

Attachment 1: Product information for AusPAR Hexaxim DTPa-hepB-IPV-Hib vaccine Sanofi Aventis Australia Pty Ltd PM-2013-02800-1-2. Date of finalisation 12 January 2015. This Product Information was approved at the time this AusPAR was published.

## AUSTRALIAN PRODUCT INFORMATION

### NAME OF THE MEDICINE

HEXAXIM<sup>®</sup>

DTPa-hepB-IPV-Hib

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

### DESCRIPTION

Hexaxim is a preservative free liquid formulation for intramuscular administration which combines: Diphtheria and Tetanus toxoids, Acellular Pertussis (2-component), Recombinant Hepatitis B surface antigen, Inactivated Poliomyelitis virus and *Haemophilus influenzae* type b polysaccharide conjugated to tetanus protein.

Each 0.5 mL, adsorbed to aluminium hydroxide (0.6 mg, expressed as Al<sup>3+</sup>), contains:

**Table 1: Hexaxim Composition**

Active substance	Quantity (per 0.5 mL dose)
Diphtheria Toxoid	≥ 20 IU <sup>1</sup>
Tetanus Toxoid	≥ 40 IU <sup>2</sup>
Bordetella Pertussis <ul style="list-style-type: none"><li>• Pertussis Toxoid</li><li>• Pertussis Filamentous Haemagglutinin</li></ul>	25 microgram 25 microgram
Hepatitis B surface antigen <sup>3</sup>	10 microgram
Poliovirus (Inactivated) <sup>4</sup> <ul style="list-style-type: none"><li>• Type 1 (Mahoney)</li><li>• Type 2 (MEF-1)</li><li>• Type 3 (Saukett)</li></ul>	40 D antigen <sup>5</sup> Units <sup>6</sup> 8 D antigen <sup>5</sup> Units <sup>6</sup> 32 D antigen <sup>5</sup> Units <sup>6</sup>
<i>Haemophilus</i> type B polysaccharide conjugated to Tetanus protein	12 microgram 22 – 36 microgram

<sup>1</sup> As lower confidence limit (p= 0.95) and not less than 30 I.U as mean value

<sup>2</sup> As lower confidence limit (p= 0.95)

<sup>3</sup> Surface antigen of hepatitis B virus produced from recombinant strain of the yeast *Hansenula polymorpha*

<sup>4</sup> Produced on vero cells

<sup>5</sup> Quantity of antigen in the final bulk product, according to WHO (TRS 910, 2002)

<sup>6</sup> Or equivalent antigenic quantity determined by a suitable immunochemical method

The vaccine also contains the excipients; sodium phosphate-dibasic, potassium phosphate-monobasic, trometamol, sucrose, essential amino acids (cystine, tyrosine, arginine hydrochloride, histidine, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan and valine) and water for injections.

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The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.

The manufacture of this product includes exposure to bovine materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

Hexaxim is a whitish, cloudy suspension.

## **PHARMACOLOGY**

### **Mechanism of action**

Hexaxim induces the production of antibodies against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b.

## **CLINICAL TRIALS**

The primary vaccination schedules that have been used are: 6, 10, 14 weeks with and without hepatitis B vaccination at birth; 2, 3, 4 months without hepatitis B vaccination at birth; 2, 4, 6 months with and without hepatitis B vaccination at birth.

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

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**Table 2: Percentage of individuals with antibody titres  $\geq$  seroprotection/seroconversion rates\* one month after primary vaccination with Hexaxim**

Antibody titres $\geq$ seroprotection/seroconversion rates		6-10-14 Weeks N $\dagger$ =123 to 220	2-3-4 Months N $\dagger$ =145	2-4-6 Months N $\dagger$ =934 to 1270
		%	%	%
Anti-diphtheria ( $\geq$ 0.01 IU/ml)		97.6	99.3	97.1
Anti-tetanus ( $\geq$ 0.01 IU/ml)		100.0	100.0	100.0
Anti-PT ( $\geq$ 4 fold rise)		93.6	93.6	96
Anti-FHA ( $\geq$ 4 fold rise)		93.1	81.9	97.0
Anti-HBs ( $\geq$ 10 mIU/ml)	With hepatitis B vaccination at birth	99.0	/	99.7
	Without hepatitis B vaccination at birth	95.7	94.0	98.8
Anti-Polio type 1 ( $\geq$ 8 (1/dilution))		100.0	97.7	99.9
Anti-Polio type 2 ( $\geq$ 8 (1/dilution))		98.5	94.7	100.0
Anti-Polio type 3 ( $\geq$ 8 (1/dilution))		100.0	97.4	99.9
Anti-PRP ( $\geq$ 0.15 $\mu$ g/ml)		95.4	90.7	98.0

\* Acceptable as correlates or surrogates of protection

$\dagger$  Number of individuals analysed according to per protocol analysis set

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**Table 3: Percentage of individuals with antibody titres  $\geq$  seroprotection/seroconversion rates\* one month after booster vaccination with Hexaxim**

Antibody titres $\geq$ seroprotection/seroconversion rates		Booster vaccination during the second year of life following a three dose primary course		
		6-10-14 weeks N†=204	2-3-4 months N†=114	2-4-6 months N†=177
		%	%	%
Anti-diphtheria ( $\geq 0.1$ IU/ml)		100.0	99.1	97.2
Anti-tetanus ( $\geq 0.1$ IU/ml)		100.0	100.0	100.0
Anti-PT ( $\geq 4$ fold rise)		94.8	96.5	91.8
Anti-FHA ( $\geq 4$ fold rise)		91.2	91.8	86.7
Anti-HBs ( $\geq 10$ mIU/ml)	With hepatitis B vaccination at birth	100.0	/	/
	Without hepatitis B vaccination at birth	98.5	97.3	99.4
Anti-Polio type 1 ( $\geq 8$ (1/dilution))		100.0	100.0	100.0
Anti-Polio type 2 ( $\geq 8$ (1/dilution))		100.0	100.0	100.0
Anti-Polio type 3 ( $\geq 8$ (1/dilution))		100.0	100.0	100.0
Anti-PRP ( $\geq 1.0$ $\mu$ g/ml)		98.5	98.2	98.3

\* acceptable as correlates or surrogates of protection

† number of individuals analysed according to per protocol analysis set

The long term capability of the acellular pertussis antigens contained in Hexaxim to reduce pertussis incidence and control pertussis disease has been demonstrated in a 15-year national pertussis surveillance on pertussis disease in Sweden with the pentavalent DTPa-IPV/Hib vaccine using a 3, 5, 12 months schedule (1). Several types of acellular pertussis vaccines were used during the 15 year follow-up. It is not possible to detect differences in vaccine effectiveness using surveillance data due to different vaccines and schedules used during the study period, variability in vaccine coverage and surveillance systems and cyclic variations in infection and disease.

The vaccine effectiveness against Hib invasive disease of DTPa 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) (2) (3).

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## INDICATIONS

Hexaxim is indicated for vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b.

Use of this vaccine should be in accordance with the national recommendation as per the current Immunisation Handbook.

## CONTRAINDICATIONS

Hexaxim should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or to any pertussis vaccine, after previous administration of the vaccine or a vaccine containing the same components or constituents.

Vaccination with Hexaxim is contraindicated if the individual has experienced an encephalopathy of unknown aetiology within 7 days of administration of a previous dose of any vaccine containing pertussis antigens (whole cell or acellular pertussis vaccines). In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria, tetanus, hepatitis B, poliomyelitis and Hib vaccines.

Progressive neurological disorder, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these common conditions until the treatment regimen has been established, the condition has stabilised and the benefit clearly outweighs the risk.

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

## PRECAUTIONS

Do not administer intravenously, intradermally or subcutaneously.

### **Prior to vaccination**

#### *Anaphylaxis*

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

#### *Hypersensitivity*

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 individuals with hypersensitivity to these substances.

#### *Bleeding disorder*

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.

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### *Previous pertussis vaccination*

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  $\geq 40^{\circ}\text{C}$  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.

### *Family and individual history*

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.

## **Protection**

Hexaxim will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Hexaxim will not protect against hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E or by other liver pathogens.

Because of the long incubation period of hepatitis B, it is possible for unrecognised hepatitis B infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B infection in such cases.

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

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

## **Special patient groups**

### *Premature and low birth weight infants*

No data are available for premature infants and infants of low birth weight  $< 2.5$  kg. Lower immune response may be observed in this population in relation with immaturity of the immune system. However, according to several national recommendations, vaccination should not be delayed.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants

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(born  $\leq$  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.

#### *Immunocompromised individuals*

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.

#### *Neurological disorder*

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 immunisation schedule has been completed. Vaccination is usually justified for infants whose primary immunisation schedules are incomplete (i.e. fewer than three doses have been received).

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

#### *Chronic renal failure*

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).

#### *Genetic polymorphism*

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

The immunogenicity of Hexaxim has not been studied in the Australian indigenous populations.

### **Effects on Fertility**

Animal studies have not been conducted to determine the effects of Hexaxim on fertility.

### **Use in Pregnancy (Category B2)**

Hexaxim is not indicated for use during pregnancy and has not been evaluated for potential harmful effects during pregnancy in animals or humans.

### **Use in Lactation**

Hexaxim is not indicated for use in lactating women and it is not known whether Hexaxim components are transferred in human milk.

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### **Paediatric Use**

The safety and efficacy of Hexaxim in children over 24 months of age have not been established.

### **Use in the elderly**

Not applicable.

### **Genotoxicity**

Hexaxim has not been evaluated for genotoxic potential.

### **Carcinogenicity**

Hexaxim has not been evaluated for carcinogenic potential.

### **Effect on Laboratory Tests**

Interference of Hexaxim with laboratory and/or diagnostic tests has not been studied.

However, antigenuria (PRP antigen) has been detected in some instances following receipt of *Haemophilus influenzae* type b conjugate vaccine. Therefore, urine antigen detection may not have definite diagnostic value in suspected *Haemophilus influenzae* type b disease within two weeks of immunisation.

## **INTERACTIONS WITH OTHER MEDICINES**

Hexaxim must not be mixed with other vaccines or other parenterally administered drugs.

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

Data on concomitant administration of Hexaxim with 7-valent pneumococcal polysaccharide conjugated vaccines have shown no clinically relevant interference in the antibody response to each of the antigens. Data on concomitant administration of Hexaxim with 13-valent pneumococcal polysaccharide conjugated vaccines are not currently available.

Data on concomitant administration of Hexaxim with measles-mumps-rubella vaccine and with varicella vaccine have shown no clinically relevant interference in the antibody response to each of the antigens when given as a booster vaccination.

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

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



## ADVERSE EFFECTS

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

Very common	$\geq 1/10$ ( $\geq 10\%$ )
Common	$\geq 1/100$ to $< 1/10$ ( $\geq 1\%$ and $< 10\%$ )
Uncommon	$\geq 1/1,000$ to $< 1/100$ ( $\geq 0.1\%$ and $< 1\%$ )
Rare	$\geq 1/10,000$ to $< 1/1000$ ( $\geq 0.01\%$ and $< 0.1\%$ )
Very rare	$< 1/10,000$ ( $< 0.01\%$ )
Not known	Cannot be estimated from available data

### Clinical Trials Experience

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.

#### Immune system disorders

Uncommon: Hypersensitivity reaction

#### Metabolism and nutrition disorders

Very common: Anorexia

#### Nervous system disorders

Very common: Crying, somnolence

Common: Abnormal crying (prolonged crying)

Very rare: Hypotonic reactions or hypotonic-hyporesponsive episodes (HHE)

#### Gastrointestinal disorders

Very common: Vomiting

Common: Diarrhoea

#### Skin and subcutaneous tissue disorders

Rare: Rash

#### General disorders and administration site conditions

Very common: Injection site pain, injection site erythema, injection site swelling, irritability, pyrexia (body temperature  $\geq 38.0^{\circ}\text{C}$ )

Common: Injection site induration

Uncommon: Injection site nodule, pyrexia (body temperature  $\geq 39.6^{\circ}\text{C}$ )

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Rare: 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.

### **Adverse Reactions from Post-Marketing Surveillance**

There are no new clinically-relevant safety data from post-marketing experience at this time.

### **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).

- Anaphylactic reaction
- Brachial neuritis and Guillain-Barré Syndrome have been reported after administration of a tetanus toxoid containing vaccine.
- 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 resolve spontaneously without sequel within 24 hours.
- Convulsion with or without fever
- Peripheral neuropathy (polyradiculoneuritis, facial paralysis), optic neuritis, central nervous system demyelination (multiple sclerosis) have been reported after administration of an hepatitis B antigen containing vaccine.
- Encephalopathy/encephalitis
- Apnoea in very premature infants ( $\leq 28$  weeks of gestation) (see PRECAUTIONS)

## **DOSAGE AND ADMINISTRATION**

### ***Primary vaccination***

The primary vaccination schedule consists of three doses of 0.5 mL to be administered at intervals of at least four weeks, in accordance with the national recommendations as per the current Immunisation Handbook.

### ***Booster vaccination***

Hexaxim can also be used for booster vaccination during the second year of life but use of this vaccine as a booster should be in accordance with the national recommendation as per the current Immunisation Handbook.

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For further information, refer to the current Immunisation Handbook.

Before use, the vaccine should be shaken in order to obtain a homogeneous whitish cloudy suspension.

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.

Do not administer via intravascular route: ensure that the needle does not penetrate a blood vessel.

Do not administer by intradermal or subcutaneous injection.

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

Hexaxim is for single use only and must not be used in more than one individual. Discard any remaining unused contents.

## **OVERDOSE**

Not documented.

## **PRESENTATION AND STORAGE CONDITIONS**

Hexaxim is supplied in:

- 0.5mL single dose in pre-filled syringe without attached needle and one separate needle in a pack.
- 0.5mL single dose in pre-filled syringe without attached needle and two separate needles in a pack.

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

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if vaccine has been frozen.

Protect from light.

## **NAME AND ADDRESS OF THE SPONSOR**

**Australia**

**sanofi-aventis australia pty ltd**

Talavera Corporate Centre – Building D

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**POISON SCHEDULE OF THE MEDICINE**

S4 Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER  
OF THERAPEUTIC GOODS (ARTG)**

11 September 2014

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**References:**

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3. Schmitt HJ et al. Haemophilus influenzae type b disease: impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (-inactivated poliovirus)/H. influenzae type b combination vaccines. *Pediatr Infect Dis J* 2001;20(8):767-774.