# AUSTRALIAN PRODUCT INFORMATION

# INFANRIX HEXA (Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Poliovirus and Haemophilus influenzae type b vaccine) powder and suspension for suspension for injection

## 1 NAME OF THE MEDICINE

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B, Poliovirus and Haemophilus influenzae type b vaccine

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

| | |
|---|---|
| Diphtheria toxoid[1] | not less than 30 International units |
| Tetanus toxoid[1] | not less than 40 International units |
| Bordetella pertussis antigens | |
| Pertussis toxoid (PT)[1] | 25 micrograms |
| Filamentous Haemagglutinin (FHA)[1] | 25 micrograms |
| Pertactin (PRN)[1] | 8 micrograms |
| Hepatitis B surface antigen (HBs)[2,3] | 10 micrograms |
| Poliovirus (inactivated) (IPV) | |
| type 1 (Mahoney strain)[4] | 40 D-antigen unit |
| type 2 (MEF-1 strain)[4] | 8 D-antigen unit |
| type 3 (Saukett strain)[4] | 32 D-antigen unit |
| Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate, PRP)[3] conjugated to tetanus toxoid as carrier protein | 10 micrograms 20 - 40 micrograms |

[1]adsorbed on aluminium hydroxide hydrate ($Al(OH)_3$) 0.5 milligrams $Al^{3+}$

[2]produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology

[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams $Al^{3+}$

[4]propagated in VERO cells

**List of excipients with known effect**

INFANRIX HEXA also contains residual amounts of neomycin sulfate and polymyxin B sulfate, which are carried over from the manufacturing process.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

This medicine contains less than 1 mmol (39 mg) per dose of potassium and less than 1 mmol (23 mg) per dose of sodium, i.e., essentially 'potassium-free' and 'sodium-free'.

# 3 PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal observation.

The Hib component is presented as a white pellet.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

INFANRIX HEXA is indicated for primary immunisation of infants from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b.

INFANRIX HEXA is also indicated for use as booster dose if boosting with hepatitis B, poliomyelitis, and *Haemophilus influenzae* type b, as well as diphtheria, tetanus and pertussis is required.

The use of INFANRIX HEXA should be in accordance with official recommendations.

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION for further information

## 4.2 DOSE AND METHOD OF ADMINISTRATION

INFANRIX HEXA is for deep intramuscular injection.

Before use of the vaccine, the INFANRIX HEXA suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib pellet should be inspected visually for any foreign particulate matter and/or any variation of physical aspect. In the event of either being observed, do not administer the vaccine.

INFANRIX HEXA must be reconstituted by adding the entire contents of the pre-filled syringe containing the liquid component to the vial containing the Hib pellet.

After the addition of the liquid component to the pellet, the mixture should be well shaken until the pellet is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

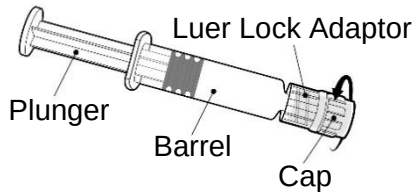
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However, the vaccine may be kept for up to 8 hours at room temperature.

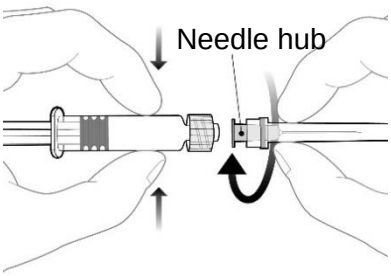
Withdraw the entire contents of the vial.

<u>Instructions for the pre-filled syringe</u>




Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.




To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Reconstitute the vaccine as described above.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

**Dosage**

After reconstitution, each dose consists of a 0.5 ml ready to use sterile suspension.

**Administration**

INFANRIX HEXA is administered by deep intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

INFANRIX HEXA should be injected intramuscularly in the anterolateral aspect of the thigh or the deltoid region of the arm. The recommended dose (0.5 ml) of vaccine must be administered.

The primary immunisation course of INFANRIX HEXA consists of two or three doses (of 0.5 ml) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials for schedules evaluated in clinical trials).

| **Primary vaccination** | **Booster vaccination** | **General considerations** |
|---|---|---|
| Full-term infants | | |
| 3-dose | A booster dose may be given.* | • There should be an interval of at least 1 month between primary doses.<br>• When giving a booster dose, this should be at least 6 months after the last priming dose and at or before 18 months of age. |
| 2-dose | A booster dose must be given.* | • There should be an interval of at least 1 month between primary doses.<br>• When giving a booster dose, this should be at least 6 months after the last priming dose and preferably between 11 and 13 months of age. |
| Preterm infants born after at least 24 weeks of gestational age | | |
| 3-dose | A booster dose must be given.* | • There should be an interval of at least 1 month between primary doses.<br>• When giving a booster dose, this should be at least 6 months after the last priming dose and at or before 18 months of age. |

* INFANRIX HEXA may be considered for the booster if the antigen composition is in accordance with the Australian Immunisation Handbook

Where a dose of hepatitis B vaccine is given at birth, INFANRIX HEXA can be used as a replacement 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.

Locally established immunoprophylactic measures against hepatitis B should be maintained.

Further guidance regarding the use of vaccines can be found in the Australian Immunisation Handbook (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials for schedules evaluated in clinical trials)

## 4.3 CONTRAINDICATIONS

INFANRIX HEXA should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients or residues (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION).

INFANRIX HEXA should not be administered to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

INFANRIX HEXA is contraindicated if the child has experienced encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer INFANRIX HEXA intravascularly or intradermally.

As with other vaccines, the administration of INFANRIX HEXA should be postponed in subjects suffering from acute severe febrile illness (with fever >38.5°C). The presence of a minor infection, however, is not a contraindication.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

A protective immune response may not be elicited in all vaccinees (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

INFANRIX HEXA 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. The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

If any of the following events are known to have occurred in temporal relation to receipt of whole cell or acellular pertussis-containing vaccine, the decision to give further doses of vaccine containing the pertussis component should be carefully considered:

- Temperature of ≥40.0°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.

No data currently exist on use of INFANRIX HEXA in these children. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

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

INFANRIX HEXA should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular injection in these subjects.

A history of febrile convulsions, a family history of convulsions, or Sudden Infant Death Syndrome (SIDS) do not constitute contra-indications for the use of INFANRIX HEXA. 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.

Data from clinical studies indicate that, when INFANRIX HEXA is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of INFANRIX HEXA alone.

Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of INFANRIX HEXA and Prevenar 13 (see Section 4.8 ADVERSE EEFECTS (UNDESIRABLE EFFECTS)).

Antipyretic treatment should be initiated according to local treatment guidelines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

INFANRIX HEXA should not be administered at birth. Infants born of HBsAg positive mothers should receive hepatitis B immune globulin and hepatitis B vaccine at birth.

The Hib component of the vaccine does not protect against diseases due to other strains of *Haemophilus influenzae* or against meningitis caused by other organisms.

**Special Populations**

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, the expected immunologic response may not be achieved. No data currently exist on use of INFANRIX HEXA in these patients.

**Preterm Infants**

Clinical data indicate that INFANRIX HEXA can be given to preterm infants, however, as expected in this population, a lower immune response has been observed for some antigens (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very preterm 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 these infants, vaccination should not be withheld or delayed.

Native populations (native Alaskans, native American Indians) with a high incidence of *Haemophilus influenzae* type b disease have shown a reduced antibody response to *Haemophilus influenzae* type b conjugate vaccines. The immunogenicity of INFANRIX HEXA has not been studied in the Australian indigenous population and the possibility of a lower antibody response to the Hib component, than that seen in clinical studies, should be borne in mind.

**Use in the elderly**

No data available

**Paediatric use**

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

**Effects on laboratory tests**

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

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

INFANRIX HEXA should not be mixed with other vaccines in the same syringe.

INFANRIX HEXA can be given concomitantly with pneumococcal conjugate, MenC conjugate, MenACWY conjugate, MenB, rotavirus, measles, mumps, rubella and varicella vaccines. Data have shown no clinically relevant interference in the antibody response to each of the individual antigens.

When Infanrix hexa was co-administered with MenB and pneumococcal conjugate vaccines, inconsistent results were seen across studies for responses to inactivated poliovirus type 2

and pneumococcal conjugate serotype 6B antigen and to the pertussis pertactin antigen but these data do not suggest clinically significant interference.

Data from clinical studies indicate that, when INFANRIX HEXA is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of INFANRIX HEXA alone. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Data from clinical studies indicate a more frequent occurrence of fever, pain at the injection site, appetite lost and irritability when Infanrix hexa is co-administered with MenB vaccine and 7-valent pneumococcal conjugate vaccine.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

No data available

**Use in pregnancy**

**(Pregnancy Category B2)**

As INFANRIX HEXA is not intended for use in adults, adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

**Use in lactation**

As INFANRIX HEXA is not intended for use in adults, adequate human data on use during lactation are not available.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Clinical trial experience**

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with INFANRIX HEXA with respect to the primary course. The below table contains data from subjects receiving booster vaccinations and those receiving primary doses.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10

Common: ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10000 to < 1/1000

Very rare: < 1/10000

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| Infections and infestations | Common | upper respiratory tract infection |
| Immune disorders | Very rare | Allergic reactions and anaphylactoid reactions (including dermatitis and urticaria*) |
| Metabolism and nutrition disorders | Very common | appetite lost |
| Psychiatric disorders | Very common | irritability, crying abnormal, restlessness |
| | Common | nervousness |
| Nervous system disorders | Very common | somnolence |
| | Very rare | convulsions (with or without fever)*** |
| Respiratory, thoracic and mediastinal disorders | Common | Bronchitis, rhinitis |
| | Uncommon Rare | bronchospasm, laryngitis, stridor, cough* |
| | | |
| Gastrointestinal disorders | Common | vomiting, diarrhoea, enteritis, gastroenteritis |
| | Uncommon | abdominal pain, constipation |
| Skin and subcutaneous tissue disorders | Common | pruritus* |
| | Rare | rash |
| | Very rare | dermatitis, urticaria* |
| Vision | Uncommon | conjunctivitis |
| General disorders and administration site conditions | Very common | pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, |
| | Common | local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration |
| | Uncommon | diffuse swelling of the injected limb, sometimes involving the adjacent joint**, fatigue |

* observed only with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

*** Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of INFANRIX HEXA with Prevenar 13 to those which reported use of INFANRIX HEXA alone.

**Post marketing experience**

The following drug-related adverse reactions were reported during post-marketing surveillance:

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|

| | | |
|---|---|---|
| Blood and lymphatic system disorders | Rare | lymphadenopathy, thrombocytopenia |
| Immune system disorders | Rare | allergic reactions (including anaphylactic and anaphylactoid reactions) |
| Nervous system disorders | Rare | convulsions (with or without fever), collapse or shock-like state (hypotonic hyporesponsive episode)*** |
| Respiratory, thoracic and mediastinal disorders | Rare | apnoea*[see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for apnoea in very preterm infants (≤ 28 weeks of gestation)] |
| Skin and subcutaneous tissue disorders | Rare | angioneurotic oedema* |
| General disorders and administration site conditions | Rare | extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site |

* Observed only with other GSK DTPa-containing vaccines
** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.
***Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of INFANRIX HEXA with Prevenar 13 to those which reported use of INFANRIX HEXA alone.

Safety in preterm infants:

INFANRIX HEXA has been administered to more than 1000 preterm infants (born after a gestation period of 24 to 36 weeks) in primary vaccination studies and in more than 200 preterm infants as a booster dose in the second year of life. In comparative studies, similar rates of symptoms were observed in preterm and full-term infants.

Safety in infants and toddlers born to mothers vaccinated with dTpa during pregnancy

In two clinical studies, Infanrix hexa has been administered to more than 500 subjects born to mothers vaccinated with dTpa (n=341) or placebo (n=346) during the third trimester of pregnancy. The safety profile of Infanrix hexa was similar regardless of exposure/non-exposure to dTpa during pregnancy.

Experience with hepatitis B vaccine which is the same antigen used in INFANRIX HEXA:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and muscular weakness, Guillain-Barré syndrome have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

**Reporting suspected adverse effects**

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

INFANRIX HEXA provides immunity against diphtheria, tetanus, pertussis, hepatitis B, poliovirus and Haemophilus influenzae type b by inducing the production of antibodies and the ability to mount an immunological memory.

**Clinical trials**

***Immunogenicity***

The immunogenicity of INFANRIX HEXA has been evaluated in clinical studies from 6 weeks of age. The vaccine was assessed in 2-dose and 3-dose priming schedules and as a booster dose. The results of these clinical studies are summarised in the tables below:

After a 3-dose primary vaccination schedule, at least 95.7% of infants had developed seroprotective or seropositive antibody levels against each of the vaccine antigens. After booster vaccination (post-dose 4), at least 98.4% of children had developed seroprotective or seropositive antibody levels against each of the vaccine antigens.

***Percentage of subjects with antibody titres ≥ assay cut-off one month after 3-dose primary and booster vaccination with INFANRIX HEXA***

| **Antibody (cut-off)** | **Post-dose 3** | | | | **Post-dose 4 (Booster vaccination during the second year of life following a 3-dose primary course)** |
|---|---|---|---|---|---|
| | **2-3-4 months N= 196 (2 studies)** | **2-4-6 months N= 1693 (6 studies)** | **3-4-5 months N= 1055 (6 studies)** | **6-10-14 weeks N= 265 (1 study)** | **N=2009 (12 studies)** |
| | **%** | **%** | **%** | **%** | **%** |
| **Anti-diphtheria (0.1 IU/ml) †** | 100.0 | 99.8 | 99.7 | 99.2 | 99.9 |
| **Anti-tetanus (0.1 IU/ml) †** | 100.0 | 100.0 | 100.0 | 99.6 | 99.9 |
| **Anti-PT (5 EL.U/ml)** | 100.0 | 100.0 | 99.8 | 99.6 | 99.9 |

| | | | | | |
|---|---|---|---|---|---|
| **Anti-FHA (5 EL.U/ml)** | 100.0 | 100.0 | 100.0 | 100.0 | 99.9 |
| **Anti-PRN (5 EL.U/ml)** | 100.0 | 100.0 | 99.7 | 98.9 | 99.5 |
| **Anti-HBs (10 mIU/ml) †** | 99.5 | 98.9 | 98.0 | 98.5* | 98.4 |
| **Anti-Polio type 1 (1/8 dilution) †** | 100.0 | 99.9 | 99.7 | 99.6 | 99.9 |
| **Anti-Polio type 2 (1/8 dilution) †** | 97.8 | 99.3 | 98.9 | 95.7 | 99.9 |
| **Anti-Polio type 3 (1/8 dilution) †** | 100.0 | 99.7 | 99.7 | 99.6 | 99.9 |
| **Anti-PRP (0.15 μg/ml) †** | 96.4 | 96.6 | 96.8 | 97.4 | 99.7 |

N = number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

After a complete vaccination according to a 2-dose primary and booster schedule with INFANRIX HEXA, at least 97.9% of the subjects had developed seroprotective or seropositive antibody levels against each of the vaccine antigens.

***Percentage of subjects with antibody titres ≥ assay cut-off one month after 2-dose primary and booster vaccination with INFANRIX HEXA***

| **Antibody (cut-off)** | **Post-dose 3 (Vaccination at 2-4-12 months of age) N=196 (1 study)** | **Post-dose 3 (Vaccination at 3-5-11 months of age) N=532 (3 studies)** |
|---|---|---|
| | **%** | **%** |
| **Anti-diphtheria (0.1 IU/ml) †** | 100.0 | 100.0 |
| **Anti-tetanus (0.1 IU/ml) †** | 100.0 | 100.0 |
| **Anti-PT (5 EL.U/ml)** | 99.5 | 100.0 |
| **Anti-FHA (5 EL.U/ml)** | 100.0 | 100.0 |
| **Anti-PRN (5 EL.U/ml)** | 100.0 | 99.2 |
| **Anti-HBs (10 mIU/ml) †** | 99.8 | 98.9 |
| **Anti-Polio type 1 (1/8 dilution) †** | 98.4 | 99.8 |
| **Anti-Polio type 2 (1/8 dilution) †** | 98.4 | 99.4 |

| | | |
|---|---|---|
| **Anti-Polio type 3 (1/8 dilution) †** | 97.9 | 99.2 |
| **Anti-PRP (0.15 μg/ml) †** | 100.0 | 99.6 |

N = number of subjects
† cut-off accepted as indicative of protection

Serological correlates of protection have been established for diphtheria, tetanus, polio, Hepatitis B and Hib. For pertussis there is no serological correlate of protection. However, as the immune response to pertussis antigens following INFANRIX HEXA administration is equivalent to that of INFANRIX, the protective efficacy of the two vaccines is expected to be equivalent.

***Protective efficacy against pertussis***

The protective efficacy of the pertussis component of INFANRIX (DTPa) against WHO-defined typical pertussis (≥21 days of paroxysmal cough with laboratory confirmation) was demonstrated after 3-dose primary immunisation in the studies tabulated below:

| Study | Country | Schedule | Vaccine efficacy | Considerations |
|---|---|---|---|---|
| Household contact study (prospective blinded) | Germany | 3,4,5 months | 88.7% | Based on data collected from secondary contacts in households where there was an index case with typical pertussis |
| Efficacy study (NIH sponsored) | Italy | 2,4,6 months | 84% | In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis. |

***Immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy***

The immunogenicity of INFANRIX HEXA in infants and toddlers born to healthy mothers vaccinated with dTpa at 27-36 weeks of pregnancy was evaluated in two clinical studies. INFANRIX HEXA was co-administered with a 13-valent pneumococcal conjugate vaccine to infants at 2, 4 and 6 months or 2, 3 and 4 months in three-dose primary vaccination schedules (n=241), or at 3 and 5 months or 2 and 4 months in two-dose primary vaccination schedules (n=27); and to the same infants/toddlers from 11 to 18 months as booster dose (n=229).

Post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with dTpa on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in

the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system.

In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.

***Immunogenicity in preterm infants***

The immunogenicity of INFANRIX HEXA was evaluated across three studies including approximately 300 preterm infants (born after a gestation period of 24 to 36 weeks) following a 3-dose primary vaccination course at 2, 4 and 6 months of age. The immunogenicity of a booster dose at 18 to 24 months of age was evaluated in approximately 200 preterm infants.

One month after primary vaccination at least 98.7% of subjects were seroprotected against diphtheria, tetanus and poliovirus types 1 and 2; at least 90.9% had seroprotective antibody levels against the hepatitis B, PRP and poliovirus type 3 antigens; and all subjects were seropositive for antibodies against FHA and PRN while 94.9% were seropositive for anti-PT antibodies.

One month after the booster dose at least 98.4% of subjects had seroprotective or seropositive antibody levels against each of the antigens except against PT (at least 96.8%) and hepatitis B (at least 88.7%). The response to the booster dose in terms of fold increases in antibody concentrations (15- to 235-fold), indicate that preterm infants were adequately primed for all the antigens of INFANRIX HEXA.

In a follow-up study, approximately 2.5 to 3 years after the booster dose, 85.3% of the children were still seroprotected against hepatitis B and at least 95.7% were seroprotected against the three poliovirus types and PRP.

***Persistence of the immune response***

The persistence of the immune response to a 3-dose primary and booster schedule with INFANRIX HEXA was evaluated in children 4-8 years of age. Protective immunity against the three poliovirus types and PRP was observed in at least 91.0% of children and against diphtheria and tetanus in at least 64.7% of children. At least 25.4% (anti-PT), 97.5% (anti-FHA) and 87.0% (anti-PRN) of children were seropositive against the pertussis components.

With regards to hepatitis B, seropositive antibody concentration following a 3-dose primary and booster schedule with INFANRIX HEXA have been shown to persist in ≥ 85% of subjects 4-5 years of age and in ≥72% of subjects 7-8 years of age, in ≥60% of subjects 12-13 years of age and in 53.7% of subjects 14-15 years of age. Additionally, following a 2-dose primary and booster schedule, seroprotective antibody concentrations against hepatitis B persisted in ≥ 48% of subjects 11-12 years of age.

Hepatitis B immunological memory was confirmed in children 4 to 15 years of age. These children had received INFANRIX HEXA as primary and booster vaccination in infancy, and when an additional dose of monovalent HBV vaccine was administered, protective immunity was observed in at least 93% of subjects.

***Post Marketing Experience***

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

The effectiveness of the Hib component of INFANRIX HEXA was investigated via an extensive post-marketing surveillance study conducted in Germany. The recommended schedule in Germany for all DTaP/Hib conjugate vaccines is a 3 dose primary series at the age of 2, 3 and 4 months with a booster at 11 to 14 months of age. Over a 7 year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was INFANRIX HEXA, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

INFANRIX HEXA has been the principal Hib-containing vaccine available in Italy since 2006. The vaccine is administered at 3, 5 and 11 months of age and coverage has exceeded 95%. Hib disease has continued to be well controlled, with no more than three confirmed Hib cases reported annually between 2006 and 2011 in Italian children aged less than 5 years.

### 5.2 PHARMACOKINETIC PROPERTIES

Not relevant to vaccines

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

No data available

**Carcinogenicity**

No data available

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

The final vaccine also contains the excipients lactose, medium 199 (as stabiliser containing amino acids, mineral salts, vitamins and other substances), sodium chloride, aluminium hydroxide hydrate, aluminium phosphate and water for injections. The vaccine also contains the following residues: neomycin sulfate and polymyxin B sulfate.

### 6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

INFANRIX HEXA should be stored at +2°C to +8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

### 6.5 NATURE AND CONTENTS OF CONTAINER

The DTPa-HBV-IPV suspension is presented in a pre-filled syringe.

The lyophilised Hib component is presented in a glass vial.

Powder in a vial (type I glass) containing 1 dose with a stopper (butyl rubber) and 0.5 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

This combination pack is supplied in packs of 1 and 10.

Not all pack sizes may be distributed in Australia.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

Not relevant to vaccines

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

# 9 DATE OF FIRST APPROVAL

15 June 2006

# 10 DATE OF REVISION

18 July 2023

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **4.2** | Introduction of pictograms for the pre-filled syringe |
| **6.5** | Update to description of syringe and cap, including a statement that tip cap and rubber plunger stopper are not made of natural rubber latex |

Version 14.0

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