ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 dose[1] (0.5 mL) contains:

Diphtheria Toxoid	not less than 20 IU[2,4] (30 Lf)
Tetanus Toxoid	not less than 40 IU[3,4] (10 Lf)
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[5]	
Type 1 (Mahoney)	29 D-antigen units[6]
Type 2 (MEF-1)	7 D-antigen units[6]
Type 3 (Saukett)	26 D-antigen units[6]
Hepatitis B surface antigen[7]	10 micrograms
Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms 22-36 micrograms

[1] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})
[2] As lower confidence limit (p= 0.95) and not less than 30 IU as mean value
[3] As lower confidence limit (p= 0.95)
[4] Or equivalent activity determined by an immunogenicity evaluation
[5] Cultivated on Vero cells
[6] These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method
[7] 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).

Excipient with known effect
Phenylalanine……85 micrograms
(See section 4.4)

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 2 doses (with an interval of at least 8 weeks) or 3 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 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.
- Hexacima can be used for a mixed hexavalent/pentavalent/hexavalent combined vaccine immunisation schedule 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. As a minimum, 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.

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.

WHO-EPI schedule (6, 10, 14 weeks):
After a WHO-EPI schedule, a booster dose should be given
- As a minimum, a booster dose of polio vaccine should be given
- In absence of hepatitis B vaccine at birth, a hepatitis B vaccine booster must be given
- Hexacima can be considered for the booster

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 sites are the antero-lateral area of the upper thigh (preferred site) or 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

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.

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 medicinal product, 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 ≥40°C within 48 hours of vaccination 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

Immunogenicity data are available for 248 preterm infants. These data support the use of Hexacima in preterm infants. As expected in preterm infants, lower immune response has been observed for some antigens, when indirectly compared to term infants, although seroprotective levels have been achieved (see section 5.1).

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.

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).

Immunogenicity data in HIV-exposed infants (infected and uninfected) showed that Hexacima is immunogenic in the potentially immunodeficient population of HIV-exposed infants whatever their HIV status at birth (see section 5.1). No specific safety concern was observed in this population.

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.

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

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.

Hexacima contains phenylalanine, potassium and sodium

Hexacima contains 85 micrograms phenylalanine in each 0.5-mL dose. Phenylalanine may be harmful for individuals with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Hexacima contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say essentially “potassium-free” and “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Hexacima can be administered simultaneously with a pneumococcal polysaccharide conjugate vaccine, measles, mumps, rubella (MMR) and varicella-containing vaccines, rotavirus vaccines, a meningococcal C conjugate vaccine or a meningococcal group A, C, W-135 and Y conjugate vaccine, or the meningococcal group B vaccine (MenB).

Due to an increased risk of fever when Hexacima was co-administered with MenB vaccine, separate vaccinations can be considered when possible.

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

Hexacima must not be mixed with any 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).

For 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

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.

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions;
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from available data)

Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse Reactions from clinical trials and post marketing surveillance

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	Pyrexia (body temperature ≥38.0°C) Irritability Injection-site pain, injection-site erythema, injection-site swelling
	Common	Injection-site induration
	Uncommon	Pyrexia (body temperature ≥39.6°C) Injection-site nodule
	Rare	Extensive limb swelling†

*Adverse reactions from spontaneous reporting.
†See section Description of selected adverse reactions

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 dose.

Safety in preterm infants

Hexacima has been administered to 143 preterm infants (born after a gestational period of 24 to 36 weeks) who received a 2-dose primary series at 2 and 4 months of age followed by a booster dose at 11 months of age (concomitantly with other routine infant vaccines). The adverse reactions were similar among all groups of preterm infants, including the extremely preterm infants, and reactions were mainly of mild intensity. No vaccine-related case of apnoea was reported in preterm infants in the clinical trial (See section 4.4 for information on apnoea).

Potential adverse events

These are adverse events that 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 below.

Table 2 presents immune responses after primary vaccination (2-dose and 3-dose primary vaccinations, with or without hepatitis B at birth).

Table 3 presents immune responses after booster vaccination.

Table 4 presents peristence of immune response for different schedules.

Additional data are then provided for immune responses in preterm infants (2-dose and 3-dose primary vaccination, including long-term persistence follow-up), immune responses in infants born to women vaccinated with Tdap during pregnancy (including long-term persistence follow-up), and immune responses in HIV-exposed infants.

Immune responses after primary vaccination

Table 2: 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

Immune responses after booster vaccination

Table 3: Seroprotection/Seroconversion rates* one month after booster vaccination with Hexacima

Antibody Thresholds		**Booster vaccination at 11-12 months of age after a two-dose 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 µg/mL were observed in 73.0% of individuals,
- anti-PT vaccine response in 97.9% of individuals,
- 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 4).

Table 4: 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) (≥0.1 IU/mL)	 98.2 75.3	 97 64.4	 100 57.2
Anti-tetanus (≥0.01 IU/mL) (≥0.1 IU/mL)	 100 89.5	 100 82.8	 100 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 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

The persistence of the immune responses against the hepatitis B component of Hexacima was evaluated in infants primed from two different schedules.

For a 2-dose primary infant series at 3 and 5 months of age without hepatitis B at birth, followed by a toddler booster at 11-12 months of age, 53.8% of children were seroprotected (anti-HBsAg ≥10 mIU/mL) at 6 years of age, and 96.7% presented an anamnestic response after a challenge dose with a standalone Hepatitis B vaccine.

For 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, 49.3% of children were seroprotected (anti-HBsAg ≥10 mIU/mL) at 9 years of age, and 92.8% presented an anamnestic response after a challenge dose with a standalone Hepatitis B vaccine.

These data support persisting immune memory induced in infants primed with Hexacima.

Immune responses to Hexacima in preterm infants

2-dose primary series and booster dose

Immune responses to Hexacima antigens were evaluated in 143 preterm infants born between 24 and 36 weeks of gestation, including extremely preterm (<28 weeks), very preterm (28–30 weeks), moderate preterm (31–33 weeks), and late preterm (34–36 weeks), were evaluated following a 2-dose primary vaccination at 2 and 4 months of age and a booster dose at 11 months of age (administered concomitantly with other routine infant vaccines: pneumococcal conjugate, rotavirus, and meningococcal C conjugate).

One month after the booster dose, 100% of subjects were seroprotected against diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL), and poliovirus types 1, 2, and 3 (≥8 [1/dilution]); 94.5% were seroprotected against hepatitis B (≥10 mIU/mL) and 92.3% against Hib invasive disease (≥1 µg/mL). Regarding pertussis, 99.2% and 100% of subjects developed antibodies ≥8 EU/mL against PT and FHA antigens, respectively.

In extremely preterm infants (<28 weeks), 81.0% of subjects were seroprotected against Hib invasive disease (≥1 µg/mL), and responses to other antigens were similar to those achieved by other preterm infants.

3-dose primary series and booster dose

Immune responses to Hexacima antigens in preterm (105) infants (born after a gestation period of 28 to 36 weeks), including 90 infants born to women vaccinated with Tdap vaccine during pregnancy and 15 to women not vaccinated during pregnancy, were evaluated following a 3-dose primary vaccination course at 2, 3, and 4 months of age, and a booster dose at 13 months of age.
One month after primary vaccination, all subjects were seroprotected against diphtheria (≥0.01 IU/mL), tetanus (≥0.01 IU/mL), and poliovirus types 1, 2 and 3 (≥8 (1/dilution)); 89.8% of subjects were seroprotected against hepatitis B (≥10 IU/mL) and 79.4% were seroprotected against Hib invasive diseases (≥0.15 µg/mL).
One month after the booster dose, all subjects were seroprotected against diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL), and poliovirus types 1, 2 and 3 (≥8 (1/dilution)); 94.6% of subjects were seroprotected against hepatitis B (≥10 IU/mL) and 90.6% were seroprotected against Hib invasive diseases (≥1 µg/mL).
Regarding pertussis, one month after primary vaccination 98.7% and 100% of subjects developed antibodies ≥8 EU/mL against PT and FHA antigens, respectively. One month after the booster dose, 98.8% of subjects developed antibodies ≥8 EU/mL against both PT and FHA antigens. Pertussis antibody concentrations increased by 13-fold after primary vaccination and by 6- to 14-fold after the booster dose.

At 5 years of age, among preterm infants (44, including 40 born to women vaccinated with Tdap vaccine during pregnancy) high persistence of immune response against diphtheria, tetanus, poliovirus 1, 2 , 3 , and Hib antigens was demonstrated, comparable to that observed in term infants. Persistence of immune response against hepatitis B and pertussis antigens in preterm infants was lower than the values presented for term infants in Table 4; the clinical relevance of this observation is unknown.

Responses to DTaP-IPV booster dose administered at 5–7 years of age were observed in 96% to 100% of children, confirming persistent immune memory induced by infant vaccination.

Immune responses to Hexacima in infants born to women vaccinated with Tdap during pregnancy

Immune responses to Hexacima antigens in term (109) and preterm (90) infants born to women vaccinated with Tdap vaccine during pregnancy (between 24 and 36 weeks of gestation) were evaluated

following a 3-dose primary vaccination course at 2, 3, and 4 months of age, and a booster dose at 13 (preterm infants) or 15 (term infants) months of age.
One month after primary vaccination, all subjects were seroprotected against diphtheria (≥0.01 IU/mL), tetanus (≥0.01 IU/mL), and poliovirus types 1 and 3 (≥8 (1/dilution)); 97.3% of subjects were seroprotected against poliovirus type 2 (≥8 (1/dilution)); 94.6% of subjects were seroprotected against hepatitis B (≥10 IU/mL) and 88.0% were seroprotected against Hib invasive diseases (≥0.15 µg/mL).
One month after the booster dose, all subjects were seroprotected against diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL), and poliovirus types 1, 2 and 3 (≥8 (1/dilution)); 93.9% of subjects were seroprotected against hepatitis B (≥10 IU/mL) and 94.0% were seroprotected against Hib invasive diseases (≥1 µg/mL).
Regarding pertussis, one month after primary vaccination 99.4% and 100% of subjects developed antibodies ≥8 EU/mL against PT and FHA antigens, respectively. One month after the booster dose, 99.4% of subjects developed antibodies ≥8 EU/mL against both PT and FHA antigens. Pertussis antibody concentrations were increased by 5- to 9-fold after primary vaccination, and by 8- to 19-fold after the booster dose.

At 5 years of age, among infants born to women vaccinated with Tdap vaccine during pregnancy (94, including 54 term and 40 preterm infants) high persistence of immune response against diphtheria, tetanus, poliovirus types 1, 2 , 3, and Hib antigens was demonstrated. Persistence of immune response against hepatitis B and pertussis antigens was lower than the values in Table 4; the clinical relevance of this observation is unknown.

Responses to DTaP-IPV booster dose given at 5–7 years of age were observed in 98.5%-100% of children confirming the persisting immune memory induced by the infant vaccination.

Immune responses to Hexacima in HIV-exposed infants

Immune responses to Hexacima antigens in 51 HIV-exposed infants (9 infected and 42 uninfected) were evaluated following a 3-dose primary vaccination course at 6, 10, and 14 weeks of age, and a booster dose at 15 to 18 months of age.
One month after primary vaccination, all infants were seroprotected against diphtheria (≥0.01 IU/mL), tetanus (≥0.01 IU/mL), poliovirus types 1, 2, and 3 (≥8 (1/dilution), hepatitis B (≥10 IU/mL), and more than 97.6% for Hib invasive diseases (≥0.15 µg/mL).
One month after the booster dose, all subjects were seroprotected against diphtheria (≥0.1 IU/mL), tetanus (≥0.1 IU/mL), poliovirus types 1, 2 and 3 (≥8 (1/dilution), hepatitis B (≥10 IU/mL), and more than 96.6% for Hib invasive diseases (≥1 µg/mL).
Regarding pertussis, one month after primary vaccination, 100% of subjects developed antibodies ≥8 EU/mL against both PT and FHA antigens. One month after the booster dose, 100% of subjects developed antibodies ≥8 EU/mL against both PT and FHA antigens. Seroconversion rates defined as minimum 4-fold increase compared to pre-vaccination level (pre-dose 1) were 100% in the HIV-exposed and infected group for anti-PT and anti-FHA; and 96.6% for anti-PT and 89.7% for anti-FHA in the HIV-exposed and uninfected group.

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 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 the 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
Sucrose
Essential amino acids including L-phenylalanine
Sodium hydroxide, acetic acid or hydrochloric acid (for pH adjustment)
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

4 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 it from the 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 of suspension in pre-filled syringe (type I glass) equipped with a plunger stopper (halobutyl) and a Luer lock adaptor with a tip cap (halobutyl + polypropylene).

Pack of 1 or 10 pre-filled syringe(s) without needle(s).
Pack of 1 or 10 pre-filled syringe(s) with separate needle(s) (stainless steel).
Pack of 1 or 10 pre-filled syringe(s) with separate needle(s) (stainless steel) with safety shield (polycarbonate).

Hexacima in vials

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

Pack size of 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

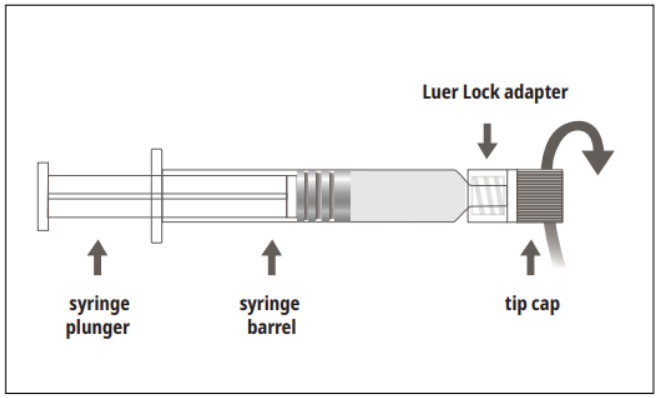
Hexacima in pre-filled syringes

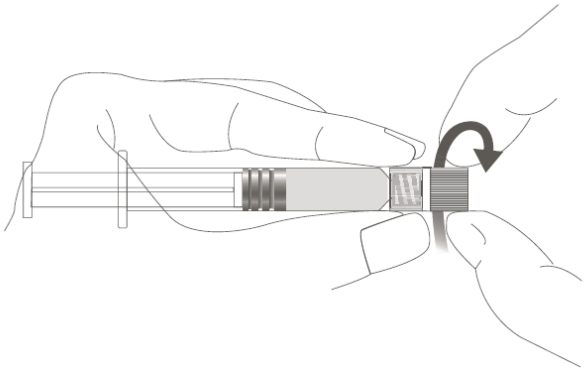
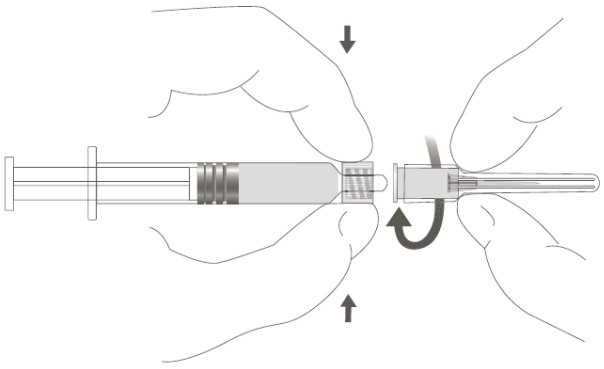
Prior to administration, the pre-filled syringe should be shaken in order to obtain a homogeneous, whitish, cloudy suspension.

Preparation for administration
The syringe with suspension for injection should be visually inspected prior to administration. In the event of any foreign particulate matter, leakage, premature activation of the plunger or faulty tip seal, discard the pre-filled syringe.
The syringe is intended for single use only and must not be reused.

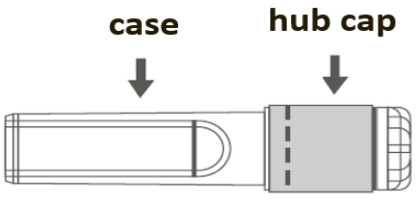
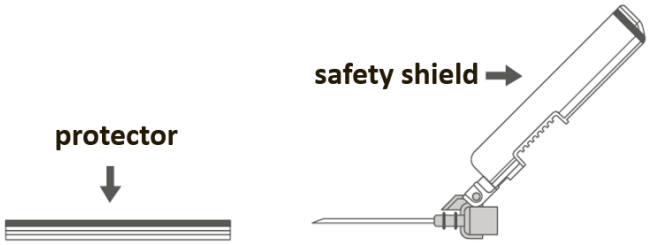
Instructions for use of Luer Lock pre-filled syringe

Picture A: Luer Lock syringe with Rigid Tip Cap



Step 1: Holding the Luer Lock adapter in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it.	
Step 2: To attach the needle to the syringe, gently twist the needle into the Luer Lock adapter of the syringe until slight resistance is felt.	

Instructions for use of safety needle with Luer Lock pre-filled syringe

Picture B: Safety Needle (inside case)	**Picture C: Safety Needle Components (prepared for use)**
	

Follow Step 1 and 2 above to prepare the Luer Lock syringe and needle for attachment.

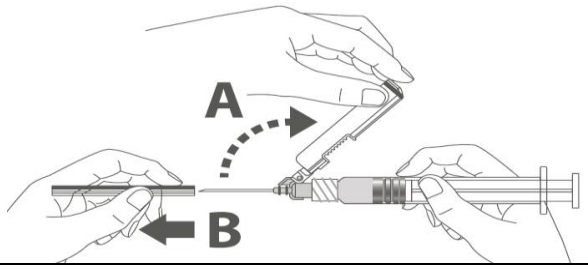
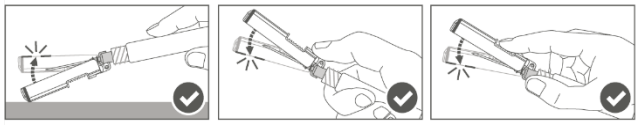
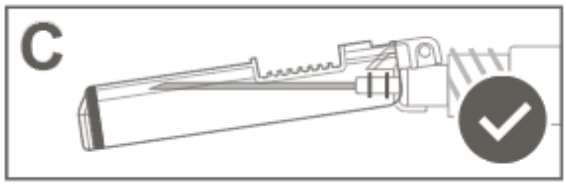
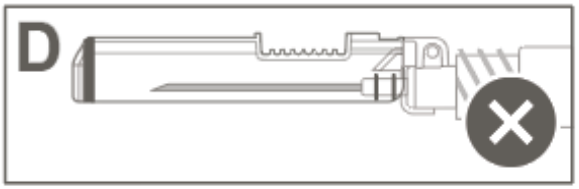
Step 3: Pull the safety needle's case straight off. The needle is covered by the safety shield and protector. **Step 4:** **A:** Move the safety shield away from the needle and toward the syringe barrel to the angle shown. **B:** Pull the protector straight off.	
Step 5: After injection is complete, lock (activate) the safety shield using one of the three (3) **one-handed** techniques illustrated: surface, thumb or finger activation. Note: Activation is verified by an audible and/or tactile "click."	
Step 6: Visually inspect the safety shield activation. The safety shield should be **fully locked (activated)** as shown in Figure C**.** Note: When fully locked (activated), the needle should be at an angle to the safety shield.	

Figure D shows the safety shield is **NOT fully locked (not activated).**	

Caution: Do not attempt to unlock (deactivate) the safety device by forcing the needle out of the safety shield.

Hexacima in vials

The vial is intended for single use only and must not be reused.
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.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, France

8. MARKETING AUTHORISATION NUMBER(S)

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

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
EU/1/13/828/008
EU/1/13/828/009

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2013
Date of latest renewal: 08 January 2018

10. DATE OF REVISION OF THE TEXT

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 Winthrop Industrie
1541 avenue Marcel Mérieux
69280 Marcy L'Etoile
France

Sanofi Health Argentina S.A
Calle 8, N° 703 (esquina 5)
Parque Industrial Pilar (1629)
Provincia de Buenos Aires
Argentina

Sanofi Winthrop Industrie
Voie de L'Institut - Parc Industriel d'Incarville
BP 101, 27100 Val de Reuil
France

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

Sanofi Winthrop Industrie
Voie de L'Institut - Parc Industriel d'Incarville
BP 101, 27100 Val de Reuil
France

Sanofi Winthrop Industrie
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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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[1] (0.5 mL) contains:

• Diphtheria Toxoid	≥20 IU (30 Lf)
• Tetanus Toxoid	≥40 IU (10 Lf)
• Bordetella pertussis antigens: Pertussis Toxoid/Filamentous Haemagglutinin	25/25 µg
• Poliovirus (Inactivated) Types 1/2/3	29/7/26 DU
• Hepatitis B surface antigen	10 µg
• *Haemophilus influenzae* type b polysaccharide	12 µg
conjugated to Tetanus protein	22-36 µg

[1] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})

3. LIST OF EXCIPIENTS

Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Trometamol
Sucrose
Essential amino acids including L-phenylalanine
Sodium hydroxide, acetic acid or hydrochloric acid (for pH adjustment)
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
1 pre-filled syringe (0.5 mL) with 1 safety needle
10 pre-filled syringes (0.5 mL) with 10 safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake before use.
Read the package leaflet before use.
Scan here QR code to be included or visit https://hexacima.info.sanofi

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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vaccine in the outer carton in order to protect it from the 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 Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, 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
EU/1/13/828/008
EU/1/13/828/009

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

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[1] (0.5 mL) contains:

• Diphtheria Toxoid	≥20 IU (30 Lf)
• Tetanus Toxoid	≥40 IU (10 Lf)
• Bordetella pertussis antigens: Pertussis Toxoid/Filamentous Haemagglutinin	25/25 µg
• Poliovirus (Inactivated) Types 1/2/3	29/7/26 DU
• Hepatitis B surface antigen	10 µg
• *Haemophilus influenzae* type b polysaccharide conjugated to Tetanus protein	12 µg 22-36 µg

[1] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})

3. LIST OF EXCIPIENTS

Disodium hydrogen phosphate
Potassium dihydrogen phosphate
Trometamol
Sucrose
Essential amino acids including L-phenylalanine
Sodium hydroxide, acetic acid or hydrochloric acid (for pH adjustment)
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.
Scan here QR code to be included or visit https://hexacima.info.sanofi

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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vaccine in the outer carton in order to protect it from the 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 Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, 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 – 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

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)

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 Hexacima is given
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 that can lead to suffocation. The bacterium that causes the disease also makes a toxin (poison) that can damage the heart, kidneys, and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacterium entering a deep wound. The bacterium makes 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) that 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. The 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 of vaccination 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 that 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.

Fainting can occur following, or even before, any needle injection. Therefore, tell your doctor or nurse your child fainted with a previous injection.

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

Hexacima contains phenylalanine, potassium and sodium

Hexacima contains 85 micrograms phenylalanine in each 0.5-mL dose. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
Hexacima contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say essentially "potassium-free" and "sodium-free".

3. How Hexacima is given

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 your child misses a 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
  - fever (temperature 38°C or higher)
  - irritability
  - pain, redness, or swelling at the injection site
- 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
  - high fever (temperature 39.6°C or higher)
  - lump (nodule) at the injection site
- Rare side effects (may affect up to 1 in 1 000people) 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 it from the 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 IU[2,4] (30 Lf)
Tetanus Toxoid	not less than 40 IU[3,4] (10 Lf)
Bordetella pertussis antigens	

Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[5]	
Type 1 (Mahoney)	29 D-antigen units[6]
Type 2 (MEF-1)	7 D-antigen units[6]
Type 3 (Saukett)	26 D-antigen units[6]
Hepatitis B surface antigen[7]	10 micrograms
Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms 22-36 micrograms

[1] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})
[2] As lower confidence limit (p= 0.95) and not less than 30 IU as mean value
[3] As lower confidence limit (p= 0.95)
[4] Or equivalent activity determined by an immunogenicity evaluation
[5] Cultivated on Vero cells
[6] These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method
[7] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The other ingredients are:
Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, sucrose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid and/or hydrochloric acid (for pH adjustment), 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.
Hexacima is available in pack containing 1 or 10 pre-filled syringes, with 1 separate safety needle.

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 Wintrop Industrie, 82 Avenue Raspail, 94250 Gentilly, France

Manufacturer
Sanofi Winthrop Industrie, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France

Sanofi Winthrop Industrie, Voie de L'Institut - Parc Industriel d'Incarville, BP 101, 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

България
Swixx Biopharma EOOD
Тел.: +359 2 4942 480

Česká republika
Sanofi s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tel: +45 4516 7000

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 54 54 010
Tel. aus dem Ausland: +49 69 305 21 130

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
BIANEΞ A.E.
Τηλ: +30.210.8009111

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tel: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland T/A SANOFI
Tel: + 353 (0) 1 4035 600

Ísland
Vistor ehf.
Tel: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800536389

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tel: +32 2 710.54.00

Magyarország
SANOFI-AVENTIS Zrt
Tel: +36 1 505 0055

Malta
Sanofi S.r.l.
Tel: +39 02 39394 275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
Sanofi-aventis Norge AS
Tel: + 47 67 10 71 00

Österreich
Sanofi-Aventis GmbH
Tel: +43 (1) 80185-0

Polska
Sanofi sp. z o.o.
Tel: +48 22 280 00 00

Portugal
Sanofi – Produtos Farmacêuticos, Lda.
Tel: + 351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 21 317 31 36

Slovenija
Swixx Biopharma d.o.o
Tel: +386 1 2355 100

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Tel: +358 (0) 201 200 300

Κύπρος
C.A. Papaellinas Ltd.
Τηλ.: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 6164 750

Sverige
Sanofi AB
Tel: +46 8-634 50 00

This leaflet was last revised in

Other sources of information

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

Latest approved information on this vaccine is available on the following URL: https://hexacima.info.sanofi or by scanning the QR code with a smartphone:
QR code to be included

The following information is intended for healthcare professionals only:

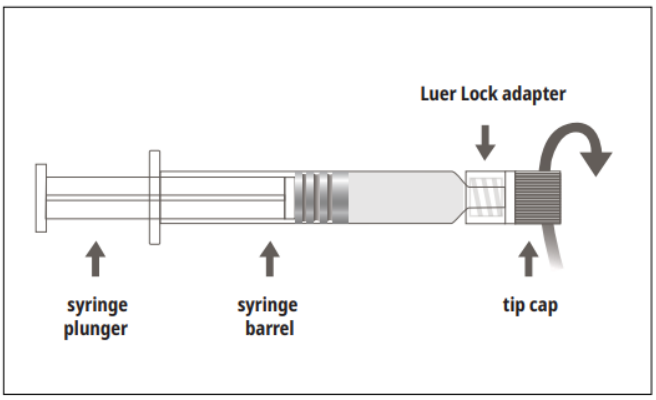
- Shake the pre-filled syringe so that the contents become homogeneous.
- Hexacima should not be mixed with other medicinal products.
- Hexacima must be administered intramuscularly. The recommended injection sites are the antero-lateral area of the upper thigh (preferred site) or the deltoid muscle 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.
- Do not use the pre-filled syringes if the carton is damaged.

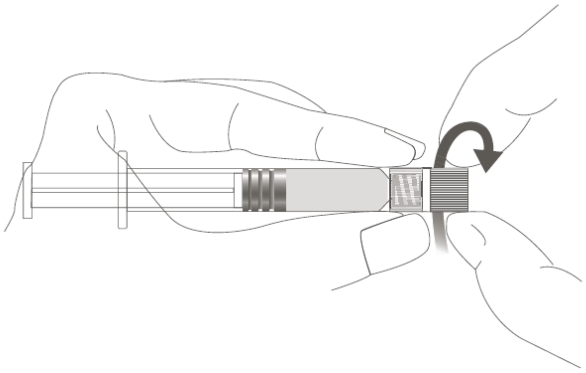
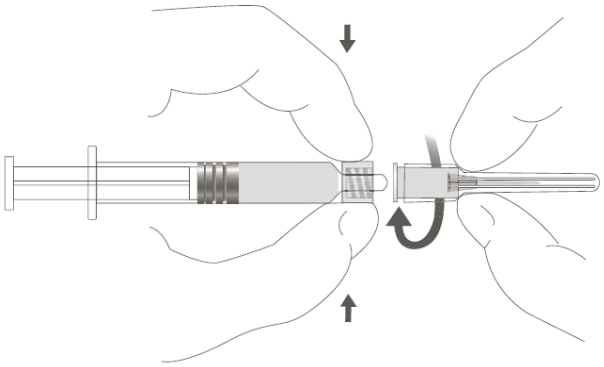
Preparation for administration

The syringe with suspension for injection should be visually inspected prior to administration. In the event of any foreign particulate matter, leakage, premature activation of the plunger or faulty tip seal, discard the pre-filled syringe.
The syringe is intended for single use only and must not be reused.

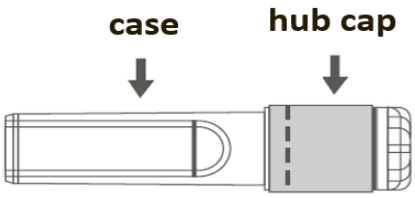
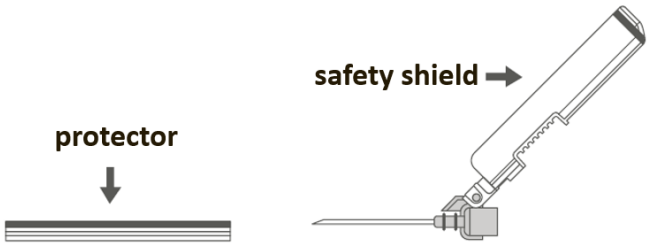
Instructions for use of Luer Lock pre-filled syringe

Picture A: Luer Lock syringe with Rigid Tip Cap



Step 1: Holding the Luer Lock adapter in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it.	
Step 2: To attach the needle to the syringe, gently twist the needle into the Luer Lock adapter of the syringe until slight resistance is felt.	

<Instructions for use of Safety Needle with Luer Lock pre-filled syringe

Picture B: Safety Needle (inside case)	**Picture C: Safety Needle Components (prepared for use)**
	

Follow Step 1 and 2 above to prepare the Luer Lock syringe and needle for attachment.

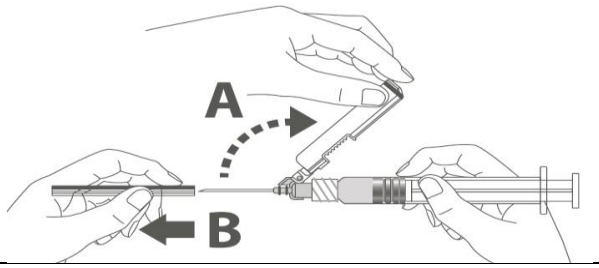
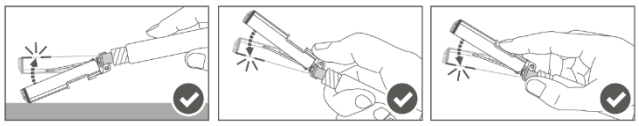
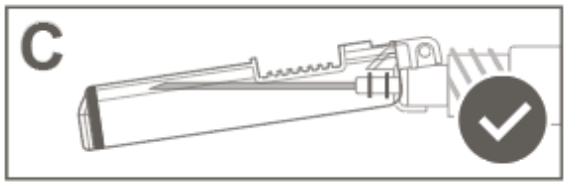
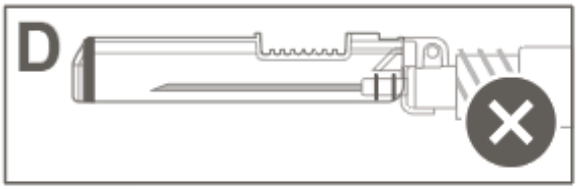
Step 3: Pull the safety needle's case straight off. The needle is covered by the safety shield and protector. **Step 4:** **A:** Move the safety shield away from the needle and toward the syringe barrel to the angle shown. **B:** Pull the protector straight off.	
Step 5: After injection is complete, lock (activate) the safety shield using one of the three (3) **one-handed** techniques illustrated: surface, thumb or finger activation. Note: Activation is verified by an audible and/or tactile "click."	
Step 6: Visually inspect the safety shield activation. The safety shield should be **fully locked (activated)** as shown in Figure C**.** Note: When fully locked (activated), the needle should be at an angle to the safety shield.	

Figure D shows the safety shield is **NOT fully locked (not activated).**	

Caution: Do not attempt to unlock (deactivate) the safety device by forcing the needle out of the safety shield.

>

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

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)

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 Hexacima is given
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 that can lead to suffocation. The bacterium that causes the disease also makes a toxin (poison) that can damage the heart, kidneys, and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacterium entering a deep wound. The bacterium makes 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) that 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. The 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 of vaccination 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 that 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.

Fainting can occur following, or even before, any needle injection. Therefore, tell your doctor or nurse your child fainted with a previous injection.

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

Hexacima contains phenylalanine, potassium and sodium

Hexacima contains 85 micrograms phenylalanine in each 0.5-mL dose. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
Hexacima contains less than 1 mmol potassium (39 mg) and less than 1 mmol sodium (23 mg) per dose, that is to say essentially "potassium-free" and "sodium-free".

3. How Hexacima is given

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 your child misses a 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
  - fever (temperature 38°C or higher)
  - irritability
  - pain, redness, or swelling at the injection site
- 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
  - high fever (temperature 39.6°C or higher)
  - lump (nodule) at the injection site
- 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 it from the 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 IU[2,4] (30 Lf)
Tetanus Toxoid	not less than 40 IU[3,4] (10 Lf)
Bordetella pertussis antigens	

Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[5]	
Type 1 (Mahoney)	29 D-antigen units[6]
Type 2 (MEF-1)	7 D-antigen units[6]
Type 3 (Saukett)	26 D-antigen units[6]
Hepatitis B surface antigen[7]	10 micrograms
Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms 22-36 micrograms

[1] Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al^{3+})
[2] As lower confidence limit (p= 0.95) and not less than 30 IU as mean value
[3] As lower confidence limit (p= 0.95)
[4] Or equivalent activity determined by an immunogenicity evaluation
[5] Cultivated on Vero cells
[6] These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method
[7] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The other ingredients are:
Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, sucrose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid and/or hydrochloric acid (for pH adjustment), 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 Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, France

Manufacturer
Sanofi Winthrop Industrie, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France

Sanofi Winthrop Industrie, Voie de L'Institut - Parc Industriel d'Incarville, BP 101, 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

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
Sanofi s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tel: +45 4516 7000

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 54 54 010
Tel. aus dem Ausland: +49 69 305 21 130

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
BIANEΞ A.E.
Τηλ: +30.210.8009111

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tel: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland T/A SANOFI
Tel: + 353 (0) 1 4035 600

Ísland
Vistor ehf.
Tel: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800536389

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tel: +32 2 710.54.00

Magyarország
SANOFI-AVENTIS Zrt
Tel: +36 1 505 0055

Malta
Sanofi S.r.l.
Tel: +39 02 39394 275

Nederland
Sanofi B.V.Tel: +31 20 245 4000

Norge
Sanofi-aventis Norge AS
Tel: + 47 67 10 71 00

Österreich
Sanofi-Aventis GmbH
Tel: +43 (1) 80185-0

Polska
Sanofi sp. z o.o.
Tel: +48 22 280 00 00

Portugal
Sanofi – Produtos Farmacêuticos, Lda.
Tel: + 351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 21 317 31 36

Slovenija
Swixx Biopharma d.o.o
Tel: +386 1 2355 100

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Tel: +358 (0) 201 200 300

Κύπρος
C.A. Papaellinas Ltd.
Τηλ.: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 6164 750

Sverige
Sanofi AB
Tel: +46 8-634 50 00

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Other sources of information

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

Latest approved information on this vaccine is available on the following URL: https://hexacima.info.sanofi or by scanning the QR code with a smartphone:
QR code to be included

The following information is intended for healthcare professionals only:

- The vial is intended for single use only and must not be reused.
- 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 sites are the antero-lateral area of the upper thigh (preferred site) or 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.
- Do not use the vials if the carton is damaged.

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