Infanrix™-IPV+Hib

1. NAME OF THE MEDICINAL PRODUCT

Infanrix™-IPV+Hib

Combined diphtheria-tetanus-acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU) (25 Lf)
Tetanus toxoid[1]	not less than 40 International Units (IU) (10 Lf)
Bordetella pertussis antigens	
Pertussis toxoid (PT)[1]	25 micrograms
Filamentous haemagglutinin (FHA)[1]	25 micrograms
Pertactin (PRN)[1]	8 micrograms
Poliovirus (inactivated) (IPV)	
type 1 (Mahoney strain)[2]	40 D-antigen unit
type 2 (MEF-1 strain)[2]	8 D-antigen unit
type 3 (Saukett strain)[2]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) (PRP)	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}

[2]propagated in VERO cells

The **Infanrix™ -IPV** component of the vaccine is a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed.

The Hib component of the vaccine is a white powder.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Infanrix™-IPV+Hib is indicated for active immunisation in infants from the age of 2 months against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b.

Infanrix™-IPV+Hib is also indicated as a booster dose for children who have previously been immunised with diphtheria, tetanus, pertussis (DTP), polio and Hib antigens.

Infanrix™-IPV+Hib does not protect against diseases caused by other types of *Haemophilus influenzae* nor against meningitis caused by other organisms.

4.2 Posology and Method of Administration

Posology

The primary vaccination schedule consists of three doses in the first 6 months of life and can start from the age of 2 months. An interval of at least 1 month should be respected between subsequent doses.

A booster dose is recommended in the second year of life, with an interval of at least 6 months after completion of primary vaccination schedule.

Method of administration

Infanrix™-IPV+Hib is for **deep** intramuscular injection, in the anterolateral thigh. It is preferable that each subsequent dose is given at alternate sites.

Infanrix™-IPV+Hib 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.

4.3 Contra-indications

Infanrix™-IPV+Hib should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, inactivated polio or Hib vaccines.

Infanrix™-IPV+Hib is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

4.4 Special Warnings and Precautions for Use

It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and the possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of **Infanrix™-IPV+Hib** should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication.

Infanrix™-IPV+Hib 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™-IPV+Hib contains traces of neomycin and polymyxin and the vaccine should be used with caution in patients with known hypersensitivity to either of these antibiotics.

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

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.

The use of **Infanrix™-IPV+Hib** is not recommended in adults, adolescents or children above 5 years of age.

As with all diphtheria, tetanus, and pertussis vaccines, the vaccine should be administered by deep intramuscular injection to the anterolateral thigh. It is preferable that each subsequent dose is given at alternate sites.

The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patients on immunosuppressive therapy.

If any of the following events occur in a temporal relationship to the receipt of a DTP-containing vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. These events include:

- temperature of ≥ 40.0 °C (rectal) 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.

However, as these events are not associated with permanent sequelae, there may be circumstances, such as a high incidence of pertussis, where the potential benefits outweigh possible risks.

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, a family history of convulsions, a family history of Sudden Infant Death Syndrome (SIDS) or a family history of an adverse event following DTP, IPV and/or Hib vaccination do not constitute contra-indications.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication.

Excretion of capsular polysaccharide antigen in the urine has been described following receipt of Hib vaccines, and therefore antigen detection may not have a diagnostic value in suspected Hib disease within 1-2 weeks of vaccination.

Infanrix™-IPV+Hib should under no circumstances be administered intravenously.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h 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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

As it is current practice in paediatric vaccination to coadminister different vaccines during the same session, **Infanrix™-IPV+Hib** can be administered concomitantly with hepatitis B vaccine. Reconstituted **Infanrix™-IPV+Hib** and a different injectable vaccine should be administered at different injection sites.

As with other vaccines it may be expected that, in patients receiving immunosuppressive therapy or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Pregnancy and Lactation

As **Infanrix™-IPV+Hib** is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

4.7 Effects on Ability to Drive and Use Machines

Not relevant.

4.8 Undesirable Effects

- **Clinical trial data**

The safety profile presented below is based on data from more than 3,500 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™-IPV+Hib** with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:
Very common : ≥ 1/10
Common : ≥ 1/100 to < 1/10
Uncommon : ≥ 1/1,000 to < 1/100
Rare : ≥ 1/10,000 to < 1/1,000
Very rare : < 1/10,000

Infections and infestations
Uncommon : upper respiratory tract infection

Blood and lymphatic system disorders
Uncommon : lymphadenopathy

Metabolism and nutrition disorders
Very common : appetite lost

Psychiatric disorders
Very common : irritability, crying abnormal, restlessness

Nervous system disorders
Very common : somnolence

Respiratory, thoracic and mediastinal disorders
Uncommon : cough, bronchitis, rhinorrhoea

Gastrointestinal disorders
Common : diarrhoea, vomiting

Skin and subcutaneous tissue disorders
Uncommon : rash, urticaria
Rare : pruritus, dermatitis

General disorders and administration site conditions
Very common : injection site reactions such as pain and redness, local swelling at the injection site (≤ 50 mm), fever (≥ 38.0°C)
Common : injection site reactions including induration, local swelling at the injection site (> 50 mm)[1]
Uncommon : fever[2] > 39.5°C, fatigue, diffuse swelling of the injected limb, sometimes involving the adjacent joint[1]

- **Post marketing data**

Blood and lymphatic system disorders
Thrombocytopenia[4]

Immune system disorders
Allergic reactions (including anaphylactic[3] and anaphylactoid reactions)
Nervous system disorders

Convulsions (with or without fever), collapse or shock-like state (hypotonic-hyporesponsiveness episode)

Respiratory, thoracic and mediastinal disorders
Apnoea[3] [see section 4.4 Special Warnings and Precautions for Use for apnoea in very premature infants (≤28 weeks of gestation)]

Skin and subcutaneous tissue disorders
Angioneurotic oedema[3]

General disorders and administration site conditions
Swelling of the entire injected limb[1], injection site vesicles[3]

[1]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.
[2]common with booster vaccination
[3]reported with GSK's DTPa containing vaccines
[4]reported with D and T vaccines.

4.9 Overdose
Some cases of overdose have been reported during post-marketing surveillance. Adverse events, when reported following overdosage, were similar to those observed after administration of the recommended dose of **Infanrix™-IPV+Hib**.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties
Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code: J07CA06

Results obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off after primary vaccination with Infanrix™-IPV+Hib:

Antibody (cut-off)	**3-5 months N= 86 (1 trial) %**	**1.5-3.5-6 months N = 62 (1 trial) %**	**2-3-4 months N=337 (3 trials) %**	**2-4-6 months N=624 (6 trials) %**	**3-4-5 months N=127 (2 trials) %**	**3-4.5-6 months N=198 (1 trial) %**
Anti-diphtheria (0.1 IU/ml)*	94.1	100	98.8	99.3	94.4	99.5
Anti-tetanus (0.1 IU/ml)*	100.0**	100	99.7	99.8	99.2	100
Anti-PT (5 EL.U/ml)	99.5**	100	99.4	100	98.4	100
Anti-FHA (5 EL.U/ml)	99.7**	100	100	100	100	100
Anti-PRN (5 EL.U/ml)	99.0**	100	100	100	100	100
Anti-Polio type 1 (1/8 dilution)*	93.0	ND	99.1	99.5	100	100

Anti-Polio type 2 (1/8 dilution)*	95.3	ND	95.7	99.0	99.2	100
Anti-Polio type 3 (1/8 dilution)*	98.8	ND	100	100	99.2	99.4
Anti-PRP (Hib) (0.15 μg/ml)*	83.7	100	98.5	98.5	100	98.4
Anti-PRP (Hib) (1.0 μg/ml)	51.2	87.1	68.5	76.0	97.6	81.2

N = number of subjects
ND = not determined
* cut-off accepted as indicative of protection
** Post dose 2 results from studies where DTPa-HBV-IPV+Hib was administered in a schedule 3, 5 and 11 months of age.

Percentage of subjects with antibody titres ≥ assay cut-off after booster vaccination with Infanrix™-IPV+Hib:

Antibody (cut-off)	**Booster vaccination at 11/12 months of age following a 3-5 month primary course N=184 (1 trial) %**	**Booster vaccination during the second year of life following a three dose primary course N=1,326 (9 trials) %**
Anti-diphtheria (0.1 IU/ml)*	100	99.8
Anti-tetanus (0.1 IU/ml)*	99.9**	99.9
Anti-PT (5 EL.U/ml)	99.9**	99.7
Anti-FHA (5 EL.U/ml)	99.9**	100
Anti-PRN (5 EL.U/ml)	99.5**	99.9
Anti-Polio type 1 (1/8 dilution)*	99.4	99.9
Anti-Polio type 2 (1/8 dilution)*	100	100
Anti-Polio type 3 (1/8 dilution)*	99.4	100
Anti-PRP (Hib) (0.15 μg/ml)*	100	100
Anti-PRP (Hib) (1.0 μg/ml)	96.7	99.2

N = number of subjects
* cut-off accepted as indicative of protection
** Post dose 3 results from studies where DTPa-HBV-IPV+Hib was administered in a schedule 3, 5 and 11 months of age.
The effectiveness of the Hib component (when combined with DTPa, DTPa-IPV or DTPa-HBV-IPV) was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 4.5 year follow-up period, the effectiveness of DTPa+Hib or DTPa-IPV+Hib vaccines was

96.7% for a full primary series and 98.5% for a booster dose (irrespective of priming). Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

5.2 Pharmacokinetic Properties
Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical studies
See 5.1 Pharmacodynamics Properties.

5.3 Preclinical Safety Data
Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, local tolerance and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Lactose, sodium chloride, Medium 199, water for injections.
Potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 80, glycine, formaldehyde, neomycin sulphate, polymyxin sulphate are present as residuals from the manufacturing process.

6.2 Incompatibilities
Reconstituted **Infanrix™-IPV+Hib** should not be mixed with other vaccines in the same syringe.

6.3 Shelf-life
The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special Precautions for Storage
The Hib component and the DTPa-IPV component should be stored at between +2^{o}C to +8^{o}C.
The **Infanrix™-IPV** component should not be frozen. Discard if it has been frozen.

6.5 Nature and Content of Container
The Hib component is presented in a glass vial.

The **Infanrix™-IPV** component is presented in a pre-filled syringe or a glass vial.

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

6.6 Instructions for Use and Handling
The Hib powder, the **Infanrix™-IPV** suspension and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

Since a white sediment may form during storage, the **Infanrix™-IPV** suspension should be shaken before reconstitution.

The vaccine must be reconstituted by adding the entire contents of the supplied container of the **Infanrix™-IPV** component to the vial containing the Hib powder. Only the components of the vaccine should be mixed together and not with other vaccines or other batches of components.

After the addition of the **Infanrix™-IPV** suspension to the Hib powder, the mixture should be well shaken.

The reconstituted **Infanrix™-IPV+Hib** vaccine presents as a slightly more cloudy suspension than the liquid DTPa-IPV component alone. This is normal and does not impair the performance of the vaccine. In the event of other variations being observed, discard the vaccines.

Remove and discard the first needle and replace it with the second needle. Administer the vaccine.

After reconstitution, the vaccine should be injected immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

7. MARKETING AUTHORIZATION HOLDER
GlaxoSmithKline (Thailand) Ltd.

8. MARKETING AUTHORIZATION NUMBER
2C 6/44 (N)

9. DATE OF AUTHORIZATION
26 Apr 2001 (conditional license)
1 Nov 2003 (unconditional license)

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