INFANRIX® hexa

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

DESCRIPTION

INFANRIX hexa vaccine is a sterile suspension which contains diphtheria toxoid, tetanus toxoid, three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), Pertussis filamentous haemagglutinin (FHA) and pertactin (PRN)], the purified major surface antigen (HBsAg) of the hepatitis B virus (HBV) and purified polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid, adsorbed on aluminium salts. It also contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain).

The diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment, and formaldehyde treatment of FHA and PRN.

The surface antigen of the HBV (HBsAg) is produced by culture of genetically-engineered *Saccharomyces cerevisiae* yeast cells which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps.

The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

The Hib polysaccharide is prepared from Hib, strain 20,752 and after activation with cyanogen bromide and derivatisation with an adipic hydrazide spacer is coupled to tetanus toxoid via carbodiimide condensation. After purification the conjugate is adsorbed on aluminium salt, and then lyophilised in the presence of lactose as stabiliser.

A 0.5 mL dose of vaccine contains not less than 30IU (25Lf U) of diphtheria toxoid, not less than 40IU (10Lf U) of tetanus toxoid 25µg of PT, 25µg of FHA, 8µg of PRN, 10µg of recombinant HBsAg protein, 40 D-antigen units of type 1 (Mahoney), 8 D-antigen units of type 2 (MEF-1) and 32 D-antigen units of type 3 (Saukett) of the polio virus. It also contains 10µg of purified capsular polysaccharide of Hib (PRP) covalently bound to 20-40µg tetanus toxoid (T). The final vaccine also contains the excipients lactose, sodium chloride, aluminium hydroxide, aluminium phosphate, phenoxyethanol 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.

The manufacture of this product includes exposure to bovine derived 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.

INFANRIX hexa meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of hepatitis B vaccines made by recombinant DNA techniques, of inactivated poliomyelitis vaccines and of Hib conjugate vaccines.

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 (when combined with DTPa based vaccines) has been, and continues to be investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 2 year follow-up period, the effectiveness of three primary doses of GSK's DTPa/Hib and DTPa-IPV/Hib was found to be 98.8%

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.

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.

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. There are no data to support the immunogenicity of *INFANRIX hexa* for anti-PRP antibodies after 1 dose at 2 months or two doses at 4 months of age. Prior to introduction of Hib vaccination the incidence of Hib disease in indigenous Australian children was considerably higher than in non-indigenous Australian children, and onset of Hib disease in indigenous children was at a much earlier age (e.g. 60% under 6 months of age in remote rural areas). *INFANRIX hexa* is not recommended for use in indigenous Australian populations.

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

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.

Antipyretic treatment should be initiated according to local treatment guidelines.

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:* local swelling at the injection site ≤ 50mm*

Common: injection site mass, local swelling at the injection site >50mm*, injection site reactions, including induration.

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

Body as a whole: *Common*: unusual crying, restlessness
Uncommon: fatigue
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

Resistance mechanism: *Common*: upper respiratory tract infection

Respiratory system: *Common*: bronchitis, rhinitis
Uncommon: bronchospasm, laryngitis, stridor

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-hyporesponsiveness episode).

Experience with hepatitis B vaccine:
Paralysis, neuropathy, Guillain-Barré syndrome, encephalopathy, encephalitis and meningitis 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.

The vaccine 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 normal and does not impair the performance of the vaccine. In the event of other variation being observed, discard the vaccine.

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

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.

STORAGE

The vaccine should be stored between +2°C and +8°C. DO NOT FREEZE. The *INFANRIX hexa* suspension and the reconstituted vaccine must not be frozen. Discard if vaccine has been frozen. Protect from light.

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

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.

MANUFACTURER:

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