AUSTRALIAN PRODUCT INFORMATION
HEXAXIM (DTPA-HEPB-IPV-HIB) – SUSPENSION FOR INJECTION

1 NAME OF THE MEDICINE

Hexaxim

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 hydrate (0.6 mg, expressed as Al3+), contains:

Table 1 - Hexaxim Composition

Active Substance	Quantity (per 0.5 mL dose)
Diphtheria Toxoid	≥ 20 IU[1, 3] (30 Lf)
Tetanus Toxoid	≥ 40 IU[2, 3] (10 Lf)
Bordetella Pertussis	
• Pertussis Toxoid	25 micrograms
• Pertussis Filamentous Haemagglutinin	25 micrograms
Hepatitis B surface antigen[6]	10 micrograms
Poliovirus (Inactivated)[4]	
Type 1 (Mahoney)	29 D antigen Units[5]
Type 2 (MEF-1)	7 D antigen Units[5]
Type 3 (Saukett)	26 D antigen Units[5]
Haemophilus type B polysaccharide	12 micrograms
conjugated to Tetanus protein	22 – 36 micrograms

[1] As lower confidence limit (p= 0.95) and not less than 30 I.U as mean value
[2] As lower confidence limit (p= 0.95)
[3] Or equivalent activity determined by an immunogenicity evaluation
[4] Cultivated on vero cells
[5] These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method
[6] Surface antigen of hepatitis B virus produced from recombinant strain of the yeast *Hansenula polymorpha*

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

Contains phenylalanine. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Hexaxim is a whitish, cloudy suspension for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Hexaxim is for intramuscular injection according to the dosing schedule below.

Table 2 - Dosing Schedule

Dose	Vaccination	Dosing Schedule	General Considerations
3 Dose	Primary*	Three doses of 0.5 mL (such as: 6, 10, 14 weeks; 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months)	There should be an interval of at least 4 weeks between primary doses in accordance with the national recommendation as per the current Immunisation Handbook.
	Booster	A booster dose may be given	The booster dose should be given at least 6 months after the last priming dose and in accordance with the national recommendation as per the current Immunisation Handbook. In case where a booster dose is not administrated, a dose of Hib vaccine should be given.
2 Dose	Primary*	Two doses of 0.5 mL (such as 2, 4 months; 3, 5 months)	There should be an interval of at least 8 weeks between primary doses in accordance with the national recommendation as per the current Immunisation Handbook.
	Booster	A booster dose must be given	The booster dose should be given at least 6 months after the last priming dose and in accordance with the national recommendation as per the current Immunisation Handbook. In case where a booster dose is not administrated, a dose of Hib vaccine must be given.

*Where a dose of hepatitis B vaccine is given at birth, Hexaxim can be used for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

For further information, refer to the current Immunisation Handbook.

Administration

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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 ≥ 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.

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 (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.

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.

Use in the elderly

Not applicable.

Paediatric use

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

Effects 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 or 13-valent pneumococcal polysaccharide conjugate vaccines have shown no clinically relevant interference in the antibody response to each of the individual antigens.

Data on concomitant administration of Hexaxim with measles-mumps-rubella 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.

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

Except in the case of immunosuppressive therapy (see Section 4.4 Special warnings and precautions for use), no significant clinical interaction with other treatments or biological products has been reported.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 breastfeeding women and it is not known whether Hexaxim components are excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 to < 1/10 (≥ 1% and < 10%)
Uncommon	≥ 1/1,000 to < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10,000 to < 1/1000 (≥ 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 (expressed per dose) 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 ≥ 38.0°C)

Common: Injection site induration

Uncommon: Injection site nodule, pyrexia (body temperature ≥ 39.6°C)

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

Immune system disorders

Very rare: Anaphylactic reactions

Nervous system disorders

Very rare: Convulsions with or without fever

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).

- 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.
- 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
- Apnoea in very premature infants (≤ 28 weeks of gestation) (see Section 4.4 Special warnings and precautions for use)

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Not documented.

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vaccines, bacterial and viral combined, ATC code: J07CA09

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: 3, 5 months without hepatitis B vaccination at birth; 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:

Table 3 - Percentage of individuals with antibody titres ≥ seroprotection/seroconversion rates[a] one month after primary vaccination with 2 or 3 doses of Hexaxim

Antibody titres ≥ seroprotection/seroconversion rates		2 Doses	3 Doses		
		3-5 months N=249[b]	6-10-14 Weeks N=123 to 220[c]	2-3-4 Months N=322[d]	2-4-6 Months N=934 to 1270[e]
		%	%	%	%
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 (≥ 4 fold rise)		93.4	93.6	88.3	96.0
Anti-FHA (≥ 4 fold rise)		92.5	93.1	90.6	97.0
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	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

N = Number of individuals analysed (per protocol set)

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

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

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

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

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

Table 4 - Percentage of individuals with antibody titres ≥ seroprotection/seroconversion rates[a] one month after booster vaccination with Hexaxim

Antibody titres ≥ seroprotection/seroconversion rates		Booster vaccination at 11-12 months of age after a two dose primary course	Booster vaccination during the second year of life following a three dose primary course		
		3-5 months N=249[b]	6-10-14 weeks N=204[c]	2-3-4 months N=178[d]	2-4-6 months N=177[e]
		%	%	%	%
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 (≥ 4 fold rise)		94.3	94.4	86.0	91.8
Anti-FHA (≥ 4 fold rise)		97.6	99.4	94.3	86.7
Anti-HBs (≥ 10 mIU/mL)	With hepatitis B vaccination at birth	/	100.0	/	/
	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

N = Number of individuals analysed (per protocol set)

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

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

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

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

e: 2, 4, 6 months without hepatitis B vaccination at birth (Mexico)

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 96.7% for the full primary series, and 98.5% for booster dose (irrespective of priming) (2) (3).

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Hexaxim has not been evaluated for genotoxic potential.

Carcinogenicity

Hexaxim has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

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.

6.2 INCOMPATIBILITIES

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

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

6.3 SHELF LIFE

48 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Protect from light.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period, Hexaxim should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 NATURE AND CONTENTS OF CONTAINER

Hexaxim is supplied in:

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely according to locally agreed procedures.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
Talavera Corporate Centre – Building D
12-24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

11 September 2014

10 DATE OF REVISION

07 October 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Updated expression of antigen units and addition of footnotes
4.8	Removal of NZ information

4.9	Removal of NZ information
5.1	Minor editorial changes
8	Removal of NZ sponsor information; include contact email

REFERENCES:

1. The Public Health Agency of Sweden, Pertussis Surveillance in Sweden - Fifteen Year Report, 2013 http://www.folkhalsomyndigheten.se/pagefiles/17379/pertussis-surveillance%20in-sweden-fifteen-year-report%282%29.pdf

2. Kalies H et al, Four and one-half year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/Haemophilus influenzae type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/H. influenzae type b combination vaccines in Germany. Pediatr Infect Dis J 2004;23(10):944-950.

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.