ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hexaxim, suspension for injection in pre-filled syringe

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose[1] (0.5 ml) contains:

Diphtheria Toxoid	not less than 20 IU[2]
Tetanus Toxoid	not less than 40 IU[2]
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[3]	
Type 1 (Mahoney)	40 D antigen units[4]
Type 2 (MEF-1)	8 D antigen units[4]
Type 3 (Saukett)	32 D antigen units[4]
Hepatitis B surface antigen[5]	10 micrograms
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)
[3] Produced on Vero cells.
[4] Or equivalent antigenic quantity determined by a suitable immunochemical method
[5] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe

Hexaxim is a whitish, cloudy suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hexaxim 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.

4.2 Posology and method of administration

Posology

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

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

Where a dose of hepatitis B vaccine is given at birth, 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.

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. At the very least, a dose of Hib vaccine must be administered.

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

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

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

Hexaxim should be administered intramuscularly. The recommended injection sites are generally the antero-lateral aspect of the upper thigh in infants and toddlers and the deltoid muscle in older children.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, to any pertussis vaccine, or after previous administration of the vaccine or a vaccine containing the same components or constituents.

Generally vaccination must be postponed in cases of moderate or severe febrile and/or acute disease. The presence of a minor infection and/or low-grade fever does not constitute a contraindication.

The vaccination with Hexaxim is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with 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, polio and Hib vaccines.

Uncontrolled neurologic disorder or uncontrolled epilepsy: Pertussis vaccine should not be administered to individuals with these conditions until the treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk.

4.4 Special warnings and precautions for use

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 unrecognized 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

Vaccination should be preceded by a review of the person's medical history (in particular previous vaccinations and possible adverse events). In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of Hexaxim vaccine must be carefully considered.

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 each dose may contain undetectable traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B, caution should be exercised when the vaccine is administered to subjects with hypersensitivity to these substances.

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.

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 $\geq$ 40°C within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination;
- Persistent, inconsolable crying lasting $\geq$ 3 hours, occurring within 48 hours of vaccination;
- Convulsions with or without fever, occurring within 3 days of vaccination.

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. Vaccinees 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 immunization schedule has been completed. Vaccination is usually justified for infants whose primary immunization 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.

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

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

In 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).

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 subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Interference with laboratory testing

Since the Hib capsular polysaccharide antigen is excreted in the urine, a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.8 Undesirable effects

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

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

b- Tabulated list of adverse reactions
The following convention has been used for the classification of adverse reactions;
Very common (≥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)

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

System Organ Class	Frequency	Adverse Events
Immune system disorders	Uncommon	Hypersensitivity reaction
	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Very common	Anorexia (decreased appetite)
Nervous system disorders	Very common	Crying, somnolence
	Common	Abnormal crying (prolonged crying)
	Rare	Convulsions with or without fever*
	Very rare	Hypotonic reactions or hypotonic-hyporesponsive episodes (HHE)
Gastrointestinal disorders	Very common	Vomiting
	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Rare	Rash
General disorders and administration site conditions	Very common	Injection-site pain, injection-site erythema, injection-site swelling Irritability Pyrexia (body temperature ≥ 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 section c

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

d- Potential adverse events (i.e. adverse events which have been reported with other vaccines containing one or more of the components or constituents of 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

Not documented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

* Generally accepted surrogates (PT, FHA) or correlates of protection (other components)
N = Number of individuals analysed (per protocol set)
** 3, 5 months without hepatitis B vaccination at birth (Finland, Sweden)
† 6, 10, 14 weeks with and without hepatitis B vaccination at birth (Republic of South Africa)
†† 2, 3, 4 months without hepatitis B vaccination at birth (Finland)
‡ 2, 4, 6 months without hepatitis B vaccination at birth (Mexico) and with hepatitis B vaccination at birth (Costa Rica and Colombia)
‡‡ Seroconversion: minimum 4-fold increase compared to pre-vaccination level (pre-dose 1)
§ Vaccine response: If pre-vaccination antibody concentration (pre-dose 1) <8 EU/ml, then the post-booster antibody concentration should be ≥8 EU/ml. Otherwise, post-booster antibody concentration should be ≥ pre-immunisation level (pre-dose 1)

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 and anti-FHA vaccine response in 98.6% of individuals.

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 randomized 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 the childhood has been demonstrated in a 10-year national pertussis surveillance on pertussis disease in Sweden with the pentavalent DTaP-IPV/Hib vaccine using a 3, 5, 12 months schedule. Results of long term follow-up demonstrated a dramatic reduction of the pertussis incidence following the second dose regardless of the vaccine used.

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 booster dose (irrespective of priming).

5.2 Pharmacokinetic properties

Not applicable. No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.
For adsorbant: see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), without needle.
0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), with 1 separate needle.
0.5 ml suspension in pre-filled syringe (type I glass) with plunger stopper (halobutyl) and tip cap (halobutyl), with 2 separate needles.

Pack size of 1 or 10 or 20 or 50.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

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

7. SCIENTIFIC OPINION HOLDER

Sanofi Pasteur SA, 2 avenue Pont Pasteur, F-69007 Lyon, France

8. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002495

9. DATE OF FIRST SCIENTIFIC OPINION / RENEWAL OF THE SCIENTIFIC OPINION

Date of first opinion: 21 June 2012

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

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]
Tetanus Toxoid	not less than 40 IU[2]
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[3]	
Type 1 (Mahoney)	40 D antigen units[4]
Type 2 (MEF-1)	8 D antigen units[4]
Type 3 (Saukett)	32 D antigen units[4]
Hepatitis B surface antigen[5]	10 micrograms
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)
[3] Produced on Vero cells.
[4] Or equivalent antigenic quantity determined by a suitable immunochemical method
[5] Produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process (see section 4.4).

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 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.

4.2 Posology and method of administration

Posology

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

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

Where a dose of hepatitis B vaccine is given at birth, 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.

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. At the very least, a dose of Hib vaccine must be administered.

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

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

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

Hexaxim should be administered intramuscularly. The recommended injection sites are generally the antero-lateral aspect of the upper thigh in infants and toddlers and the deltoid muscle in older children.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, to any pertussis vaccine, or after previous administration of the vaccine or a vaccine containing the same components or constituents.

Generally vaccination must be postponed in cases of moderate or severe febrile and/or acute disease. The presence of a minor infection and/or low-grade fever does not constitute a contraindication.

The vaccination with Hexaxim is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with 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, polio and Hib vaccines.

Uncontrolled neurologic disorder or uncontrolled epilepsy: Pertussis vaccine should not be administered to individuals with these conditions until the treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk.

4.4 Special warnings and precautions for use

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 unrecognized 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 Immunization

Vaccination should be preceded by a review of the person's medical history (in particular previous vaccinations and possible adverse events). In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of Hexaxim vaccine must be carefully considered.

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 each dose may contain undetectable traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B, caution should be exercised when the vaccine is administered to subjects with hypersensitivity to these substances.

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.

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 within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination;
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination;
- Convulsions with or without fever, occurring within 3 days of vaccination.

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. Vaccinees 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 immunization schedule has been completed. Vaccination is usually justified for infants whose primary immunization 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.

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

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

In 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).

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 subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Interference with laboratory testing

Since the Hib capsular polysaccharide antigen is excreted in the urine, a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.8 Undesirable effects

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

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

b- Tabulated list of adverse reactions
The following convention has been used for the classification of adverse reactions;
Very common (≥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)

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

System Organ Class	Frequency	Adverse Events
Immune system disorders	Uncommon	Hypersensitivity reaction
	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Very common	Anorexia (decreased appetite)
Nervous system disorders	Very common	Crying, somnolence
	Common	Abnormal crying (prolonged crying)
	Rare	Convulsions with or without fever*
	Very rare	Hypotonic reactions or hypotonic-hyporesponsive episodes (HHE)
Gastrointestinal disorders	Very common	Vomiting
	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Rare	Rash
General disorders and administration site conditions	Very common	Injection-site pain, injection-site erythema, injection-site swelling Irritability Pyrexia (body temperature ≥ 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 section c

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

d- Potential adverse events (i.e. adverse events which have been reported with other vaccines containing one or more of the components or constituents of 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

Not documented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: 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 doses primary course	Booster vaccination during the second year of life following a three dose primary course		
		3-5 Months	6-10-14 Weeks	2-3-4 Months	2-4-6 Months
		N=249**	N=204†	N=178††	N=177 to 396‡
		%	%	%	%
Anti-diphtheria (≥ 0.1 IU/ml)		100.0	100.0	100.0	97.2
Anti-tetanus (≥ 0.1 IU/ml)		100.0	100.0	100.0	100.0
Anti-PT					
(Seroconversion‡‡)		94.3	94.4	86.0	96.2
(Vaccine response§)		98.0	100.0	98.8	100.0
Anti-FHA					
(Seroconversion‡‡)		97.6	99.4	94.3	98.4
(Vaccine response§)		100.0	100.0	100.0	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)

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 and anti-FHA vaccine response in 98.6% of individuals.

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 randomized 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 the childhood has been demonstrated in a 10-year national pertussis surveillance on pertussis disease in Sweden with the pentavalent DTaP-IPV/Hib vaccine using a 3, 5, 12 months schedule. Results of long term follow-up demonstrated a dramatic reduction of the pertussis incidence following the second dose regardless of the vaccine used.

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 booster dose (irrespective of priming).

5.2 Pharmacokinetic properties

Not applicable. No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.
For adsorbant: see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

Pack size of 1 or 10 or 20 or 50.
Not all pack sizes may be marketed.

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. SCIENTIFIC OPINION HOLDER

Sanofi Pasteur SA, 2 avenue Pont Pasteur, F-69007 Lyon, France

8. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002495

9. DATE OF FIRST SCIENTIFIC OPINION / RENEWAL OF THE SCIENTIFIC OPINION

Date of first opinion: 21 June 2012

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. RECOMMENDATIONS REGARDING SUPPLY AND USE

C. OTHER RECOMMENDATIONS AND REQUIREMENTS OF THE SCIENTFIC OPINION HOLDER

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

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

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

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

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

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

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

B. RECOMMENDATIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER RECOMMENDATIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION HOLDER

Pharmacovigilance system
The Scientific Opinion Holder must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Scientific Opinion Application is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The Scientific Opinion Holder shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the Risk Management Plan presented in Module 1.8.2. of the Scientific Opinion Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted.
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the medicinal product should follow the standard requirements until otherwise agreed by the CHMP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Syringe Presentation

1. NAME OF THE MEDICINAL PRODUCT

Hexaxim, suspension for injection in pre-filled syringe

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose[1] (0.5 ml) contains:

Diphtheria Toxoid	not less than 20 IU
Tetanus Toxoid	not less than 40 IU
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[2]	
Type 1 (Mahoney)	40 D antigen units
Type 2 (MEF-1)	8 D antigen units
Type 3 (Saukett)	32 D antigen units
Hepatitis B surface antigen[2]	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] For detailed information, see leaflet.

3. LIST OF EXCIPIENTS

Excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

0.5 ml – pack size of 1 pre-filled syringe without needle

0.5 ml – pack size of 10 pre-filled syringes without needle

0.5 ml – pack size of 20 pre-filled syringes without needle

0.5 ml – pack size of 50 pre-filled syringes without needle

0.5 ml – pack size of 1 pre-filled syringe with 1 separate needle

0.5 ml – pack size of 10 pre-filled syringes with 10 separate needles

0.5 ml – pack size of 20 pre-filled syringes with 20 separate needles

0.5 ml – pack size of 50 pre-filled syringes with 50 separate needles

0.5 ml – pack size of 1 pre-filled syringe with 2 separate needles

0.5 ml – pack size of 10 pre-filled syringes with 20 separate needles

0.5 ml – pack size of 20 pre-filled syringes with 40 separate needles

0.5 ml – pack size of 50 pre-filled syringes with 100 separate needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular injection only.
Shake before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Sanofi Pasteur SA, 2 avenue Pont Pasteur, 69007 Lyon, France

12. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002495

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Vial Presentation

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. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose[1] (0.5 ml) contains:

Diphtheria Toxoid	not less than 20 IU
Tetanus Toxoid	not less than 40 IU
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[2]	
Type 1 (Mahoney)	40 D antigen units
Type 2 (MEF-1)	8 D antigen units
Type 3 (Saukett)	32 D antigen units
Hepatitis B surface antigen[2]	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] For detailed information, see leaflet.

3. LIST OF EXCIPIENTS

Excipients: disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

0.5 ml – pack size of 1 vial

0.5 ml – pack size of 10 vials

0.5 ml – pack size of 20 vials

0.5 ml – pack size of 50 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular injection only.
Shake before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Sanofi Pasteur SA, 2 avenue Pont Pasteur, 69007 Lyon, France

12. SCIENTIFIC OPINION NUMBER(S)

EMEA/H/W/002495

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{NATURE/TYPE}

Not relevant

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE SCIENTIFIC OPINION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label – Syringe Presentation

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

Hexaxim, suspension for injection
DTaP-IPV-HB-Hib vaccine
IM

2. METHOD OF ADMINISTRATION

Shake before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose = 0.5 ml

6. OTHER

Sanofi Pasteur SA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label – Vial Presentation

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

Hexaxim, suspension for injection
DTaP-IPV-HB-Hib vaccine
IM

2. METHOD OF ADMINISTRATION

Shake before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose = 0.5 ml

6. OTHER

Sanofi Pasteur SA

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Hexaxim, suspension for injection in pre-filled syringe

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

Read all of this leaflet carefully before your child is vaccinated because it contains important information for him/her.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them.
- 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.

What is in this leaflet:

1. What Hexaxim is and what it is used for

Hexaxim is a vaccine. Vaccines are 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 which can lead to suffocation. The bacteria that cause the disease also make a toxin (poison) that can damage the heart, kidneys and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacteria entering a deep wound. The bacteria make a toxin (poison) that causes spasms of the muscles, leading to inability to breathe and the possibility of suffocation.
- Pertussis (often called whooping cough) is a bacterial infection of the airways that can occur at any age but mostly affects infants and young children. Increasingly severe coughing spells that can last for several weeks are a characteristic of the disease. Coughing spells may be followed by a whooping noise.
- Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people.
- 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), infections of the blood, lungs, inflammation of the tissue under the skin, inflammation of the joints and bones and inflammation of part of the back of the throat, causing difficulty in swallowing and breathing.

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 or by other liver pathogens.
- Because of the long incubation period of hepatitis B, it is possible for unrecognized 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 an allergic reaction
  - to the active substances,
  - to any of the excipients listed in section 6,
  - to any pertussis vaccine (any vaccine that protects against whooping cough),
  - after previous administration of the vaccine or to any vaccine containing the same components or constituents.
- 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.
- suffered from encephalopathy (cerebral lesions) within 7 days of a previous dose of a pertussis vaccine (acellular or whole cell pertussis).
- has an uncontrolled condition or severe illness affecting the brain (uncontrolled neurologic disorder) and nervous system or uncontrolled epilepsy.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before vaccination if your child:
- is allergic to glutaraldehyde, formaldehyde, neomycin, streptomycin or polymyxin B, as these substances are used during the manufacturing process.
- if any of the following events are known to have occurred after receiving any vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered:
  - Fever of 40°C or above within 48 hours not due to another identifiable cause.
  - Collapse or shock-like state with hypotonic-hyporesponsive episode (drop in energy) within 48 hours of vaccination.
  - Persistent, inconsolable crying lasting 3 hours or more, occurring within 48 hours of vaccination.
  - Convulsions with or without fever, occurring within 3 days of vaccination.
- presented Guillain-Barré syndrome (abnormal sensitivity, paralysis) or brachial neuritis (paralysis, diffuse pain in the arm and shoulder) following receipt of a prior vaccine containing tetanus toxoid (vaccine against tetanus), the decision to give any further vaccine containing tetanus toxoid should be evaluated by your doctor.

- follows a treatment that suppresses her/his immune defenses or if your child presents with immunodeficiency: in these cases the immune response to the vaccine may be decreased. It is then recommended to wait until the end of the treatment or disease before vaccinating. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.
- suffers from an acute or chronic illness including chronic renal insufficiency (or failure).
- suffers from any undiagnosed illness of the brain or epilepsy which is not controlled. Your doctor will assess the potential benefit offered by vaccination.
- has any problems with the blood that cause easy bruising or bleeding for a long time after minor cuts. Your doctor will advise you whether your child should have Hexaxim.

Other medicines or vaccines and Hexaxim

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

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

Your doctor will give the injections at different sites and will use separate syringes and needles for each injection.

Pregnancy, breast-feeding and fertility

Not applicable.

Driving and using machines

Not relevant.

3. How to use Hexaxim

The vaccination should be given by medical or healthcare professionals who are trained in the use of vaccines and who are equipped to deal with any uncommon severe allergic reaction to the injection. Please refer to section 4.
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 should never be given into a blood vessel or into or under the skin.

Always use this vaccine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

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 primary vaccination when indicated by the local vaccination schedule, your child should receive a booster dose, in accordance with local recommendations, at least 6 months after the last dose of the primary vaccination. Your doctor will tell you when this dose should be given.

If you forget one dose of Hexaxim

If you miss a scheduled injection, your doctor will decide when to give the missed dose.
Make sure your child finishes the complete vaccination course. If not, your child may not be fully protected against the diseases.

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

4. Possible side effects

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

Serious allergic reactions (anaphylactic reaction)

If any of these symptoms occur after leaving the place where your child received his/her injection, you must consult a doctor IMMEDIATELY:
- difficulty in breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- sudden and serious malaise with drop in blood pressure causing dizziness and loss of consciousness, accelerated heart rate associated with respiratory disorders.

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

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

Other side effects

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

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

Potential side effects

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

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

6. Contents of the pack and other information

What Hexaxim contains
The active substances are per dose (0.5 ml)[1]:

Diphtheria Toxoid	not less than 20 IU[2]
Tetanus Toxoid	not less than 40 IU[2]
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Poliovirus (Inactivated)[3]	
Type 1 (Mahoney)	40 D antigen units[4]

Type 2 (MEF-1)	8 D antigen units[4]
Type 3 (Saukett)	32 D antigen units[4]
Hepatitis B surface antigen[5]	10 micrograms
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] *IU International Unit*
[3] *Produced on Vero cells*
[4] *Equivalent antigenic quantity in the vaccine*
[5] *Produced in yeast Hansenula polymorpha cells by recombinant DNA technology*

The other ingredients are:
Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.

What Hexaxim looks like and contents of the pack

Hexaxim is provided as a suspension for injection in pre-filled syringe (0.5 ml).
Hexaxim is available in pack containing 1, 10, 20 or 50 pre-filled syringes without attached needle.
Hexaxim is available in pack containing 1, 10, 20 or 50 pre-filled syringes with 1 separate needle.
Hexaxim is available in pack containing 1, 10, 20 or 50 pre-filled syringes with 2 separate needles.

Not all pack sizes may be marketed.

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

Scientific Opinion Holder
Sanofi Pasteur SA - 2 avenue Pont Pasteur - 69007 Lyon - France

Manufacturer

The manufacturing sites responsible for batch release are:
Sanofi Pasteur SA - 1541 avenue Marcel Mérieux - 69280 Marcy l'Etoile - France
Sanofi Pasteur SA – Parc Industriel d'Incarville - 27100 Val de Reuil - France

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

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The following information is intended for medical or healthcare professionals only:

Instructions for use - Hexaxim, suspension for injection in pre-filled syringe or vial.
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed).

- For syringes without attached needles, the needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.
- Shake the pre-filled syringe so that the contents become homogeneous.
- Hexaxim should not be mixed with other medicinal products.

Hexaxim must be administered intramuscularly. The recommended injection sites are the antero-lateral aspect of the upper thigh in infants and the deltoid muscle in older children.

The intradermal or intravenous routes must not be used. Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

PACKAGE LEAFLET: INFORMATION FOR THE USER

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.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them.
- 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.

What is in this leaflet:

1. What Hexaxim is and what it is used for

Hexaxim is a vaccine. Vaccines are 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 which can lead to suffocation. The bacteria that cause the disease also make a toxin (poison) that can damage the heart, kidneys and nerves.
- Tetanus (often called lock jaw) is usually caused by the tetanus bacteria entering a deep wound. The bacteria make a toxin (poison) that causes spasms of the muscles, leading to inability to breathe and the possibility of suffocation.
- Pertussis (often called whooping cough) is a bacterial infection of the airways that can occur at any age but mostly affects infants and young children. Increasingly severe coughing spells that can last for several weeks are a characteristic of the disease. Coughing spells may be followed by a whooping noise.
- Hepatitis B is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people.
- 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), infections of the blood, lungs, inflammation of the tissue under the skin, inflammation of the joints and bones and inflammation of part of the back of the throat, causing difficulty in swallowing and breathing.

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 or by other liver pathogens.
- Because of the long incubation period of hepatitis B, it is possible for unrecognized 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 an allergic reaction
  - to the active substances,
  - to any of the excipients listed in section 6,
  - to any pertussis vaccine (any vaccine that protects against whooping cough),
  - after previous administration of the vaccine or to any vaccine containing the same components or constituents.
- 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.
- suffered from encephalopathy (cerebral lesions) within 7 days of a previous dose of a pertussis vaccine (acellular or whole cell pertussis).
- has an uncontrolled condition or severe illness affecting the brain (uncontrolled neurologic disorder) and nervous system or uncontrolled epilepsy.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before vaccination if your child:
- is allergic to glutaraldehyde, formaldehyde, neomycin, streptomycin or polymyxin B, as these substances are used during the manufacturing process.
- if any of the following events are known to have occurred after receiving any vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered:
  - Fever of 40°C or above within 48 hours not due to another identifiable cause.
  - Collapse or shock-like state with hypotonic-hyporesponsive episode (drop in energy) within 48 hours of vaccination.
  - Persistent, inconsolable crying lasting 3 hours or more, occurring within 48 hours of vaccination.
  - Convulsions with or without fever, occurring within 3 days of vaccination.

- presented Guillain-Barré syndrome (abnormal sensitivity, paralysis) or brachial neuritis (paralysis, diffuse pain in the arm and shoulder) following receipt of a prior vaccine containing tetanus toxoid (vaccine against tetanus), the decision to give any further vaccine containing tetanus toxoid should be evaluated by your doctor.
- follows a treatment that suppresses her/his immune defenses or if your child presents with immunodeficiency: in these cases the immune response to the vaccine may be decreased. It is then recommended to wait until the end of the treatment or disease before vaccinating. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.
- suffers from an acute or chronic illness including chronic renal insufficiency (or failure).
- suffers from any undiagnosed illness of the brain or epilepsy which is not controlled. Your doctor will assess the potential benefit offered by vaccination.
- has any problems with the blood that cause easy bruising or bleeding for a long time after minor cuts. Your doctor will advise you whether your child should have Hexaxim.

Other medicines or vaccines and Hexaxim

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

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

Your doctor will give the injections at different sites and will use separate syringes and needles for each injection.

Pregnancy, breast-feeding and fertility

Not applicable.

Driving and using machines

Not relevant.

3. How to use Hexaxim

The vaccination should be given by medical or healthcare professionals who are trained in the use of vaccines and who are equipped to deal with any uncommon severe allergic reaction to the injection. Please refer to section 4.
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 should never be given into a blood vessel or into or under the skin.

Always use this vaccine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

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 primary vaccination when indicated by the local vaccination schedule, your child should receive a booster dose, in accordance with local recommendations, at least 6 months after the last dose of the

primary vaccination. Your doctor will tell you when this dose should be given.

If you forget one dose of Hexaxim

If you miss a scheduled injection, your doctor will decide when to give the missed dose.
Make sure your child finishes the complete vaccination course. If not, your child may not be fully protected against the diseases.

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

4. Possible side effects

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

Serious allergic reactions (anaphylactic reaction)

If any of these symptoms occur after leaving the place where your child received his/her injection, you must consult a doctor IMMEDIATELY:
- difficulty in breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- sudden and serious malaise with drop in blood pressure causing dizziness and loss of consciousness, accelerated heart rate associated with respiratory disorders.

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

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

Other side effects

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

- fits (convulsions) with or without fever

- Very rare side effects (may affect up to 1 in 10,000 people) are:
  - episodes when your child goes into a shock-like state or is pale, floppy and unresponsive for a period of time (hypotonic reactions or hypotonic hyporesponsive episodes HHE).

Potential side effects

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

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

6. Contents of the pack and other information

What Hexaxim contains

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

Diphtheria Toxoid	not less than 20 IU[2]
Tetanus Toxoid	not less than 40 IU[2]
Bordetella pertussis antigens	
Pertussis Toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms

Poliovirus (Inactivated) [3]	
Type 1 (Mahoney)	40 D antigen units[4]
Type 2 (MEF-1)	8 D antigen units[4]
Type 3 (Saukett)	32 D antigen units[4]
Hepatitis B surface antigen[5]	10 micrograms
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] IU International Unit
[3] Produced on Vero cells
[4] Equivalent antigenic quantity in the vaccine
[5] Produced in yeast Hansenula polymorpha cells by recombinant DNA technology

The other ingredients are:
Disodium hydrogen phosphate, potassium dihydrogen phosphate, trometamol, saccharose, essential amino acids including L-phenylalanine, sodium hydroxide and/or acetic acid glacial and/or hydrochloric acid concentrated (for pH adjustment), and water for injections.

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 1, 10, 20 or 50 vials.

Not all pack sizes may be marketed.

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

Scientific Opinion Holder
Sanofi Pasteur SA - 2 avenue Pont Pasteur - 69007 Lyon - France

Manufacturer

The manufacturing sites responsible for batch release are:
Sanofi Pasteur SA - 1541 avenue Marcel Mérieux - 69280 Marcy l'Etoile - France
Sanofi Pasteur SA – Parc Industriel d'Incarville - 27100 Val de Reuil - France

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

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The following information is intended for medical or healthcare professionals only:

Instructions for use - Hexaxim, suspension for injection in pre-filled syringe or vial.
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed).

- Shake the vial so that the contents become homogeneous.
- Hexaxim should not be mixed with other medicinal products.

Hexaxim must be administered intramuscularly. The recommended injection sites are the antero-lateral aspect of the upper thigh in infants and the deltoid muscle in older children.
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.