INFANRIX-IPV+HIB

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

Powder and suspension for suspension for injection

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.

CLINICAL INFORMATION

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 regards 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 ≥ 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) 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 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 48-72 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.

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, 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 *Warnings and Precautions* 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

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***.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic 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 = 1326 (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, 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

Not relevant for vaccines.

Clinical Studies

See section *Pharmacodynamics*.

Non-Clinical Information

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

PHARMACEUTICAL INFORMATION

List of Excipients

Lactose, sodium chloride, aluminium salts, Medium 199 (as stabilizer containing amino acids, mineral salts and vitamins), water for injections.

Neomycin sulphate and polymyxin B sulphate are present as residuals from the manufacturing process.

Shelf Life

The expiry date is indicated on the label and packaging.

Storage

The Hib component and the DTPa-IPV component should be stored at 2°C - 8°C.

The Infanrix-IPV component should not be frozen. Discard if it has been frozen.

The storage conditions are detailed on the packaging.

Nature and Contents of Container

The Infanrix-IPV component is presented in a pre-filled syringe.

The Hib component is presented in a glass vial.

Powder in a vial (type I glass) containing 1 dose with a stopper (butyl rubber) and 0.5mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

Pack sizes of 1 and 10, with or without needles.

Not all presentations are available in every country.

Incompatibilities

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

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 pre-filled syringe 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.

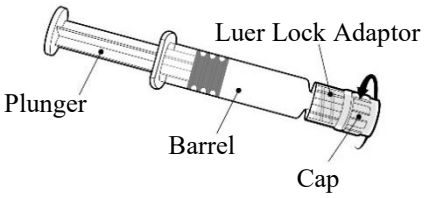
The reconstituted ***Infanrix-IPV+Hib*** vaccine presents as a slightly more cloudy suspension than the liquid DTPa-IPV component alone. This is normal and does not impair the performance of the vaccine. In the event of other variations being observed, discard the vaccines.

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

After reconstitution, the vaccine should be injected immediately.

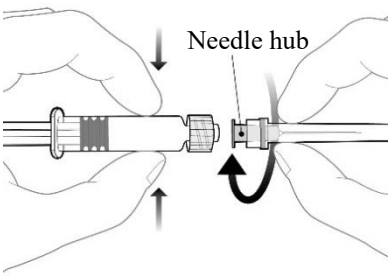
Withdraw the entire contents of the vial.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Reconstitute the vaccine as described above.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal:

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

For further information, please contact the manufacturer.

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Manufacturer responsible for batch release:
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