

INFANRIX® PENTA

Combined Diphtheria-Tetanus-acellular Pertussis (DTPa), Hepatitis B and Inactivated Poliovirus Vaccine

DESCRIPTION

INFANRIX® PENTA 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)] and the purified major surface antigen (HBsAg) of the hepatitis B virus (HBV), 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 diphtheria toxoid, tetanus toxoid and acellular pertussis components are adsorbed onto aluminium salts.

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.

A 0.5 mL dose of vaccine contains 30IU (25 Lf U) of diphtheria toxoid, 40IU (10 Lf U) of tetanus toxoid, 25µg of adsorbed PT, 25µg of adsorbed pertussis FHA, 8µg of adsorbed PRN, 10µg of adsorbed 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. The final vaccine also contains the excipients aluminium hydroxide, aluminium phosphate, sodium chloride, phenoxyethanol and water for injections and 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 PENTA 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 and of inactivated poliomyelitis vaccines.

CLINICAL PHARMACOLOGY

Clinical Trials

Primary Immunisation - Immunogenicity Studies

The immunogenicity of INFANRIX PENTA has been evaluated in >2400 infants during clinical trials. In these studies, INFANRIX PENTA was shown to induce antibodies against all of the components contained in the vaccine. The immunogenicity of INFANRIX PENTA was comparable to DTPa, Hepatitis B and OPV or IPV vaccines administered separately. A variety of primary vaccination schedules were used including vaccination at 2, 4 and 6 months (n= 681) and at 3, 4 and 5 months (n= 856). Immune responses from a pivotal clinical study that used a 2, 4, 6 month schedule are presented in the following table.

Immune responses one month following primary vaccination with INFANRIX PENTA vaccine at 2, 4, 6 months of age

Antigens (n)	Antibody Response (% Seropositive)	GMT (95% confidence intervals)
Diphtheria Toxoid (n= 328)	99.7	1.0 IU/mL (1.0-1.2)
Tetanus Toxoid (n= 328)	100	2.7 IU/mL (2.5-2.9)
Hepatitis B (n= 328)	99.1	1681.5 mIU/mL (1428.2 –1979.6)
Pertussis Toxoid (n= 328)	100	99.1 EL.U/mL (92.6-106.1)
Pertussis FHA (n= 303)	100	167.7 EL.U/mL (158.7-177.3)
Pertactin (n=328)	100	111.8 EL.U/mL (102.1-122.4)
Poliovirus Type 1 (n=326)	100	327.7 (291.7-368.2)
Poliovirus Type 2 (n=326)	100	319.1 (283.6-359.0)
Poliovirus Type 3 (n=325)	100	895.2 (793.2-1010.2)

IU = International Units; EL.U = ELISA Units.

The cut-off values for diphtheria and tetanus (≥ 0.1 IU/mL), hepatitis B (≥ 10 mIU/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 was 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.

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 84% up to four years of age.

INFANRIX (DTPa) is an integral part of the INFANRIX PENTA combination vaccine. It is therefore expected that INFANRIX PENTA will provide similar protective efficacy.

INDICATIONS

INFANRIX PENTA is indicated for immunisation of infants from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis.

CONTRAINDICATIONS

INFANRIX PENTA should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients or residues (see Description). INFANRIX PENTA should not be administered to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or polio vaccines.

INFANRIX PENTA is contraindicated if the child has experienced an 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 and polio vaccines.

PRECAUTIONS

INFANRIX PENTA 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.

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 PENTA 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 $\geq 40.0^{\circ}\text{C}$ within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 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 PENTA. 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.

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

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

INFANRIX PENTA should not be administered at birth. Infants born of HBsAg positive mothers should receive Hepatitis B immune globulin and Hepatitis B vaccine at birth. Only limited data exists on subsequent immunisation of these infants with INFANRIX PENTA.

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 PENTA in these patients.

INFANRIX PENTA will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus or poliovirus. 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 PENTA.

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

Use In Pregnancy (Category B2)

INFANRIX PENTA is not indicated or recommended for use in pregnant women, and has not been evaluated for potential harmful effects during pregnancy in animals or humans.

Use In Lactation

INFANRIX PENTA is not indicated or recommended for use in lactating women, and it is not known whether INFANRIX PENTA is transferred in human or animal milk.

Interactions

Clinical studies have demonstrated that INFANRIX PENTA can be administered simultaneously with *Haemophilus influenzae* type b vaccines. In these clinical studies, the injectable vaccines were given at different injection sites.

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

ADVERSE REACTIONS

Clinical Trial Experience

INFANRIX PENTA has been assessed for safety and reactogenicity in controlled clinical trials in over 7000 infants. Diary cards were used to actively monitor signs and symptoms following vaccination.

Primary Immunisation

In a large clinical study involving more than 3000 subjects, the following solicited symptoms were reported during the first four days after vaccination. 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 following immunisation with INFANRIX PENTA at 3, 4, and 5 months

Solicited Symptoms	% incidence (N = 9032)
<i>Local Reactions</i>	
Pain at the injection site	11.6
Redness (>20mm)	1.1
Swelling (>20mm)	1.5
<i>General Symptoms</i>	
Fever $\geq 38.0^{\circ}\text{C}$	20.0
$>39.5^{\circ}\text{C}$	0.5
Loss of appetite	14.3
Restlessness	34.3
Unusual crying	12.9
Vomiting	7.6
Diarrhoea	10.9

N = Total number of doses administered

The incidence of solicited symptoms following vaccination with INFANRIX PENTA was compared to separate administration of INFANRIX, Hepatitis B, and either oral or inactivated injectable polio vaccine. No significant difference in the frequency of solicited symptoms was observed between the INFANRIX PENTA 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 observed in a comparative clinical study using a 2, 4, 6 month schedule.

Solicited Symptoms	INFANRIX PENTA % (N=291)	INFANRIX-HepB +IPV % (N=278)		INFANRIX + Enderix B + OPV % (N=269)	
		<u>INFANRIX -HepB</u>	<u>IPV</u>	<u>INFANRIX</u>	<u>EnderixB</u>
Local Reactions					
Pain at the injection site	27.8	27.3	22.3	25.3	20.4
Redness (>20mm)	1.0	0.4	0.0	0.0	0.0
Swelling (>20mm)	2.1	1.1	0.4	0.7	0.0
General Symptoms					
Fever ($\geq 38.0^{\circ}\text{C}$)	19.2	15.5		14.1	
Fever ($> 39.5^{\circ}\text{C}$)	1.0	0.0		0.7	
Loss of appetite	18.2	22.3		18.2	
Fussiness	55.0	61.2		53.9	
Unusual crying	2.1	2.5		2.2	
Sleeping less than usual	19.6	23.4		22.3	
Sleeping more than usual	33.3	34.2		34.2	
Vomiting	5.2	7.2		7.8	
Diarrhoea	11.0	9.4		14.9	

N = Total number of doses administered

No significant differences were found between the study groups with respect to the incidence of any of the individual symptoms.

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:* $\geq 10\%$;
- Common events:* $\geq 1\%$ and $< 10\%$;
- Uncommon events:* $\geq 0.1\%$ and $< 1\%$;
- Rare events:* $\geq 0.01\%$ and $< 0.1\%$;
- Very rare events:* $< 0.01\%$.

Injection site: *Very common:* local swelling at the injection site $\leq 50\text{mm}^*$

Common: injection site mass, local swelling at the injection site $> 50\text{mm}^*$

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

*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.

Body as a whole: *Common:* fatigue

Central Nervous System: *Very common:* restlessness, abnormal crying, irritability

Common: nervousness

Resistance Mechanism: *Common:* viral infection, otitis media, upper respiratory tract infection

Respiratory System: *Common:* bronchitis, rhinitis

Skin and subcutaneous tissue disorders: *Common:* dermatitis

Uncommon: rash

Very rare: urticaria

Allergic reactions including anaphylactoid reactions may occur very rarely following vaccination with INFANRIX combination vaccines.

Post-marketing Experience

During post marketing surveillance, other reactions have been reported in temporal association with INFANRIX PENTA. 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, swelling of the entire injected limb.

Body as a whole: *very rare:* allergic reactions (including rash and pruritus), anaphylactoid reactions (including urticaria).

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

All parenteral drug and vaccine products should be inspected visually for any particulate matter or discolouration prior to administration. Before use of INFANRIX PENTA, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise. The vaccine should be administered immediately after opening.

Dosage

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

Administration

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

INFANRIX PENTA 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 vaccination course consists of three doses. INFANRIX PENTA is recommended for administration at 2, 4 and 6 months of age.

STORAGE

INFANRIX PENTA should be stored between +2°C and +8°C. DO NOT FREEZE. Discard if vaccine has been frozen. Protect from light.

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

PRESENTATIONS

INFANRIX PENTA is presented as a turbid white suspension in a prefilled syringe or in a vial*. Upon storage, a white deposit and clear supernatant can be observed.

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

MANUFACTURER:

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*** The vial presentation is not currently marketed in Australia.**