INFANRIX™-IPV+HIB
Combined diphtheria-tetanus-acellular pertussis, inactivated polio and
Haemophilus influenzae type b vaccine

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 purified capsular polysaccharide\(^3\)
(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, purified and inactivated with formaldehyde
\(^3\) prepared from *Haemophilus influenzae* type b, strain 20,752; after purification, the conjugate is lyophilised in the presence of lactose as stabiliser.

The diphtheria and tetanus toxoids obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* are inactivated and purified. The acellular pertussis vaccine components (PT, FHA and pertactin) are prepared by growing phase I *Bordetella pertussis* from which the PT, FHA and pertactin are extracted, purified and treated with formaldehyde; PT is irreversibly inactivated.

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.

PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.
CLINICAL PARTICULARS

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.

Dosage and 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 maintained 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.

Contraindications

*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 contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

Warnings and Precautions

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 contraindication.

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 \( \geq 40.0 \) °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 \( \geq 3 \) 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 contraindications.

Human Immunodeficiency Virus (HIV) infection is not considered as a contraindication.
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.

**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.

**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.

**Effects on Ability to Drive and Use Machines**

Not relevant.

**Adverse Reactions**

- **Clinical Trial Data**

The safety profile presented below is based on data from more than 3500 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:** ≥ 1/1000 to < 1/100
- **Rare:** ≥ 1/10,000 to < 1/1000
- **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, rhinorrhea

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: fever² >39.5°C, fatigue, diffuse swelling of the injected limb, sometimes involving the adjacent joint¹

- Post Marketing Data

Blood and lymphatic system disorders
Thrombocytopenia⁴

Immune system disorders
Allergic reactions (including anaphylactic³ and anaphylactoid reactions)

Nervous system disorders
Convulsions (with or without fever), collapse or shock-like state (hypotonic-hyposponsiveness episode)

Respiratory, thoracic and mediastinal disorders:
Apnoea³[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]

Skin and subcutaneous tissue disorders
Angioneurotic oedema³

General disorders and administration site conditions
Swelling of the entire injected limb¹, injection site vesicles³

¹Children 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.
²common with booster vaccination
³reported with GSK’s DTPa containing vaccines
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*.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

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***:

<table>
<thead>
<tr>
<th>Antibody (cut-off)</th>
<th>3-5 months N= 86 (1 trial) %</th>
<th>1.5-3.5-6 months N= 62 (1 trial) %</th>
<th>2-3-4 months N= 337 (3 trials) %</th>
<th>2-4-6 months N= 624 (6 trials) %</th>
<th>3-4-5 months N= 127 (2 trials) %</th>
<th>3-4.5-6 months N=198 (1 trial) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diphtheria (0.1 IU/ml)*</td>
<td>94.1</td>
<td>100</td>
<td>98.8</td>
<td>99.3</td>
<td>94.4</td>
<td>99.5</td>
</tr>
<tr>
<td>Anti-tetanus (0.1 IU/ml)*</td>
<td>100.0**</td>
<td>100</td>
<td>99.7</td>
<td>99.8</td>
<td>99.2</td>
<td>100</td>
</tr>
<tr>
<td>Anti-PT (5 EL.U/ml)</td>
<td>99.5**</td>
<td>100</td>
<td>99.4</td>
<td>100</td>
<td>98.4</td>
<td>100</td>
</tr>
<tr>
<td>Anti-FHA (5 EL.U/ml)</td>
<td>99.7**</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-PRN (5 EL.U/ml)</td>
<td>99.0**</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-Polio type 1 (1/8 dilution)*</td>
<td>93.0</td>
<td>ND</td>
<td>99.1</td>
<td>99.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-Polio type 2 (1/8 dilution)*</td>
<td>95.3</td>
<td>ND</td>
<td>95.7</td>
<td>99.0</td>
<td>99.2</td>
<td>100</td>
</tr>
<tr>
<td>Anti-Polio type 3 (1/8 dilution)*</td>
<td>98.8</td>
<td>ND</td>
<td>100</td>
<td>100</td>
<td>99.2</td>
<td>99.4</td>
</tr>
<tr>
<td>Anti-PRP (Hib) (0.15 µg/ml)*</td>
<td>83.7</td>
<td>100</td>
<td>98.5</td>
<td>98.5</td>
<td>100</td>
<td>98.4</td>
</tr>
<tr>
<td>Anti-PRP (Hib) (1.0 µg/ml)</td>
<td>51.2</td>
<td>87.1</td>
<td>68.5</td>
<td>76.0</td>
<td>97.6</td>
<td>81.2</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Antibody (cut-off)</th>
<th>Booster vaccination at 11/12 months of age following a 3-5 month primary course N = 184 (1 trial)</th>
<th>Booster vaccination during the second year of life following a three dose primary course N = 1326 (9 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diphtheria (0.1 IU/ml)*</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td>Anti-tetanus (0.1 IU/ml)*</td>
<td>99.9**</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-PT (5 EL.U/ml)</td>
<td>99.9**</td>
<td>99.7</td>
</tr>
<tr>
<td>Anti-FHA (5 EL.U/ml)</td>
<td>99.9**</td>
<td>100</td>
</tr>
<tr>
<td>Anti-PRN (5 EL.U/ml)</td>
<td>99.5**</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-Polio type 1 (1/8 dilution)*</td>
<td>99.4</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-Polio type 2 (1/8 dilution)*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-Polio type 3 (1/8 dilution)*</td>
<td>99.4</td>
<td>100</td>
</tr>
<tr>
<td>Anti-PRP (Hib) (0.15 µg/ml)*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-PRP (Hib) (1.0 µg/ml)</td>
<td>96.7</td>
<td>99.2</td>
</tr>
</tbody>
</table>

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, of which one was Infanrix hexa, 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).

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See Pharmacodynamics.
Pre-clinical Safety Data

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose, sodium chloride, aluminum salts, 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.

Incompatibilities

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

Shelf Life

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

Special Precautions for Storage

The Hib component and the DTPa-IPV component should be stored at between +2°C to +8°C.
The Infanrix™-IPV component should not be frozen. Discard if it has been frozen.

Nature and Contents 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.

Instructions for Use/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.

For further information, please contact the manufacturer.

Not all presentations are available in every country.

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Manufacturer: GlaxoSmithKline Biologicals s.a. Rue de l’Institut 89, B-1330 Rixensart, Belgium.