PRODUCT INFORMATION

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

For WHO (based on Hexacima centralised procedure texts)

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	- Addition of a general precaution regarding syncopal reactions. - VVM pictogram updated according to WHO 2020. Text based on EMA CHMP opinion dated 18 February 2021. **Annotated VV-LBL-0207470 / Clean VV-LBL-0207466 (VV-LBL-0005422)** Content for the purpose of the WHO variation "CCDS version 10 pretem", excipient guideline with known effect and editorial changes - Text based on EMA CHMP opinion dated 24 September 2020 (VV-LBL-0005549 - version 84.0) and adapted for International registrations/variations **Annotated VV-LBL-0203585 / Clean VV-LBL-0203591 (VV-LBL-0005422)** Content for the purpose of the WHO variation "CCDS version 9 shelf life extension to 4 years": - Text based on EMA CHMP opinion dated 28 March 2019 (VV-LBL-0005549 - version 82.0) and adapted for International registrations/variations, corresponding to CCDS version 8.0 (SIA variation and addition of pH adjusters highlighted in yellow) already notified to WHO - Text based on EMA CHMP opinion dated 25 June 2020 (VV-LBL-0005549 - version 83.0) and adapted for International registrations/variations, corresponding to CCDS version 9.0 (extension of the shelf life from 3 to 4 years.) **Annotated VV-LBL-0201744 / Clean VV-LBL-0201745 (VV-LBL-0005422)** Content for the purpose of the WHO variation "CCDS version 7 without OOF": - Variation based on EMA CHMP opinion dated 21 April 2017 (RA_0459155 - version 61.0) for addition of a sequential infant primary hexavalent/pentavalent/hexavalent immunization schedule and addition of immune persistence data corresponding to CCDS version 7. - Address set as "Sanofi Pasteur, 14 Espace Henry Vallée, 69007 Lyon, France" as HQ relocation variation is approved by WHO - Renewal date set as 8 January 2018 as the European Commission decision for the renewal of Hexacima is 8 January 2018 - Addition of VDR address in Annex II section A/subsection "Name and address of the manufacturer(s) of the biological active substance(s)" as amended in the renewal PI approved in January 2018. Linked to a variation regarding the Polio antigens manufacturing site previously approved but not included in the PI yet. **RA 1264641 - v4.0 / VV-LBL-0005422 v4.0** **Version 4.0:** correction of the date in the foot-page **Version 3.0:** text based on EMA CHMP opinion dated 21 April 2017 (RA_0459155 - version 61.0_EMA approved) and CHMP Decision dated 8 January 2018 for renewal and HQ relocation (RA_0459155 – version 71.0) *To be noticed: RA_1264641 version 4.0 does not include the OOF claim CHMP approved in April2017 according to CCDS version 7* **Version 2.0:** VVM explanation added in the leaflet, label amended (storage condition) to meet WHO requirement (see ENR 352 1115). **Version 1.0:** text based on EMA CHMP opinion dated 19 Nov 2015 (RA_0459155 - version 42.0_EMA approved / RA_0459155 - version 39.0_submitted) and international registrations/variations text (RA_1212298 version 1.0) under the name of Hexaxim (international name) instead of Hexacima (European name).
Content Gaps between	- **Only vial presentation included**

Hexacima centralised procedure texts and WHO PI	- No OOF claim in SmPC section 6.4 as WHO presentation includes VVM, confirmed by WHO on 6 November 2020. - Temperature (2°C - 8°C) specified in the outer packaging. - Storage conditions and VVM in the label. - Revision dates blanked to avoid any confusion.
Annex III: Grey-shaded text will not appear in the final printed material.	

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 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.

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 ≥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 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

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.

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 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.

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 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 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) (≥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 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 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 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 (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.

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 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 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
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.

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 Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, 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

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

Hexaxim – Carton for vial. Pack of 10.

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)

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.
10 vials (0.5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
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)

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

Hexaxim suspension for injection
Vaccine
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

Store 2°C - 8°C
Do not freeze

VVM7

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hexaxim 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 Hexaxim is and what it is used for

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

Hexaxim helps to protect against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and serious diseases caused by *Haemophilus influenzae* type b. Hexaxim 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

- Hexaxim 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.
- Hexaxim 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, Hexaxim may not protect 100% of children who receive the vaccine.

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

To make sure that Hexaxim 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 Hexaxim if your child:

- has had respiratory disorder or swelling of the face (anaphylactic reaction) after administration of Hexaxim
- 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 Hexaxim 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 Hexaxim 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 Hexaxim, 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 Hexaxim.

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 Hexaxim

Tell your doctor or nurse if your child is taking, has recently taken, or might take any other medicines or vaccines.
Hexaxim 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, Hexaxim will be given at different injection sites.

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".

3. How to use Hexaxim

Hexaxim 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).
Hexaxim 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:

<u>First course of vaccination (primary vaccination)</u>
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.

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

If you forget one dose of Hexaxim

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 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 Hexaxim:

- 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. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hexaxim

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 Hexaxim 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 Hexaxim looks like and contents of the pack

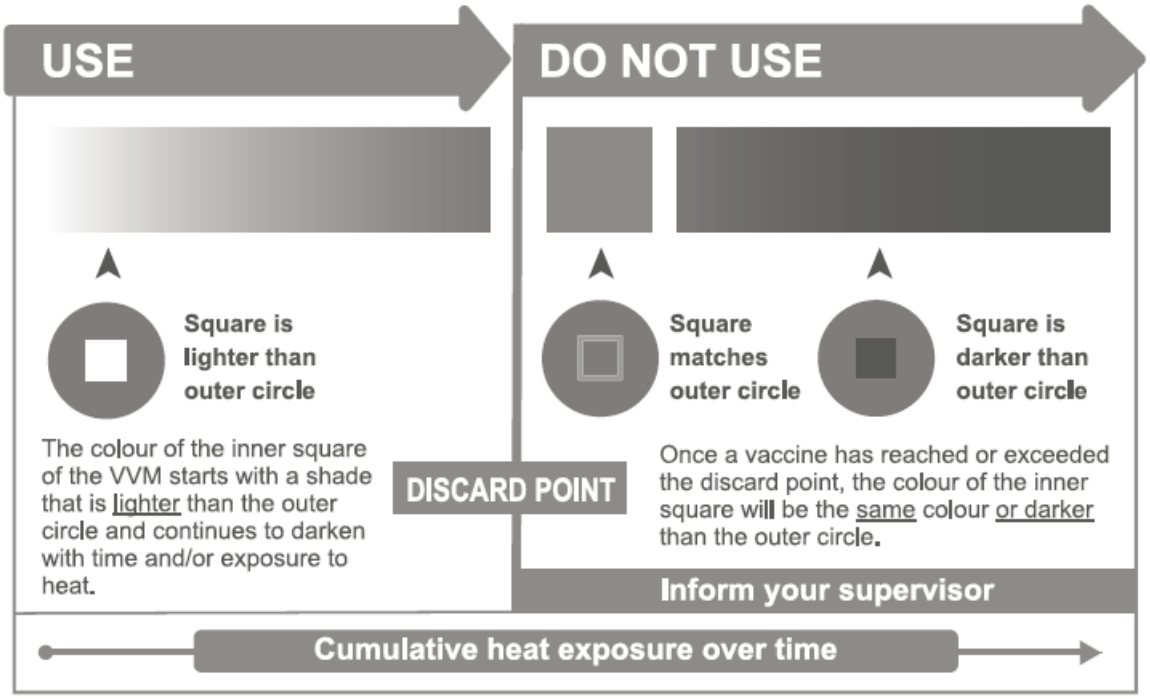
Hexaxim is provided as a suspension for injection in vial (0.5 mL).
Hexaxim is available in pack containing 10 vials.

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

Marketing Authorisation Holder: Sanofi Winthrop Industrie, 82 Avenue Raspail, 94250 Gentilly, France.

This leaflet was last revised in .

The Vaccine Vial Monitors (VVM) are on the label of HEXAXIM vaccine supplied through SANOFI WINTHROP INDUSTRIE. The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the circle or of a darker colour than the circle, then the vial should be discarded.

The following information is intended for healthcare professionals only:

- Shake the vial so that the contents become homogeneous.
- A dose of 0.5 mL is withdrawn using a syringe for injection
- Hexaxim should not be mixed with other medicinal products.
- Hexaxim must be administered intramuscularly. The recommended injection site is preferably the antero-lateral area of the upper thigh and the deltoid muscle in older children (possibly from 15 months of age).
  The intradermal or intravenous routes must not be used. Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.