SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

HEXAXIM suspension for injection in pre-filled syringe

HEXAXIM suspension for injection in single-dose vial

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 mL adjuvanted dose contains*:	**Component**	**Quantity (per 0,5 ml dose)**
Active substances	Purified diphtheria toxoid	≥ 20 IU[1] (30 Lf)
	Purified tetanus toxoid	≥ 40 IU[2,3] (10 Lf)
	Bordetella pertussis antigens Pertussis toxoid Filamentous haemagglutinin	 25 µg 25 µg
	Inactivated poliomyelitis virus:[4] Type 1 (Mahoney) Type 2 (MEF 1) Type 3 (Saukett)	 D antigen: 40 units[5] D antigen: 8 units[5] D antigen: 32 units[5]
	Hepatitis B surface antigen[6]	10 µg

	Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate), conjugated to tetanus protein [tetanus protein: 22 – 36 µg]	12 µg (expressed as amount of polysaccharide)

* Adsorbed on $Al(OH)_3$

[1] As lower confidence limit (p = 0,95) and not less than 30 IU as mean value

[2] As lower confidence limit (p = 0,95)

[3] Or equivalent activity determined by an immunogenicity evaluation

[4] Produced on Vero cells

[5] Or equivalent antigenic quantity determined by a suitable immunochemical method

[6] Surface antigen of hepatitis B virus produced from recombinant strain of the yeast *Hansenula polymorpha*

Contains sugar (11 mg sucrose per 0,5 mL dose).

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

Excipients with known effect:

HEXAXIM contains phenylalanine, potassium and sodium (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 from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b (such as meningitis, septicaemia, cellulitis, arthritis, epiglottitis, respiratory illness (pneumopathy), osteomyelitis).

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

4.2 Posology and method of administration

Posology

Primary vaccination:

The South African Official Guidelines recommend a three-dose primary vaccination schedule.

The primary vaccination schedule consists of three doses of 0,5 mL (such as 6, 10, 14 weeks; 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) with an interval of at least 4 weeks or two doses of 0,5 mL (such as 3, 5 months) with an interval of at least 8 weeks.

All vaccination schedules including the WHO Expanded Programme 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 six weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

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

Booster vaccination:

A booster dose should be given at least 6 months after the priming dose and in accordance with the official recommendation. At the very least, a dose of Hib must be administered.

After a 3-dose primary vaccination schedule of HEXAXIM (such as 6, 10, 14 weeks; 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months), a booster dose should be given, preferably during the second year of life, at least 6 months after the last priming dose.

After a 2-dose primary vaccination schedule with HEXAXIM at 3 and 5 months, a booster dose must be given.

When hepatitis B vaccine is given at birth, after a 3-dose primary series (i.e. 6, 10, 14 weeks; 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months), HEXAXIM or a pentavalent DTaP-IPV/Hib vaccine can be administered for the booster.

In the absence of hepatitis B vaccination at birth and after a 3-dose EPI schedule (6, 10, 14 weeks), hepatitis B vaccine booster must be given. HEXAXIM can be considered for the booster.

In the absence of hepatitis B vaccination at birth and after a 2-dose or 3-dose schedule at 3 and 5 or 2, 3, 4; or 3, 4, 5; or 2, 4, 6 months, it is preferable to give a hepatitis B vaccine booster dose. HEXAXIM can be considered for the booster.

Paediatric population:

This vaccine may be considered until the age of 5 years.

Method of administration

HEXAXIM should be administered intramuscularly. The recommended injection sites are the antero-lateral aspect of the upper thigh (preferred site) in infants and toddlers or the deltoid muscle in older children (possibly from 15 months of age).

In infants presenting with low body mass and/or low muscle mass (born pre-term or with low body mass conditions) the use of adapted needles (more than 23G and with a reduced length of 16 mm) should be considered to avoid bone injuries while maintaining intra-muscular delivery (see section

4.4).

Do not administer via intravascular route. Ensure that the needle does not penetrate a blood vessel (see section 4.4).

Separate syringes, separate injection sites and preferably separate limbs must be used in case of concomitant administration with other vaccines (see section 4.5).

For instructions on handling, see section 6.6.

4.3 Contraindications

- History of an anaphylactic reaction after a previous administration of HEXAXIM.
- HEXAXIM should not be administered to anyone with a history of allergic reaction (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.
- Encephalopathy of unknown aetiology, occurring within 7 days of administration of a previous dose of any vaccine containing pertussis antigens (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.
- Progressive neurological disorder, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these common conditions until the treatment regimen 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 medicines, the name and the batch number of the

administered product should be clearly recorded.

Protection:

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.

As with any vaccine, vaccination with HEXAXIM may not protect 100 % of susceptible individuals.

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, 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 in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered:

- Temperature of 40 °C or above 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 or more, 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 a 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 immunisation schedule has been completed. Vaccination is usually justified for infants whose primary immunisation schedules are 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 subjects 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 – 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 HEXAXIM have not been studied in the context of genetic polymorphism.

In chronic renal failure subjects, 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).

Some case reports of multiple sclerosis have been reported after administration of hepatitis B vaccine. To date, a causal relationship has not been demonstrated with hepatitis B vaccine.

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.

Special precautions:

Do not administer by intravascular, intradermal or subcutaneous injection.

As with all injectable vaccines, the vaccine must be administered with caution to subjects 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.

Before the injection of any biological, the person responsible for administration must take 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 event following administration of the vaccine. Epinephrine (adrenaline) injection (1:1 000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (e.g. anaphylaxis).

Pre-terms and other small infants (malnourished, small for gestational age, multiple births, etc.) need to be vaccinated at chronological age:

- Only when well.
- If hospitalised, only on discharge from hospital when well.
- Appropriate needle selected.

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 if you have 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 medicines and other forms of interaction

Data on concomitant administration of HEXAXIM with pneumococcal polysaccharide conjugated vaccines have shown no clinically relevant interference in the antibody response to each of the individual antigens.

Data on concomitant administration of HEXAXIM with measles-mumps-rubella (MMR) and varicella-containing vaccines have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a booster vaccination. There may be a clinically relevant interference in the antibody response of HEXAXIM and a varicella vaccine and these vaccines should not be administered at the same time.

Historical data on concomitant administration of rotavirus vaccines have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3-dose primary vaccination.

Data on concomitant administration of HEXAXIM with meningococcal C-TT conjugate vaccine or meningococcal A/C/W-135/Y-TT conjugate vaccine have shown no clinically relevant interference

in the antibody response to each of the antigens.

HEXAXIM must not be mixed with other vaccines or other parenterally administered medicines.

Separate injection sites must be used in case of concomitant administration.

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

4.6 Fertility, pregnancy and lactation

Not applicable. This vaccine is not intended for administration to women of childbearing age.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

The adverse events are ranked under headings of frequency per dose, using the following convention:

Very common: ≥ 1/10 (≥ 10 %)

Common: ≥ 1/100 to < 1/10 (≥ 1 % and < 10 %)

Uncommon: ≥ 1/1 000 to < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 to < 1/1 000 (≥ 0,01 % and < 0,1 %)

Very rare: < 1/10 000 (< 0,01 %)

Not known: Cannot be estimated from available data.

Adverse reactions from clinical trails and reported during 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 disorders	Rare	Rash
General disorders and administration site conditions	Very common	Injection-site pain, injection-site erythema, injection-site swelling Irritability Pyrexia (body temperature ≥ 38,0 °C)
	Common	Injection-site induration
	Uncommon	Injection-site nodule

		Pyrexia (body temperature ≥ 39,6 °C)
	Rare	Extensive limb swelling[#]

* Adverse reactions from spontaneous reporting

[#] See Description of selected adverse reactions below.

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.

Potential adverse events

(i.e. adverse events which 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 is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolve spontaneously without sequelae within 24 hours.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of HEXAXIM is important. It allows continued monitoring of the benefit/risk balance of HEXAXIM. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

None known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 30.1 Antigens.

Pharmacotherapeutic group: Vaccines, Bacterial and viral vaccines combined.

ATC code: J07CA09.

Results obtained in the clinical studies 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		**Three doses**			**Two doses**
		6 – 10 – 14 weeks	**2 – 3 – 4 months**	**2 – 4 – 6 months**	**3 – 5 months**
		N = 123 to 220††	N = 322‡‡	N = 934 to 1 270‡	N = 249†
		%	**%**	**%**	**%**
Anti-diphtheria (≥ 0,01 IU/mL)		97,6	99,7	97,1	99,6
Anti-tetanus (≥ 0,01 IU/mL)		100,0	100,0	100,0	100,0
Anti-PT (Seroconversion¥) (Vaccine response§)		93,6 100,0	88,3 99,4	96,0 99,7	93,4 98,4
Anti-FHA (Seroconversion¥) (Vaccine response§)		93,1 100,0	90,6 99,7	97,0 99,9	92,5 99,6
Anti-HBs (≥ 10 mIU/mL)	With hepatitis B vaccination at birth	99,0	/	99,5	/
	Without hepatitis B vaccination at birth	95,7	96,8	98,8	97,2
Anti-polio type 1		100,0	99,4	99,9	90,8

(≥ 8 (1/dilution))				
Anti-polio type 2 (≥ 8 (1/dilution))	98,5	100,0	100,0	95,0
Anti-polio type 3 (≥ 8 (1/dilution))	100,0	99,7	99,9	96,7
Anti-PRP (≥ 0,15 µg/mL)	95,4	96,2	98,0	71,5

* Generally acceptable 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 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.

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 and 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 2-dose priming given at 3 and 5 months of age: anti-PRP titres ≥ 0,15 µg/mL were observed in 73,0 % of individuals, anti-PT vaccine response in 97,9 % of individuals and anti-FHA vaccine response in 98,6 % of individuals.

Table 2: Seroprotection/seroconversion rates* one month after booster vaccination with HEXAXIM

Antibody thresholds		**Booster vaccination during the second year of life following a three-dose primary course**		**Booster vaccination at 11 – 12 months of age after a two-dose primary course**	
		6 – 10 – 14 weeks	**2 – 3 – 4 months**	**2 – 4 – 6 months**	**3 – 5 months**
		N = 204[††]	N = 178 [‡‡]	N = 177 – 396[‡]	N = 249[†]
		%	**%**	**%**	**%**
Anti-diphtheria (≥ 0,1 IU/mL)		100,0	100,0	97,2	100,0
Anti-tetanus (≥ 0,1 IU/mL)		100,0	100,0	100,0	100,0
Anti-PT (Seroconversion[¥]) (Vaccine response[§])		94,4 100,0	86,0 98,8	96,2 100,0	94,3 98,0
Anti-FHA (Seroconversion[¥]) (Vaccine response[§])		99,4 100,0	94,3 100,0	94,8 100,0	97,6 100,0
Anti-HBs (≥ 10 mIU/mL)	With hepatitis B vaccination at birth	100,0	/	99,7	/
	Without hepatitis B vaccination at birth	98,5	98,9	99,4	96,4

Anti-polio type 1 (≥ 8 (1/dilution))	100,0	98,9	100,0	100,0
Anti-polio type 2 (≥ 8 (1/dilution))	100,0	100,0	100,0	100,0
Anti-polio type 3 (≥ 8 (1/dilution))	100,0	100,0	100,0	99,6
Anti-PRP (≥ 1,0 µg/mL)	98,5	98,9	98,3	93,5

* 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 and 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 titres ≥ 0,15 µg/mL were observed in 73,0 % of individuals, anti-PT vaccine response in 97,9 % of individuals and anti-FHA vaccine response in 98,6 % of individuals.

Persistence of immune response

Studies on long-term persistence of vaccine-induced antibodies following varying infant/toddler primary series and following hepatitis B vaccine given at birth or not have shown maintenance of levels above the recognised 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-FHAe (≥ 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 response to HEXAXIM in preterm infants

Immune responses to HEXAXIM 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 were 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 HEXAXIM antigens in term (119) 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.

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 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 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 long-term capability of the acellular pertussis (aP) antigens contained in HEXAXIM to reduce pertussis incidence and control pertussis disease 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) has been demonstrated in Germany via an extensive (over five years follow-up period) post-marketing surveillance study. The vaccine effectiveness was 96,7 % for the full primary series, and 98,5 % for booster dose (irrespective of priming).

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate

Potassium dihydrogen phosphate

Essential amino acids including L-phenylalanine

Trometamol

Sucrose

Sodium hydroxide (for pH adjustment)

Acetic acid (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, HEXAXIM must not be mixed with other vaccines or medicines.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store in a refrigerator (+2 °C to +8 °C). Stability data indicate that the vaccine components are stable at temperatures up to 25 °C for 72 hours. At the end of this period, HEXAXIM should be used or discarded. These data are intended to guide health care providers in case of temporary temperature excursion only.

Do not freeze.

Shake before use.

Protect from light.

Keep in original packaging until required for use.

6.5 Nature and contents of container

Containers and devices	**Container element**	**Nature**
Syringe (without attached needle or with one or two separate needles)	Syringe	Colourless, transparent type I glass
	Plunger stopper	Grey bromobutyl
	Tip cap	Black chlorobromobutyl

Needle	25 G – 5/8 and 23 G-1	Stainless steel
Vial (no needles supplied with vials)	Vial	Colourless, transparent type I glass
	Stopper with flip-off cap	Grey bromobutyl, light blue aluminium

List of presentations:

Container	**Volume per container**	**Number of doses per container**	**Number of containers per box**
Pre-filled syringe	0,5 mL	1	1 or 10
Vial	0,5 mL	1	1 or 10

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before use, the vaccine 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 vaccine.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

Pre-filled syringes:

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

Vials:

A dose of 0,5 mL is withdrawn using a syringe for injection.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

Name and address of the manufacturer

Sanofl Pasteur SA

Parc Industriel d'Incarville 27100, Val de Reuil, FRANCE

8. REGISTRATION NUMBER

46/30.1/0447

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2013

10. DATE OF REVISION OF THE TEXT

09 September 2024

Zimbabwe PP	2015/18.2/5072
Namibia S2	14/30.2/0015
Botswana S2	BOT1402586