

INFANRIX® PRODUCT INFORMATION

NAME OF THE MEDICINE

Diphtheria-tetanus-acellular pertussis (DTPa) vaccine

DESCRIPTION

INFANRIX DTPa vaccine is a sterile suspension which contains diphtheria toxoid, tetanus toxoid and three purified antigens of *Bordetella pertussis* [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)] adsorbed onto aluminium hydroxide.

The diphtheria and tetanus toxins are obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* and are then detoxified and purified. The acellular pertussis vaccine components (PT, FHA and PRN) are extracted from phase I *Bordetella pertussis*, and are then purified and stabilised.

Each 0.5 mL dose of INFANRIX contains not less than 30 IU of diphtheria toxoid, 40 IU of tetanus toxoid, 25 µg of PT, 25 µg of FHA and 8 µg of PRN. The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine (DTPa) components are adsorbed on 0.5 mg aluminium in the form of aluminium hydroxide, and suspended in isotonic sodium chloride and water for injections.

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 meets the World Health Organisation requirements for biological substances and for diphtheria and tetanus vaccines. No substances of human origin are used in its manufacture.

CLINICAL PHARMACOLOGY

INFANRIX DTPa vaccine, induces antibodies against all vaccine components.

Clinical Trials

Primary Immunisation - Protective Efficacy Studies

In a randomised, double-blind, controlled clinical study conducted in Italy, the efficacy of a primary vaccination course of INFANRIX against pertussis was assessed. Pertussis was defined as illness with paroxysmal cough of ≥ 21 days, and confirmation of *B. pertussis* infection by culture or serology. Infants were administered three vaccine doses at 2, 4, and 6 months of age, and followed for an average of 17 months. Of 4481 infants receiving 3 doses of INFANRIX, 37 confirmed cases of pertussis were reported. Of 1470 infants in the control group receiving 3 doses of diphtheria and tetanus antigens only, 74 confirmed cases of pertussis were reported. INFANRIX vaccine efficacy was calculated to be 83.9% with a two sided 95% confidence interval of 75.8% to 89.4%. Blood samples were collected from a 10% subset of children. Response to

diphtheria and tetanus antigens (antibody titre >0.1 IU/mL dose) was recorded in 96.6% and 99.8% respectively of this subset (>0.01 IU/mL is considered the minimum protective level).

A prospective blinded household contact study conducted in Germany assessed the vaccine efficacy (VE) of a primary course of INFANRIX against typical pertussis (defined by World Health Organization as spasmodic cough of ≥ 21 days, with confirmation of *B.pertussis* infection by culture or serology) up until the time of booster dosing. Of the 360 evaluable secondary contacts in households where there was an index case of typical pertussis, 173 were unvaccinated, 112 received INFANRIX, and 75 received a whole cell DTP vaccine. Of the 173 unvaccinated contacts, 96 developed typical pertussis, compared with 7 of the 112 contacts vaccinated with INFANRIX. The VE for INFANRIX was calculated at 88.7% with a two sided 95% confidence interval of 76.6% to 94.6%. Protection did not wane until at least the time recommended for booster vaccination.

Primary Immunisation - Immunogenicity Studies

The immunogenicity of primary vaccination schedules of INFANRIX have been evaluated in over 1700 infants administered the vaccine at either 2, 4, and 6 months (n=417) or 3, 4, and 5 months of age (n=1302). For the 2, 4, 6 month schedule, over 99% of vaccinees displayed antibody titres ≥ 0.1 IU/mL for diphtheria and tetanus one month after the third dose. The pre and post GMT values for the three pertussis antigens are provided in the following table.

Antigen	N	GMT (EI.U/mL) pre	GMT (EI.U/mL) post #
PT	417	3.5	68
FHA	417	8.9	218
PRN	417	5.3	142

One month after the third vaccine dose

The overall response rates observed with INFANRIX for the diphtheria, tetanus, and three pertussis antigens, were equal or superior to those obtained after immunisation with a whole-cell DTP (DTPw) vaccine.

INFANRIX Booster Dosing - following primary DTPw vaccination

The response to INFANRIX booster doses after a primary DTPw vaccination course has been assessed in 559 children administered doses at 15-20 months (n=400) or at 3 to 7 years of age (n=159). Similar booster responses following the fourth at 15-20 months of age or fifth vaccine dose at 3-7 years of age, were observed for each of the vaccine antigens studied. Following the fourth vaccine dose, diphtheria and tetanus antibodies one month after vaccination were demonstrated in 94.0% and 99.3% of vaccinees respectively; compared to antibody responses of 99.4% and 98.1% respectively following the fifth vaccine dose. All vaccinees had antibody titres of

≥ 0.1 IU/mL against diphtheria and tetanus. The pre and post GMT values for the three pertussis antigens following a fourth or fifth vaccine dose are provided in the following tables. Overall the booster response following INFANRIX was equal or superior to that obtained following DTPw booster vaccination.

Antigen	15-20 months of age (N)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	400	7	136
FHA	382	7	232
PRN	396	9	376

One month after vaccination

Antigen	3-7 years of age (N)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	159	6	108
FHA	159	17	536
PRN	158	7	207

One month after vaccination

INFANRIX Booster Dosing following primary INFANRIX (DTPa) vaccination

The response to INFANRIX booster doses after a primary DTPa vaccination course has been assessed in over 520 children administered a fourth dose between 15 and 24 months of age. A booster response to the diphtheria and tetanus antigens occurred in 97% and 100% of vaccinees respectively, one month after vaccination. All vaccinees had antibody titres of ≥0.1 IU/mL against diphtheria and tetanus, and 98% displayed antibody titres ≥ 1IU/mL for both antigens. The pre and post GMT values for the three pertussis components are provided in the table below.

Antigen	15-24 months of age (N)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	174	8	93
FHA	167	37	502
PRN	174	18	631

One month after vaccination

INFANRIX Booster Dosing in children 4-6 years of age following primary DTPa vaccination

The response to a first booster dose of INFANRIX in children 4-6 years of age previously primed with three doses of DTPa-containing vaccines (3, 5, 11 month schedule) has been assessed. A marked increase in GMTs for all components was observed after the booster dose. All vaccinees had antibody titres of ≥ 0.1 IU/mL against diphtheria and tetanus, and > 95% displayed antibody titres ≥ 1 IU/mL for both antigens. The pre and post GMT values for the three pertussis components are provided in the table below.

Antigen	4-6 years of age (N)	GMT (EI.U/mL) pre-booster	GMT (EI.U/mL) post-booster#
PT	189 (pre)/192 (post)	3.6	77.9
FHA	189 (pre)/195 (post)	31.8	830.0
PRN	189 (pre)/195 (post)	23.9	1021.3

One month after vaccination

INDICATIONS

INFANRIX (DTPa) is indicated for active primary immunisation against diphtheria, tetanus and pertussis when commenced between 2 months and 12 months of age.

INFANRIX (DTPa) is also indicated as fourth and fifth dose for children from 15 months of age up to and including 6 years of age who have been immunised previously with three or four doses of diphtheria, tetanus and pertussis (whole-cell or acellular) vaccine.

CONTRAINDICATIONS

INFANRIX should not be administered to subjects with known hypersensitivity to any components of the vaccine, and should not be administered to subjects having shown signs of hypersensitivity after previous administration of INFANRIX, diphtheria and tetanus vaccine and DTPw.

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

INFANRIX 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 the vaccination course should be continued with diphtheria and tetanus vaccine.

PRECAUTIONS

INFANRIX should under no circumstances be administered intravenously.

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.

If any of the following events have occurred in temporal relation to receipt of DTPw or DTPa the decision to give subsequent doses of INFANRIX, containing the pertussis component, should be carefully considered. 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 $\geq 40.5^{\circ}\text{C}$ within 48 hours of vaccination, 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.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization 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.

A history of febrile convulsions and a family history of convulsive fits do not constitute contraindications. 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.

Acute encephalopathy has been reported rarely (estimated rate 0-10.5 cases per million vaccinations) following whole-cell DTP vaccination; however a causal relationship has not been established. No such cases have been reported to date with acellular DTP vaccines.

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

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

Human Immunodeficiency Virus (HIV) infection is not considered a contraindication for diphtheria, tetanus and pertussis (whole-cell or acellular) immunisation. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, an adequate immunologic response may not be achieved. No data currently exist on use of INFANRIX in these patients.

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.

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.

Use in Pregnancy (Category B2):

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

INTERACTIONS WITH OTHER MEDICINES

INFANRIX was administered simultaneously with other paediatric vaccines (eg. Hib and oral polio) in some studies during the clinical trial programme, however immune responses to the other vaccines were not assessed.

Different injectable vaccines should always be administered at different injection sites.

INFANRIX must not be mixed with other vaccines.

ADVERSE EFFECTS

Clinical Trial Experience

The safety profile presented below is based on data from more than 11,400 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 with respect to the primary course.

Frequencies per dose are defined as follows:

<i>Very common:</i>	$\geq 10\%$;
<i>Common:</i>	$\geq 1\%$ and $< 10\%$;
<i>Uncommon:</i>	$\geq 0.1\%$ and $< 1\%$;
<i>Rare:</i>	$\geq 0.01\%$ and $< 0.1\%$;
<i>Very rare:</i>	$< 0.01\%$.

Blood and lymphatic system disorders

Very rare: Lymphadenopathy¹

Metabolism and nutrition disorders

Common: appetite lost²

Psychiatric disorders:

Very common: irritability

Common: restlessness², crying abnormal

Nervous system disorders:

Very common: somnolence

Uncommon: headache¹

Respiratory, thoracic and mediastinal disorders:

Uncommon: cough¹, bronchitis¹

Gastrointestinal disorders:

Common: gastrointestinal disorders such as diarrhoea and vomiting

Skin and subcutaneous tissue disorders

Common: pruritus

Uncommon: rash

Rare: urticaria

General disorders and administration site conditions:

Very common: redness, local swelling at the injection site (≤ 50 mm), fever $\geq 38.0^{\circ}\text{C}$,

Common: pain², local swelling at the injection site (>50 mm)³

Uncommon: injection site reactions including indurations, fatigue¹, fever $\geq 39.1^{\circ}\text{C}$, diffuse swelling of the injected limb, sometimes involving the adjacent joint³

Post-marketing experience

Blood and lymphatic system disorders:

Thrombocytopenia⁴

Immune system disorders:

Allergic reactions, including anaphylactic and anaphylactoid reactions

Nervous system disorders:

Collapse or shock-like state (hypotonic-hyporesponsiveness episode), convulsions (with or without fever) within 2 to 3 days of vaccination

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

General disorders and administration site conditions:

Swelling of the entire injected limb³

¹ reported only with booster vaccination

² very common for booster vaccination

³ 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. Local swelling at the injection site (>50 mm) and diffuse swelling may be more frequent (very common and common, respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days.

⁴ reported with D and T vaccines

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, the vaccine should be well shaken to obtain a homogenous turbid suspension. Discard the vaccine if it appears otherwise.

Dosage

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

Administration

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

INFANRIX should be injected intramuscularly in the lateral 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 consists of 3 doses at 2, 4 and 6 months of age with a fourth dose at 18 months of age and a fifth dose at 4 to 6 years of age.

INFANRIX can also be used as the fourth and/or fifth dose for children 18 months of age and 4 to 6 years of age, who have previously been immunised with three or four doses of diphtheria, tetanus and pertussis (whole-cell or acellular) vaccine.

Further guidance regarding the use of vaccines can be found in the Australian Immunisation Handbook (see CLINICAL PHARMACOLOGY section for schedules evaluated in clinical trials).

OVERDOSAGE

Cases of overdose have been reported during post-marketing surveillance. Adverse events, when reported, are not specific but similar to adverse events reported with normal vaccine administration.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

STORAGE

INFANRIX should be stored at +2°C and +8°C. DO NOT FREEZE; discard if vaccine has been frozen. The expiry date of the vaccine is indicated on the label and packaging. The shelf life of INFANRIX is 36 months from the date of manufacture at a temperature of +2°C to +8°C.

PRESENTATIONS

INFANRIX is presented as a turbid white suspension in a glass vial or glass prefilled syringe, supplied in packs of 1's or packs of 10's.

Upon storage a white deposit and clear supernatant can be observed.

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

Not all pack sizes and presentations may be distributed in Australia.

MANUFACTURER

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 2 December 2009

Date of most recent amendment: 12 May 2016

Version 4.0

INFANRIX is a registered trade mark of the GSK group of companies.