

# Infanrix IPV

## MIMS Abbreviated Prescribing Information

Diphtheria toxoid; pertussis vaccine; poliomyelitis vaccine; tetanus toxoid

GlaxoSmithKline Australia

**Section:** 10(a) Vaccines - Immunology

**Use in pregnancy:** B2

**Permitted in sport**

**Use:** Primary immunisation, children greater than or equal to 6 wks; single booster, children less than or equal to 6 yrs previously immunised against DTP and polio

**Contraindications:** Hypersensitivity to excipients, residues incl neomycin, polymyxin; hypersensitivity following prior diphtheria, tetanus, pertussis, polio vaccination; encephalopathy less than or equal to 7 days following previous pertussis vaccine; IV admin

**Precautions:** Medical, immunisation history; clinical examination; medical supervision; prior adverse events after pertussis vaccine (see full PI); progressive neurological disorders incl infantile spasms, uncontrolled epilepsy, progressive encephalopathy; acute severe febrile illness (postpone); thrombocytopenia, bleeding disorder; immunosuppression; pregnancy, lactation

**Adverse Reactions:** Local effects incl inj site mass; fever; loss of appetite; restlessness; unusual crying; GI upset; somnolence; URTI; others, see full PI

## Infanrix IPV (Suspension for injection) Rx (S4) CMI

Diphtheria toxoid 30 IU, tetanus toxoid 40 IU, adsorbed pertussis antigens (PT 25 mcg, FHA 25 mcg, pertactin 8 mcg),

polioviruses (type 1 (Mahoney): 40 D-antigen U, type 2 (MEF-1): 8 D-antigen U; type 3(Saukett): 32 D-antigen U);

phenoxyethanol, NaCl, polysorbate 80, formaldehyde, neomycin sulfate, polymyxin B sulfate; white susp

**Dose:** Shake well. 0.5 mL by deep IMI (infants: anterolateral thigh; older children: deltoid). Primary vaccination: dose at 2, 4, 6 mths of age. Booster: single dose

**Pack** 0.5 mL (prefilled syringe) [1]

## MIMS Full Prescribing Information

**MIMS revision date:** 01 Aug 2007

**Name of the medicine** Combined diphtheria, tetanus, acellular pertussis (DTPa) and inactivated poliovirus vaccine.

**Excipients.** The final vaccine also contains the excipients aluminium hydroxide, phenoxyethanol, sodium chloride and water for injections. The vaccine also contains the following residues: medium 199, polysorbate 80, formaldehyde, glycine, potassium chloride, sodium phosphate dibasic dihydrate, potassium phosphate monobasic, neomycin sulfate and polymyxin B sulfate.

**Description** Infanrix IPV vaccine is a sterile suspension which contains diphtheria toxoid (D), tetanus toxoid (T), three purified antigens of *Bordetella pertussis* (pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertussis 69 kilodalton outer membrane protein (69 kDa OMP) (pertactin)) and three types of inactivated polioviruses (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 pertactin. The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

A 0.5 mL dose of vaccine contains not less than 30 IU (25 Lf U (lime flocculation unit)) of diphtheria toxoid, not less than 40 IU (10 Lf U) of tetanus toxoid, 25 microgram of adsorbed PT, 25 microgram of adsorbed pertussis FHA, 8 microgram of adsorbed pertactin, 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) polioviruses. The final vaccine is formulated in saline and contains phenoxyethanol as preservative.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (variant Creutzfeldt-Jakob disease) (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

Infanrix IPV vaccine meets the World Health Organization requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, and of inactivated poliomyelitis vaccines.

**Clinical trials** More than 1,800 doses of Infanrix IPV have been administered in clinical studies evaluating use in primary vaccination schedules. In addition, 721 doses have been administered as a single booster dose in infants and children ranging from 15 months to 13 years.

**Immune response to the DT components.** One month after a three dose primary vaccination course with Infanrix IPV, more than 99% of vaccinated infants had antibody titres of  $\geq 0.1$  IU/mL to both tetanus and diphtheria.

Following administration of a booster dose of Infanrix IPV, more than 99.5% of children had antibody titres of  $\geq 0.1$  IU/mL for both antigens.

Antibody titres  $\geq 0.1$  IU/mL are deemed to correlate with seroprotection against diphtheria and tetanus.

**Immune response to the Pa component.** One month after the three dose primary vaccination course with Infanrix IPV, 100% of infants were seropositive (antibodies  $\geq 5$  EL.U/mL) for the three pertussis components (PT, FHA, pertactin). Overall response rates for each of the three individual pertussis antigens were  $\geq 94\%$ . A vaccine response was defined as induction of antibodies to the individual pertussis antigens, taking into account the age and the prevaccination serological status of the subject.

In booster studies, a vaccine response was seen in  $\geq 96.6\%$  of vaccinees against the pertussis antigens; lower response rates were seen in studies where the prevaccination levels of antibodies were high. A vaccine response was defined as a postvaccination titre  $\geq 2x$  the prevaccination titre for subjects initially seropositive, and a titre  $\geq$  the assay cut-off (5 EL.U/ml) for subjects initially seronegative. All subjects were seropositive one month after this dose.

**Protective efficacy of the Pa component.** As the immune response to pertussis antigens following Infanrix IPV administration is equivalent to that of Infanrix, it can be assumed that the protective efficacy of the two vaccines will also be equivalent.

The clinical protection of the DTPa component, against WHO defined typical pertussis ( $\geq 21$  days of paroxysmal cough) was demonstrated in the following.

A prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was calculated to be 88.7%.

A US National Institutes of Health (NIH) sponsored efficacy study was performed in Italy (2, 4, 6 months schedule). This study determined the vaccine efficacy to be 84%. In a follow up of the same cohort the efficacy was confirmed for up to 4 years of age.

**Immune response to the IPV component.** One month after the three dose primary vaccination course with Infanrix IPV, the overall seropositivity for each of the three polio serotypes (type 1, 2 and 3) was  $\geq 99.5\%$ . Antibody titres  $\geq 8$  are deemed to correlate with seroprotection against poliomyelitis.

Following administration of a booster dose of Infanrix IPV, 100% of children were seropositive for the three polio serotypes. In all booster trials vaccination with Infanrix IPV induced a marked increase in antibody levels with respect to prebooster values (see Tables 1 to 3).

**Infanrix IPV** **Table 1**  
Geometric mean antibody titres (GMTs) following primary immunisation with Infanrix IPV vaccine in children at 7 months of age

Antigen	Primary immunisation GMT (95% confidence interval)
Diphtheria toxoid (n = 203)	1.83 (1.69 - 1.98)
Tetanus toxoid (n = 193)	3.72 (3.47 - 3.99)
Pertussis toxoid (n = 198)	87.2 (81.7 - 93.0)
Pertussis FHA (n = 188)	91.1 (80.6 - 102.9)
Pertactin (n = 188)	166.6 (151.6 - 183.1)
Poliovirus type 1 (n = 174)	374.5 (326.8 - 429.1)
Poliovirus type 2 (n = 175)	406.1 (352.9 - 467.2)
Poliovirus type 3 (n = 175)	1115.0 (978.4 - 1,270.6)

IU: international units

EL.U: ELISA units

n = number of subjects

Assay cutoffs for each antigen are as follows: D & T:  $\geq 0.1$  IU/mL; PT, FHA & PRN: 5 EL.U/mL;

Polio types 1, 2, 3:  $\geq 8$

The cutoff values for diphtheria, tetanus and polio correlate with seroprotection.

Currently there are no known serological correlates for protection for the pertussis antigens

**Infanrix IPV** **Table 2**  
Geometric mean antibody titres (GMTs) from a study of booster immunisation with Infanrix IPV at 4 to 6 years of age, following primary immunisation

Antigen	Booster immunisation GMT (95% confidence interval)	
	Prebooster	Postbooster
Diphtheria toxoid (n = 201 (pre) and 208 (post))	0.08 (0.07 - 0.09)	6.24 (5.39 - 7.23)
Tetanus toxoid (n = 200 (pre) and 208 (post))	0.15 (0.12 - 0.17)	9.96 (8.79 - 11.28)
Pertussis toxoid (n = 200 (pre) and 208 (post))	3.6 (3.2 - 4.0)	63.2 (56.1 - 71.2)
Pertussis FHA (n = 201 (pre) and 208 (post))	30.0 (24.9 - 36.2)	735.2 (653.4 - 827.4)
Pertactin (n = 201 (pre) and 208 (post))	27.2 (23.0 - 32.3)	995.6 (863.5 - 1,147.9)
Poliovirus type 1 n = 193 (pre) and 193 (post))	65.3 (49.9 - 85.4)	2,096.0 (1,817.6 - 2,417.0)
Poliovirus type 2 (n = 194 (pre) and 197 (post))	41.4 (32.0 - 53.5)	1,702.4 (1,482.1 - 1,955.4)
Poliovirus type 3	23.5	2,542.6

(n = 192 (pre) and 189 (post)) | (19.3 - 28.7) | (2,122.0 - 3,046.5)

Note: Primary immunisation with DTPa-containing vaccines at 3, 5 and 11 months of age

IU: International Units

EL.U: ELISA Units

n = number of subjects

Assay cutoffs for each antigen are as follows: D & T:  $\geq 0.1$  IU/mL; PT, FHA & PRN: 5 EL.U/mL;

Polio types 1, 2, 3:  $\geq 8$

The cutoff values for diphtheria, tetanus and polio correlate with seroprotection.

Currently there are no known serological correlates for protection for the pertussis antigens

### Infanrix IPV

**Table 3**

Geometric mean antibody titres (GMTs) from a study of booster immunisation with Infanrix IPV at 5 to 6 years of age, following primary and first booster immunisation

Antigen	Booster immunisation GMT (95% confidence interval)	
	Prebooster	Postbooster
Diphtheria toxoid (n = 72 (pre) and 73 (post))	0.12 (0.09 - 0.15)	6.19 (4.83 - 7.93)
Tetanus toxoid (n = 72 (pre) and 73 (post))	0.25 (0.20 - 0.32)	13.58 (11.30 - 16.31)
Pertussis toxoid (n = 72 (pre) and 66 (post))	3.6 (3.0 - 4.3)	84.7 (62.5 - 114.9)
Pertussis FHA (n = 70 (pre) and 72 (post))	31.8 (22.1 - 45.9)	1051.1 (898.3 - 1,299.8)
Pertactin (n = 72 (pre) and 73 (post))	16.8 (12.7 - 22.3)	820.1 (656.8 - 1024.0)
Poliovirus type 1 (n = 72)	15.6 (11.7 - 20.8)	1,533.2 (1,156.6 - 2,032.2)
Poliovirus type 2 (n = 72 (pre) and 71 (post))	21.8 (16.3 - 29.0)	1,053.4 (819.7 - 1,353.6)
Poliovirus type 3 (n = 71)	44.4 (31.9 - 61.7)	1,740.7 (1,315.7 - 2,303.0)

Note: Primary and first booster immunisation with DTPw-IPV or DTPw-IPV/Hib vaccine

IU: International Units

EL.U: ELISA Units

n = number of subjects

Assay cutoffs for each antigen are as follows: D & T:  $\geq 0.1$  IU/mL; PT, FHA & PRN: 5 EL.U/mL;

Polio types 1, 2, 3:  $\geq 8$

The cut-off values for diphtheria, tetanus and polio correlate with seroprotection.

Currently there are no known serological correlates for protection for the pertussis antigens.

**Indications** For use in a three dose primary schedule for immunisation of infants from 6 weeks of age and over, against diphtheria, tetanus, pertussis and poliomyelitis.

As a single booster dose for children, up to and including 6 years of age, who have previously been immunised against DTP and polio.

**Contraindications** Known hypersensitivity to the active substances or to any of the excipients or residues (see Composition). Signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis or inactivated polio vaccines.

Encephalopathy of unknown aetiology occurring within seven days following previous vaccination with a pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria/ tetanus and polio vaccines.

**Precautions** Infanrix IPV 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.

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. There may be circumstances, such as a high incidence of pertussis, when the potential benefits of vaccination outweigh the 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  $\geq 3$  hours, occurring within 48 hours of vaccination.

Convulsions with or without fever, occurring within three 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) 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.

A history of febrile convulsions, a family history of convulsions, a family history of sudden infant death syndrome (SIDS) or a family history of an adverse event following DTPa (diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine) and/or IPV (inactivated poliomyelitis vaccine) vaccination do not constitute contraindications.

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

Infanrix IPV should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

Infanrix IPV contains traces of neomycin sulfate and polymyxin sulfate. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Human immunodeficiency virus (HIV) infection is not considered a contraindication to Infanrix IPV vaccination. However in patients with immunodeficiency or in patients receiving immunosuppressive therapy, the expected immunological response may not be achieved. No data currently exist on use of Infanrix IPV in these patients.

**Use in pregnancy.** Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

**Use in lactation.** Adequate human data on use during lactation and adequate animal reproduction studies are not available.

**Interactions with other medicines** It is current practice in paediatric vaccination to coadminister different vaccines during the same session. Injectable vaccines should always be given at different injection sites.

Infanrix IPV can be administered concomitantly with hepatitis B vaccine and/or *Haemophilus influenzae* type b (Hib) vaccine, the injections being administered at different injection sites. Routine simultaneous administration of Hib vaccine and hepatitis B vaccine may be performed for children who are at the recommended age to receive these vaccines.

Concomitant administration of Infanrix IPV and the PRP-OMP type Hib vaccine, measles, mumps and rubella combined vaccine, and varicella vaccine has not been assessed in clinical studies. The *Australian Immunisation Handbook* (2000) accepts that these vaccines may be given at the same time if separate injection sites are used.

Infanrix IPV should not be mixed with other vaccines in the same syringe.

**Adverse effects Clinical trial experience.** Adverse reactions associated with Infanrix IPV vaccination have been evaluated in 13 clinical trials with more than 2,400 doses administered. Adverse event data were actively collected using diary cards and by questioning parents at clinic visits (see Table 4).

## Infanrix IPV

**Table 4**

Incidence (%) of general solicited symptoms reported within 48 hours following primary immunisation of infants with Infanrix IPV at a 3, 4.5, 6 month schedule

Solicited symptoms	% Incidence (n = 726)
<b>Local reactions</b>	
Pain at the injection site	16.3
Redness (> 20 mm)	4.4
Swelling (> 20 mm)	3.4
<b>General symptoms</b>	
Fever	
Any <sup>#</sup>	6.1
Grade 3 <sup>@</sup>	0.1
Loss of appetite	10.7
Restlessness	22.7
Unusual crying	18.2
Vomiting	6.5
Diarrhoea	11.6

n: total number of doses administered over a 3 dose primary vaccination course

#: a temperature of  $\geq 37.5^{\circ}\text{C}$  (axillary or oral) or  $\geq 38^{\circ}\text{C}$  (rectal)

@: a temperature of  $> 39^{\circ}\text{C}$  (axillary or oral) or  $> 39.5^{\circ}\text{C}$  (rectal)

The following events were also reported in temporal association with vaccination in clinical trials evaluating the three dose primary vaccination schedules. 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. Common events:  $\geq 1\%$ ; uncommon events:  $\geq 0.1\%$  and  $< 1\%$ ; rare events:  $< 0.1\%$ .

**Body as a whole.** Uncommon: bacterial infection, fungal infection, viral infection, herpes zoster (chicken pox), moniliasis.

**Cardiovascular.** Uncommon: haematoma.

**Nervous system.** Common: somnolence. Uncommon: insomnia.

**Dermatological.** Uncommon: rash, dermatitis, contact dermatitis, eczema, erythematous rash.

**Gastrointestinal.** Common: toothache. Uncommon: dyspepsia, hiccup, abdominal pain, gastroenteritis, gastroesophageal reflux, constipation, flatulence.

**Injection site.** Common: injection site mass.

**Respiratory.** Common: rhinitis, pharyngitis, upper respiratory tract infection. Uncommon: asthma, coughing, pneumonia, respiratory disorder, bronchitis.

**Special senses.** Common: otitis media. Uncommon: conjunctivitis.

**Urogenital.** Uncommon: pyelonephritis.

**Booster vaccination with Infanrix IPV at 4 to 6 years of age.** See Table 5.

### Infanrix IPV

**Table 5**

Incidence (%) of solicited symptoms reported within 48 hours from a study of booster immunisation with Infanrix IPV at 4 to 6 years of age

Solicited symptoms	Following primary immunisation (study A)	Following primary and first booster immunisation (study B)
	% incidence (*n = 210)	% incidence (*n = 73)
<b>Local reactions</b>		
Pain at the injection site		
Any	71.4	82.2
Grade 3	2.9	5.5
Redness		
Any	61.0	65.8
> 50 mm	25.7	9.6
Swelling		
Any	53.3	52.1
> 50 mm	13.3	5.5
<b>General symptoms</b>		
Fever		
Any <sup>#</sup>	21.0	9.6
Grade 3 <sup>@</sup>	0.5	0.0
Irritability	16.7	13.7
Vomiting	not solicited	1.4
Diarrhoea	not solicited	2.7
Loss of appetite	19.0	12.3
Restlessness	not solicited	6.8
Sleeping more than usual/drowsiness	24.8	17.8

Note: Study A: Primary immunisation with DTPa-containing vaccines at 3, 5, 11 months of age. Study B: Primary and first booster immunisation with DTPw-IPV or DTPw-IPV/Hib vaccine. The occurrence and severity of symptoms was assessed using diary cards listing the events tabulated. 'Not solicited' indicates that the event was not listed on the diary card for evaluation

n: number of subjects

<sup>#</sup>: a temperature of  $\geq 37.5^{\circ}\text{C}$  (axillary or oral) or  $\geq 38^{\circ}\text{C}$  (rectal)

<sup>@</sup>: a temperature of  $\geq 39.0^{\circ}\text{C}$  (axillary or oral) or  $\geq 39.5^{\circ}\text{C}$  (rectal)

The following events were also reported in temporal association with vaccination in clinical trials evaluating booster vaccination schedules. 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 ( $\leq 50$  mm). Common: local swelling at the injection site ( $> 50$  mm). Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint.

**Body as a whole.** Common: asthenia. Uncommon: viral infection.

**Dermatological.** Common: pruritus.

**Gastrointestinal.** Uncommon: abdominal pain.

**Musculoskeletal.** Uncommon: myalgia.

**Respiratory.** Common: coughing, rhinitis, pharyngitis. Uncommon: bronchitis.

**Special senses.** Common: otitis media.

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 four days.

**Postmarketing experience.** During postmarketing surveillance, other reactions have been reported in temporal association with

Infanrix IPV or with other DTPa containing vaccines. None of the reactions were reported with a frequency higher than 0.01%. Note that exact incidence rates cannot be calculated under postmarketing 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).

**Dosage and administration** All parenteral drug and vaccine products should be inspected visually for any particulate matter or discoloration prior to administration. Before use of Infanrix IPV 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 0.5 mL ready to use sterile suspension.

**Administration.** Infanrix IPV is administered by deep intramuscular injection. For infants the preferred site of injection is the anterolateral aspect of the thigh because of the small size of their deltoid muscle. In older children, the booster vaccination should be administered in the deltoid region of the arm. The recommended dose (0.5 mL) of vaccine must be administered. Each dose of Infanrix IPV is for single use only. Any residual vaccine must be discarded.

Infanrix IPV vaccine should never be administered intravenously.

**Immunisation schedule. Primary.** The primary vaccination course consists of three doses of Infanrix IPV. Infanrix IPV is recommended for administration at 2, 4 and 6 months of age. An interval of at least one month should be maintained between subsequent doses.

**Booster.** A single booster dose of Infanrix IPV can be given up to and including 6 years of age.

**Presentation** Injection, 0.5 mL (turbid white, ready to use, sterile suspension; upon storage, a white deposit and clear supernatant can be observed) (vial\*, prefilled syringe).

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

**Storage** Infanrix IPV 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.

**Poison Schedule** S4.

**Source Reference** Date of TGA approved information: 23/02/2007

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[Jump To Top](#)