits, brain damage and even death.
- Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). In some people, the virus can stay in the body for a long time, and can eventually lead to serious liver problems, including liver cancer.
- Poliomyelitis (often just called polio) is caused by viruses that affect the nerves. It can lead to paralysis or muscle weakness most commonly of the legs. Paralysis of the muscles that control breathing and swallowing can be fatal.

- *Haemophilus influenzae* type b infections (often just called Hib) are serious bacterial infections and can cause meningitis (inflammation of the outer covering of the brain), which can lead to brain damage, deafness, epilepsy, or partial blindness. Infection can also cause inflammation and swelling of the throat, leading to difficulties in swallowing and breathing, and infection can affect other parts of the body such as the blood, lungs, skin, bones, and joints.

Important information about the protection provided

- Hexacima will only help to prevent these diseases if they are caused by the bacteria or viruses targeted by the vaccine. Your child could get diseases with similar symptoms if they are caused by other bacteria or viruses.
- The vaccine does not contain any live bacteria or viruses and it cannot cause any of the infectious diseases against which it protects.
- This vaccine does not protect against infections caused by other types of *Haemophilus influenzae* nor against meningitis due to other micro-organisms.
- Hexacima will not protect against hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E.
- Because symptoms of hepatitis B take a long time to develop, it is possible for unrecognised hepatitis B infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B infection in such cases.
- As with any vaccine, Hexacima may not protect 100% of children who receive the vaccine

2. What you need to know before Hexacima is given to your child

To make sure that Hexacima is suitable for your child, it is important to talk to your doctor or nurse if any of the points below apply to your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not use Hexacima if your child:

- has had respiratory disorder or swelling of the face (anaphylactic reaction) after administration of Hexacima
- has had an allergic reaction
 - to the active substances,
 - to any of the excipients listed in section 6,
 - to glutaraldehyde, formaldehyde, neomycin, streptomycin or polymyxin B, as these substances are used during the manufacturing process
 - after previous administration of Hexacima or any other diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines.
- suffered from a severe reaction affecting the brain (encephalopathy) within 7 days of a prior dose of a pertussis vaccine (acellular or whole cell pertussis).
- has an uncontrolled condition or severe illness affecting the brain and nervous system (uncontrolled neurologic disorder) or uncontrolled epilepsy.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before vaccination if your child:

- has a moderate or high temperature or an acute illness (e.g. fever, sore throat, cough, cold or flu). Vaccination with Hexacima may need to be delayed until your child is better.
- has had any of the following events after receiving a pertussis vaccine, as the decision to give further doses of pertussis containing vaccine will need to be carefully considered:
 - fever of 40°C or above within 48 hours not due to another identifiable cause.
 - collapse or shock-like state with hypotonic-hyporesponsive episode (drop in energy) within 48 hours of vaccination.

- persistent, inconsolable crying lasting 3 hours or more, occurring within 48 hours of vaccination.
- fits (convulsions) with or without fever, occurring within 3 days of vaccination.
- previously had Guillain-Barré syndrome (temporary inflammation of nerves causing pain, paralysis and sensitivity disorders) or brachial neuritis (severe pain and decreased mobility of arm and shoulder) after being given a vaccine containing tetanus toxoid (an inactivated form of tetanus toxin). In this case, the decision to give any further vaccine containing tetanus toxoid should be evaluated by your doctor.
- is having a treatment that suppresses her/his immune system (the body's natural defenses) or has any disease that causes the weakness of the immune system. In these cases the immune response to the vaccine may be decreased. It is normally recommended to wait until the end of the treatment or disease before vaccinating. However children with long standing problems with their immune system such as HIV infection (AIDS) may still be given Hexacima but the protection may not be as good as in children whose immune system is healthy.
- suffers from an acute or chronic illness including chronic renal insufficiency or failure (inability of the kidneys to work properly).
- suffers from any undiagnosed illness of the brain or epilepsy which is not controlled. Your doctor will assess the potential benefit offered by vaccination.
- has any problems with the blood that cause easy bruising or bleeding for a long time after minor cuts. Your doctor will advise you whether your child should have Hexacima.

Other medicines or vaccines and Hexacima

Tell your doctor or nurse if your child is taking, has recently taken or might take any other medicines or vaccines.

Hexacima can be given at the same time as other vaccines such as pneumococcal vaccines, measles-mumps-rubella vaccines, rotavirus vaccines or meningococcal vaccines.

When given at the same time with other vaccines, Hexacima will be given at different injection sites.

3. How to use Hexacima

Hexacima will be given to your child by a doctor or nurse trained in the use of vaccines and who are equipped to deal with any uncommon severe allergic reaction to the injection (see section 4 Possible side effects).

Hexacima is given as an injection into a muscle (intramuscular route IM) in the upper part of your child's leg or upper arm. The vaccine will never be given into a blood vessel or into or under the skin.

The recommended dose is as follows:

First course of vaccination (primary vaccination)

Your child will receive either two injections given at an interval of two months or three injections given at an interval of one to two months (at least four weeks apart). This vaccine should be used according to the local vaccination programme.

Additional injections (booster)

After the first course of injections, your child will receive a booster dose, in accordance with local recommendations, at least 6 months after the last dose of the first course. Your doctor will tell you when this dose should be given.

If you forget one dose of Hexacima

If your child misses a scheduled injection, it is important that you discuss with your doctor or nurse who will decide when to give the missed dose.

It is important to follow the instructions from the doctor or nurse that your child completes the course of injections. If not, your child may not be fully protected against the diseases.

If you have any further questions on the use of this vaccine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Serious allergic reactions (anaphylactic reaction)

If any of these symptoms occur after leaving the place where your child received his/her injection, you must consult a doctor IMMEDIATELY:

- difficulty in breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- sudden and serious malaise with drop in blood pressure causing dizziness and loss of consciousness, accelerated heart rate associated with respiratory disorders.

When these signs or symptoms (signs or symptoms of anaphylactic reaction) occur they usually develop quickly after the injection is given and while the child is still in the clinic or doctor's surgery.

Serious allergic reactions are a rare possibility (may affect up to 1 in 1,000 people) after receiving this vaccine.

Other side effects

If your child experiences any of the following side effects, please tell your doctor, nurse or pharmacist.

- Very common side effects (may affect more than 1 in 10 people) are:
 - loss of appetite (anorexia)
 - crying
 - sleepiness (somnolence)
 - vomiting
 - pain, redness or swelling at the injection site
 - irritability
 - fever (temperature 38°C or higher)
- Common side effects (may affect up to 1 in 10 people) are:
 - abnormal crying (prolonged crying)
 - diarrhoea
 - injection site hardness (induration)
- Uncommon side effects (may affect up to 1 in 100 people) are:
 - allergic reaction
 - lump (nodule) at the injection site
 - high fever (temperature 39.6°C or higher)
- Rare side effects (may affect up to 1 in 1,000 people) are:
 - rash
 - large reactions at the injection site (larger than 5 cm), including extensive limb swelling from the injection site beyond one or both joints. These reactions start within 24-72 hours after vaccination, may be associated with redness, warmth, tenderness or pain at the injection site, and get better within 3-5 days without the need for treatment.
 - fits (convulsions) with or without fever
- Very rare side effects (may affect up to 1 in 10,000 people) are:

- episodes when your child goes into a shock-like state or is pale, floppy and unresponsive for a period of time (hypotonic reactions or hypotonic hyporesponsive episodes HHE).

Potential side effects

Other side effects not listed above have been reported occasionally with other diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines and not directly with Hexacima:

- Temporary inflammation of nerves causing pain, paralysis and sensitivity disorders (Guillain-Barré syndrome) and severe pain and decreased mobility of arm and shoulder (brachial neuritis) have been reported after administration of a tetanus containing vaccine.
- Inflammation of several nerves causing sensory disorders or weakness of limbs (polyradiculoneuritis), facial paralysis, visual disturbances, sudden dimming or loss of vision (optic neuritis), inflammatory disease of brain and spinal cord (central nervous system demyelination, multiple sclerosis) have been reported after administration of a hepatitis B antigen containing vaccine.
- Swelling or inflammation of the brain (encephalopathy/encephalitis).
- In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2 - 3 days after vaccination.
- Swelling of one or both feet and lower limbs which may occur along with bluish discoloration of the skin (cyanosis), redness, small areas of bleeding under the skin (transient purpura) and severe crying following vaccination with *Haemophilus influenzae* type b containing vaccines. If this reaction occurs, it is mainly after first injections and within the first few hours following vaccination. All symptoms should disappear completely within 24 hours without need for treatment.

Reporting of side effects

If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hexacima

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the vaccine in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Hexacima contains

The active substances are per dose (0.5 ml)¹:

Diphtheria Toxoid

not less than 20 IU²

Tetanus Toxoid

not less than 40 IU²

Bordetella pertussis antigens

| | |
|--|---------------------------------------|
| Pertussis Toxoid | 25 micrograms |
| Filamentous Haemagglutinin | 25 micrograms |
| Poliovirus (Inactivated) ³ | |
| Type 1 (Mahoney) | 40 D antigen units ⁴ |
| Type 2 (MEF-1) | 8 D antigen units ⁴ |
| Type 3 (Saukett) | 32 D antigen units ⁴ |
| Hepatitis B surface antigen ⁵ | 10 micrograms |
| <i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein | 12 micrograms 22-36 micrograms |

¹ Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al³⁺)

² IU International Unit

³ Produced on Vero cells

⁴ Equivalent antigenic quantity in the vaccine

⁵ Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The other ingredients are:

Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, and water for injections.

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.

What Hexacima looks like and contents of the pack

Hexacima is provided as a suspension for injection in vial (0.5 ml).

Hexacima is available in pack containing 10 vials.

After shaking, the normal appearance of the vaccine is a whitish cloudy suspension.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Sanofi Pasteur, 14 Espace Henry Vallée, 69007 Lyon, France

Manufacturer:

Sanofi Pasteur, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France

Sanofi Pasteur, Parc Industriel d'Incarville, 27100 Val de Reuil, France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

| | |
|---|---|
| België/ Belgique /Belgien Sanofi Belgium tel.: +32 2 710.54.00 | Lietuva Sanofi – Aventis Lietuva, UAB Tel.: +370 5 2730967 |
| България Sanofi Bulgaria EOOD Тел.: +359 2 970 53 00 | Luxembourg/Luxemburg Sanofi Belgium tel.: +32 2 710.54.00 |

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|--|---|
| Česká republika Sanofi Pasteur divize. vakcín sanofi-aventis, s.r.o. Tel: +420 233 086 111 | Magyarország sanofi-aventis zrt Tel.: +36 1 505 0055 |
| Danmark sanofi-aventis Denmark A/S Tel: +45 4516 7000 | Malta Cherubino Ltd Tel.: +356 21 343270 |
| Deutschland Sanofi-Aventis Deutschland GmbH Tel.: 0800 54 54 010 Tel. aus dem Ausland: +49 69 305 21 130 | Nederland sanofi-aventis Netherlands B.V. Tel: +31 182 557 755 |
| Eesti Sanofi-Aventis Estonia OÜ Tel.: +372 627 3488 | Norge Sanofi-aventis Norge AS Tel: + 47 67 10 71 00 |
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This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

- Shake the vial so that the contents become homogeneous.
- A dose of 0.5 ml is withdrawn using a syringe for injection
- Hexacima should not be mixed with other medicinal products.
- Hexacima must be administered intramuscularly. The recommended injection site is preferably the antero-lateral area of the upper thigh and the deltoid muscle in older children (possibly from 15 months of age).
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.