Infanrix Hexa (thiomersal free)

MIMS Abbreviated Prescribing Information
Diphtheria toxoid; haemophilus influenzae vaccine; hepatitis B vaccine; pertussis vaccine; poliomyelitis vaccine; tetanus toxoid
GlaxoSmithKline Australia
Section: **10(a)** Vaccines - Immunology
Use in pregnancy: B2
Permitted in sport

Use: Active primary immunisation, infants greater than or equal to 6 wks (diphtheria, tetanus, pertussis, hepatitis (hep) B, poliomyelitis, Haemophilus influenzae type b (Hib))
Contraindications: Encephalopathy of unknown aetiology within 7 days of previous pertussis containing vaccine; neomycin, polymyxin hypersensitivity
Precautions: Not for intravascular, intradermal, at birth admin; review history esp previous immunisation; ensure adequate supervision; previous adverse reactions assoc with pertussis vaccine (within 48 hrs: temperature greater than or equal to 40.0 deg. C, collapse or shock-like state (hypotonic hyporesponsive episode), persistent, inconsolable crying lasting greater than or equal to 3 hrs; within 72 hrs: convulsions +/- fever); acute severe febrile illness (postpone vaccination); febrile convulsion history; progressive neurological disorder incl infantile spasm, uncontrolled epilepsy, progressive encephalopathy (defer until corrected, stabilised); thrombocytopenia, bleeding disorder; immunosuppression, deficiency; indigenous Australians; infants born to hep B surface antigen (HBsAg) +ve mothers (admin hep B Ig + hep B vaccine at birth); pregnancy, lactation, prematurity (respiratory immaturity history, less than or equal to 28 gestation wks (consider respiratory monitoring for 48-72 hrs))
Adverse Reactions: Inj site reaction incl pain, redness, swelling, mass; fatigue; fever; drowsiness; bronchitis; rhinitis; URTI; GI upset; appetite loss; unusual crying, restlessness; nervousness; apnoea (very premature infants); convulsion +/- fever, allergy incl anaphylactoid reaction (very rare); others, see full PI
Interactions: Prevenar pneumococcal vaccine; do not admix with other vaccines; lab tests: urinary Hib antigen within 1-2 wks

Infanrix Hexa (thiomersal free) (Injection) **Rx** (S4) **CMI**
Combination pack for reconstitution. Suspension: diphtheria toxoid greater than or equal to 30 IU, tetanus toxoid greater than or equal to 40 IU, acellular pertussis vaccine (PT 25 mcg, FHA 25 mcg, PRN 8 mcg), inactivated polioviruses (type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-1) 8 D-antigen units, type 3 (Saukett) 32 D-antigen units), HBsAg 10 mcg; turbid white sterile; prefilled syringe. Pellet: Hib capsular polysaccharide (PRP) 10 mcg; lyophilised, white; vial. Reconstituted vaccine: also contains lactose, NaCl, $Al(OH)_3$, Al phosphate, residues of polysorbates, neomycin, polymyxin; cloudy sterile suspension
Dose: Reconstitute by adding entire syringe contents to vial containing pellet, shake well until pellet is completely dissolved; admin 0.5 mL IM (anterolateral thigh, deltoid); may consider antipyretic treatment. Primary course: 1 dose at age 2, 4, 6 mths
Pack 0.5 mL [1]
Pack 0.5 mL [10]

MIMS Full Prescribing Information
MIMS revision date: 01 Sep 2009
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 physicochemical 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 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 PT, 25 microgram of FHA, 8 microgram of PRN, 10 microgram 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 10 microgram of purified capsular polysaccharide of Hib (PRP) covalently bound to 20 to 40 microgram tetanus toxoid (T). 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.
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 Hexa meets the World Health Organization 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 trials **Primary immunisation. Immunogenicity studies.** The immunogenicity of Infanrix Hexa has been evaluated in > 2,390 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 Table 1.

Infanrix Hexa (thiomersal free) **Table 1**

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 (≥ 0.15 mcg/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 cut off 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 (diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine)) 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 (diphtheria toxoid, tetanus toxoid and whole cell pertussis vaccine) 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 = 5,951). 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 GlaxoSmithKline's (GSK's) Hib component (when combined with DTPa based vaccines) has been, and continues to be, investigated via an extensive postmarketing surveillance study conducted in Germany. Over a two year follow-up period, the effectiveness of three primary doses of GSK's DTPa/ Hib and DTPa-IPV (inactivated poliovirus vaccine)/ 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 seven 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 the 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°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 ≥ three hours, occurring within 48 hours of vaccination.
Convulsions with or without fever, occurring within three days of vaccination.
A history of febrile convulsions, a family history of convulsions, or sudden infant death syndrome (SIDS) do not constitute contraindications 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 two to three 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 to 72 hours should be considered when administering the primary immunisation 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.
Human immunodeficiency virus (HIV) infection is not considered as a contraindication. 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 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 Actions, 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 one to two 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 *H. influenzae* type b disease have shown a reduced antibody response to *H. 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 one 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 nonindigenous 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 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 (pneumococcal vaccine) compared to infants receiving the hexavalent vaccine alone.
Antipyretic treatment should be initiated according to local treatment guidelines.

Adverse effects Clinical trial experience. Infanrix Hexa has been assessed for safety and reactogenicity in controlled clinical trials in over 6,000 infants. Diary cards were used to actively monitor signs and symptoms following vaccination.

Primary immunisation. In a large clinical study involving 1,076 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. (See Table 2.)

Infanrix Hexa (thiomersal free) **Table 2**

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 ≥ 20 mm	1.7	2.1	1.2	1.3	0.7
Swelling ≥ 20 mm	2.9	2.2	1.2	1.4	0.6
General symptoms	**N=3063**	**N=978**			
Fever:					
Any#	18.1	17.1			

Grade 3@	0.5	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 of events according to the following definitions. Very common: ≥ 10%; common: ≥ 1% and < 10%; uncommon ≥ 0.1% and < 1%; rare: ≥ 0.01% and < 0.1%; very rare: < 0.01%.
Injection site. Very common: pain, redness, local swelling at the injection site ≤ 50 mm*. Common: injection site mass, local swelling at the injection site > 50 mm*, injection site reactions including induration, fever > 39.5°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: somnolence. 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 four days.
Postmarketing experience. During postmarketing 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 for postmarketing 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).
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.
Experience with hepatitis B vaccine. Paralysis, neuropathy, Guillain-Barré syndrome, encephalopathy, encephalitis and meningitis have been reported during postmarketing 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 eight hours at room temperature.
Dosage. Each dose consists of a 0.5 mL 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 (0.5 mL) 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 ***Combination pack.*** Infanrix Hexa suspension (sterile, turbid white suspension; a white deposit and clear supernatant can be observed upon storage; prefilled neutral glass type I syringe), lyophilised Hib vaccine (white pellet; neutral glass type I vial), 0.5 mL on reconstitution: 1's, 10's.
Storage The vaccine should be stored between +2 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.
Poison Schedule S4.
Source Reference Date of TGA approved information: 12/03/2008

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