

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hexaxim suspension for injection

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose¹ (0.5 mL) contains:

Diphtheria Toxoid	not less than 20 IU ^{2,4} (30 Lf)
Tetanus Toxoid	not less than 40 IU ^{3,4} (10 Lf)
<i>Bordetella pertussis</i> antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated) ⁵	
Type 1 (Mahoney)	40 D-antigen units ⁶
Type 2 (MEF-1)	8 D-antigen units ⁶
Type 3 (Saukett)	32 D-antigen units ⁶
Hepatitis B surface antigen ⁷	10 micrograms
<i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms 22-36 micrograms

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

² As lower confidence limit (p= 0.95) 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 Produced on Vero cells

⁶ Or equivalent antigenic quantity determined by a 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.

Hexaxim is a whitish, cloudy suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hexaxim (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;

- Hexaxim 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.
- Hexaxim 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 Hexaxim, a booster dose must be given.

After a 3-dose primary vaccination with Hexaxim, 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. Hexaxim can be considered for the booster.

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

Hexaxim 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
- Hexaxim can be considered for the booster

Other paediatric population

The safety and efficacy of Hexaxim 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 Hexaxim.

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 Hexaxim or a vaccine containing the same components or constituents.

Vaccination with Hexaxim 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.

Hexaxim 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.

Hexaxim 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.

Hexaxim 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 Hexaxim 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 $\geq 40^{\circ}\text{C}$ 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 Hexaxim. 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 105 preterm infants. These data support the use of Hexaxim 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). No safety data were collected in preterm infants (born ≤ 37 weeks of gestation) in clinical trials.

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 Hexaxim 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.

Hexaxim contains phenylalanine, potassium and sodium

Hexaxim 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.

Hexaxim 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

Hexaxim 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, as no clinically relevant interference in the antibody response to each of the antigens has been shown.

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

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

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

Interference with laboratory testing: see section 4.4.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

a- Summary of the safety profile

In clinical studies in individuals who received Hexaxim, 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 Hexaxim in children over 24 months of age has not been studied in clinical trials.

b- Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from available data)

Table 1: Adverse Reactions from clinical trials and 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	Injection-site pain, injection-site erythema, injection-site swelling Irritability Pyrexia (body temperature $\geq 38.0^{\circ}\text{C}$)
	Common	Injection-site induration
	Uncommon	Injection-site nodule Pyrexia (body temperature $\geq 39.6^{\circ}\text{C}$)
	Rare	Extensive limb swelling†

* Adverse reactions from spontaneous reporting.

† See section c

c- Description of selected adverse reactions

Extensive limb swelling: Large injection-site reactions (> 50 mm), including extensive limb swelling from the injection site beyond one or both joints, have been reported in children. These reactions start within 24-72 hours after vaccination, may be associated with erythema, warmth, tenderness or pain at the injection site and resolve spontaneously within 3-5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine, with a greater risk following the 4th dose.

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

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.

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 Hexaxim in children over 24 months of age has not been studied in clinical trials.

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

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

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

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

N = Number of individuals analysed (per protocol set)

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

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

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

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

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

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

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

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 Hexaxim (N=148) at 2, 4, 6 months of age. The immune responses to PRP, PT and FHA antigens one month after 2 doses given at 2 and 4 months of age were similar to those observed one month after a 2-dose priming given at 3 and 5 months of age:

- anti-PRP titers ≥ 0.15 $\mu\text{g/mL}$ were observed in 73.0% of individuals,
- anti-PT vaccine response in 97.9% of individuals,
- anti-FHA vaccine response in 98.6% of individuals.

Persistence of immune response

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

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

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

N = Number of individuals analysed (per protocol set)

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

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

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

d Due to an OPV National Immunisation Days in the country, Polio results have not 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 Hexaxim 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 Hexaxim.

Immune responses to Hexaxim in preterm infants

Immune responses to Hexaximantigens 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 μ g/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 μ g/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.

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

Immune responses to Hexaximantigens 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 μ g/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 μ g/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.

Immune responses to Hexaxim in HIV-exposed infants

Immune responses to Hexaxim 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 μ g/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 μ g/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 Hexaxim 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 Hexaxim 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 Hexaxim) 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

Saccharose

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.

6.5 Nature and contents of container

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

Pack size of 10.

6.6 Special precautions for disposal and other handling

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2013

Date of latest renewal: 8 January 2018

10. DATE OF REVISION OF THE TEXT