INFANRIX® hexa

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

NAME OF THE MEDICINE

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DESCRIPTION

Powder and suspension for suspension for injection.
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[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
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)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms 20 - 40 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 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

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

The Hib component is presented as a white powder.

The final vaccine also contains the excipients lactose, sodium chloride, aluminium hydroxide, aluminium phosphate and water for injections. The vaccine also contains the following residues: medium 199 (as stabiliser containing amino acids, mineral salts, vitamins and other substances), potassium chloride, polysorbate 20 and 80, formaldehyde, glycine, sodium phosphate dibasic dihydrate, potassium phosphate monobasic, neomycin sulfate and polymyxin B sulfate.

CLINICAL PHARMACOLOGY

Clinical Trials

Primary Immunisation - Immunogenicity Studies

The immunogenicity of *INFANRIX hexa* has been evaluated in >2390 infants during clinical trials. In these studies, *INFANRIX hexa* was shown to induce antibodies against all of the components contained in the vaccine. A variety of primary vaccination schedules were used including vaccination at 2, 4 and 6 months and at 3, 4 and 5 months. Immune responses from a pivotal clinical study using a 2, 4, 6 month schedule are presented in the following table.

Immune responses [#] one month following primary vaccination with INFANRIX hexa vaccine at 2, 4, 6 months of age

Antigen (n)	**Antibody response (% Seropositive)**	**GMT** **[95% confidence intervals]**
Diphtheria toxoid (n= 985)	99.6 [99.0 – 99.9]	1.31 IU/mL [1.24 – 1.39]
Tetanus toxoid (n= 985)	100 [99.6 – 100.0]	2.27 IU/mL [2.17 – 2.38]
Hepatitis B (n= 989)	98.5 [97.5 – 99.1]	1157.2 mIU/mL [1049.6 – 1275.7]
Pertussis toxoid (n= 986)	100.0 [99.6 – 100.0]	74.3 EL.U/mL [71.4 – 77.3]
Pertussis FHA (n= 917)	100.0 [99.6 – 100.0]	315.0 EL.U/mL [303.1 – 327.5]
Pertactin (n=990)	99.8 [99.3 – 100.0]	116.9 EL.U/mL [110.7 – 123.4]
Poliovirus type 1 (n=953)	99.7 [99.1 – 99.9]	458.1 [422.2 497.0]
Poliovirus type 2 (n=952)	99.9 [99.4 – 100.0]	425.1 [393.0 – 459.8]
Poliovirus type 3 (n=939)	99.9 [99.4 – 100.0]	933.0 [863.4 – 1008.2]
Hib PRP capsular polysaccharide (n=865)	95.9 [94.5– 97.1]	2.53 [2.31 – 2.77]

n = number of subjects tested
# = ITT cohort for immunogenicity
IU = International Units; EL.U = ELISA Units.
The cut-off values for diphtheria and tetanus (≥0.1 IU/mL), hepatitis B (≥10 mIU/mL), PRP-T (≥0.15μg/mL) and the three poliovirus serotypes (≥8) correlate with seroprotection.
The results for poliovirus are expressed as a titre which is the reciprocal of the highest dilution of serum showing 50% virus neutralisation effect in a microneutralisation test.
Currently there are no known serological correlates for protection for the pertussis antigens. The assay cutoff used for the pertussis antigens is ≥5 EL.U/mL.

Protective efficacy against pertussis following primary immunisation - INFANRIX® (DTPa)

The protective efficacy of *INFANRIX®* (DTPa) following primary immunisation has been established using WHO-defined typical pertussis (≥21 days of paroxysmal cough with laboratory confirmation) in two clinical studies.

In a prospective blinded household contact study conducted in Germany, data were collected from 360 evaluable secondary contacts in households where there was an index case of typical pertussis. Vaccine efficacy was calculated at 88.7% with a two sided 95% confidence interval of 76.6% to 94.5%. This was not statistically different from the DTPw vaccine used in the trial.

In a randomised, double-blind, controlled clinical study conducted in Italy, infants were administered three doses of *INFANRIX®* at 2, 4 and 6 months of age, and followed for an average of 17 months (n=5951). *INFANRIX®* vaccine efficacy was calculated to be 83.9% with a two sided 95% confidence interval of 75.8% to 89.4% against pertussis.

In a follow-up of the same cohort, the efficacy for *INFANRIX®* vaccine was found to be 86% up to 6 years of age.

Protective efficacy against *Haemophilus influenzae* type b following primary immunisation – field effectiveness

The humoral immune response (as measured by serum antibody levels) is complemented by the induction of a cellular immune response (including immune memory), which has been shown to be present as early as four months after completion of the primary immunisation schedule with *INFANRIX hexa*. Data from field studies in the UK have shown that Hib vaccine effectiveness remains high for several years after primary vaccination, despite low levels of serum antibodies, and without administration of a booster dose. Immune memory has thus been proposed

as an important mechanism resulting in the long term protection against invasive Hib disease seen in these studies.

The effectiveness of GSK's Hib component of *INFANRIX hexa* was investigated via an extensive post-marketing surveillance study conducted in Germany. 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).

As the antigen components of the vaccines are identical, it is expected that efficacy data from GSK's DTPa and DTPa/Hib conjugate combination studies can be extrapolated to *INFANRIX hexa*, and that *INFANRIX hexa* will provide similar protective efficacy against pertussis and Hib disease.

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.

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 Description). *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.

PRECAUTIONS

INFANRIX hexa **should under no circumstances be administered intravascularly or intradermally.**

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.

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.

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.

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. 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.

- 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.

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.

As with other vaccines, the administration of *INFANRIX hexa* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

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.

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 immune response to some Hib conjugate vaccines has been reported to be reduced in infants born prematurely compared to term infants. There are no data on the use of *INFANRIX hexa* in infants born prematurely.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h 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.

High incidence of fever (> 39.5°C) was reported in infants receiving *INFANRIX hexa* and Prevenar compared to infants receiving the hexavalent vaccine 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 Adverse Reactions).

Antipyretic treatment should be initiated according to local treatment guidelines.

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.

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. 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.

As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by vaccination with *INFANRIX hexa*.

A protective immune response may not be elicited in all vaccinees (see Clinical Trials).

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.

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.

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 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.

INTERACTIONS WITH OTHER MEDICINES

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

High incidence of fever (>39.5°C) was reported in infants receiving *INFANRIX hexa* and PREVENAR® compared to infants receiving the hexavalent vaccine alone (see Precautions)

ADVERSE REACTIONS

Clinical trial experience

INFANRIX hexa has been assessed for safety and reactogenicity in controlled clinical trials in over 6000 infants. Diary cards were used to actively monitor signs and symptoms following vaccination.

Primary Immunisation

In a large clinical study involving 1076 subjects, the following solicited symptoms were reported within 48 hours following vaccination with *INFANRIX hexa* or following separate administration of DTPa, hepatitis B, Hib and oral polio vaccines. The incidence of solicited symptoms following vaccination with *INFANRIX hexa* was compared to concomitant administration of *INFANRIX*, Hepatitis B, oral polio vaccine and Hib vaccine. No significant difference in the frequency of solicited symptoms was observed between the *INFANRIX hexa* group and the comparator groups. Virtually all symptoms reported resolved within four days and all subjects recovered without sequelae. A causal relationship between vaccine use and the recorded event has not been established for each individual event.

Incidence (%) of solicited symptoms reported within 48 hours following primary immunisation with INFANRIX hexa in a comparative clinical study using a 2, 4, 6 month schedule

Solicited symptoms	**INFANRIX hexa**	**DTPa(INFANRIX™) + HepB(ENGERIX-B™) + Hib(OmniHIB®) + OPV(ORIMUNE®)**			
Local reactions:	**N=3058**	**N=975**			
		Any site	**INFANRIX™**	**ENGERIX-B™**	**OmniHIB®**
Pain at the injection site:	20.6	27.6	20.2	23.5	19.0
Redness ≥20mm	1.7	2.1	1.2	1.3	0.7
Swelling ≥20mm	2.9	2.2	1.2	1.4	0.6
General symptoms:	**N=3063**	**N=978**			
Fever: Any# Grade 3@	 18.1 0.5	 17.1 0.3			
Drowsiness	38.9	43.1			

Irritability	55.0	57.5
Loss of appetite	17.4	18.5

N = Total number of doses administered
 # = A temperature of ≥37.5°C (axillary or oral) or ≥38°C (rectal)
@ = A temperature of ≥39.1°C (axillary or oral) or ≥39.6°C (rectal)

Other events

The following unsolicited events have been reported in clinical trials. It should be noted that causality has not necessarily been established for these events.

Events are listed within body systems and categorised by frequency according to the following definitions:

Very common events: *≥10%;*
Common events: *≥1% and <10%;*
Uncommon events: *≥0.1% and <1%;*
Rare events: *≥0.01% and <0.1%;*
Very rare events: *<0.01%.*

Injection site: *Very common:* pain, redness, local swelling at the injection site ≤ 50mm*

Common: injection site mass, local swelling at the injection site >50mm*, injection site reactions, including induration, fever > 39.5^{o}C.

Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint*

Body as a whole: *Very common:* fatigue

Common: unusual crying, restlessness

Rare: rash

Very rare: allergic reactions (including pruritus**) and anaphylactoid reactions (including dermatitis and urticaria**)

Central Nervous System: *Common*: nervousness

Uncommon: somnolescence

Very rare: convulsions (with or without fever)***

Gastrointestinal system: *Common:* diarrhoea, vomiting, enteritis, gastroenteritis,

Uncommon: abdominal pain, constipation

Metabolism and nutrition disorders: *Very common:* loss of appetite

Resistance mechanism: *Common*: upper respiratory tract infection

Respiratory system: *Common*: bronchitis, rhinitis

Uncommon: bronchospasm, laryngitis, stridor, cough**

Vision: *Uncommon:* conjunctivitis

*During clinical trials, it has been observed that 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.

Post marketing experience

During post marketing surveillance, other reactions have been reported in temporal association with *INFANRIX* hexa. None of the reactions were reported with a frequency higher than 0.01%.

Note that exact incidence rates cannot be calculated under post-marketing experience.

Administration site conditions: *very rare:* injection site mass, extensive swelling reactions, swelling of the entire injected limb, vesicles at the injection site.

Blood and lymphatic system disorders: *very rare:* lymphadenopathy, thrombocytopenia.

Body as a whole: *very rare:* allergic reactions (including anaphylactic and anaphylactoid reactions).

Neurological disorders: *very rare:* convulsions (with or without fever), collapse or shock-like state (hypotonic-hyporesponsive episode)***.

Respiratory, thoracic and mediastinal disorders: Apnoea** [*see Precautions for apnoea in very premature infants (≤28 weeks of gestation)]*

Skin and subcutaneous tissue disorders: Angioneurotic oedema **

** observed with other GSK DTPa-containing vaccines
*** 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.

Experience with hepatitis B vaccine:

Paralysis, neuropathy, Guillain-Barré syndrome, encephalopathy, encephalitis, meningitis, mimicking serum sickness, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and muscular weakness 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.

DOSAGE AND ADMINISTRATION

Before use of the vaccine, the *INFANRIX hexa* suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The *INFANRIX hexa* suspension and the Hib pellet should be inspected visually for any foreign particulate matter or discolouration prior to administration. In the event of either being observed, discard the vaccine.

INFANRIX hexa must be reconstituted by adding the entire contents of the supplied 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.

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.

Dosage

Each dose consists of a 0.5mL ready to use sterile suspension.

Administration

INFANRIX hexa is administered by 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 (0.5mL) of vaccine must be administered.

Immunisation Schedule

The primary immunisation course of *INFANRIX hexa* consists of three doses. *INFANRIX hexa* is recommended for administration at 2, 4 and 6 months of age.

PRESENTATION AND STORAGE CONDITIONS

Presentations

INFANRIX hexa is presented as a turbid white suspension in a pre-filled syringe. Upon storage, a white deposit and clear supernatant can be observed.

The lyophilised Hib vaccine is presented as a white pellet in a glass vial.

The vials and syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

This combination pack is supplied in packs of 1's or packs of 10's.

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.

The expiry date of the vaccine is indicated on the label and packaging.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty. Ltd.
Level 4,
436 Johnston Street,
Abbotsford, Victoria, 3067

Manufacturer:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium.

POISON SCHEDULE OF THE MEDICINE:
Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 15 June 2006

DATE OF MOST RECENT AMENDMENT: 26 June 2014

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