GlaxoSmithKline

Infanrix™ Hib

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1. Name of the medicinal product
Infanrix™-Hib
Diphtheria, tetanus, acellular pertussis and adsorbed conjugated *Haemophilus influenzae* type b vaccine.

2. Qualitative and quantitative composition
Infanrix™-Hib contains diphtheria toxoid, tetanus toxoid and three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (69 kiloDalton outer membrane protein)] adsorbed onto aluminium salts. It also contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of Hib, covalently bound to tetanus toxoid.
The diphtheria and tetanus toxins obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* are detoxified and purified. The acellular pertussis vaccine components (PT, FHA and pertactin) are prepared by growing phase I *Bordetella pertussis* from which the PT and FHA and pertactin are extracted, purified and irreversibly detoxified.
The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine components are adsorbed on aluminium salts. The final vaccine is formulated in saline.
The Hib polysaccharide is prepared from Hib, strain 20,752 and coupled to tetanus toxoid. After purification the conjugate is lyophilised in the presence of lactose as stabiliser.
Infanrix™-Hib meets the World Health Organisation requirements for manufacture of biological substances, of Hib conjugate vaccines and of diphtheria, tetanus, pertussis and combined vaccines.
An 0.5 ml dose of the vaccine contains not less than 30 International Units (IU) of diphtheria toxoid, not less than 40 IU of adsorbed tetanus toxoid, 25 mcg of PT, 25 mcg of FHA, 8 mcg of pertactin and 10 mcg of purified capsular polysaccharide of Hib covalently bound to approximately 30 mcg tetanus toxoid.

3. Pharmaceutical form
Powder and suspension for suspension for injection

4. Clinical particulars

4.1 Therapeutic indications
Infanrix™-Hib is indicated for active immunisation of all infants from the age of 2 months against diphtheria, tetanus, pertussis (DTP) and Hib.
Infanrix™-Hib does not protect against diseases due to other types of *H. 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.
As vaccination schemes vary from country to country, the schedule for each country may be used in accordance with the different national recommendations.
To ensure long term protection, a booster dose is recommended for DTP and Hib in the second year of life.

Method of administration:
The reconstituted vaccine is for **deep intramuscular** injection preferably at alternate sites for each injection.

4.3 Contra-indications
Infanrix™-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 or Hib vaccines.

Infanrix™-Hib is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus and Hib vaccines.

4.4 Special warnings and special precautions for use
As with other vaccines, the administration of ***Infanrix™-Hib*** should be postponed in subjects suffering from acute severe febrile illness.
The presence of a minor infection, however, is not a contra-indication.
It is good clinical practice that vaccination should be preceded by a review of medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.
If any of the following events occur in temporal relation to receipt of DTP-containing vaccines, the decision to give subsequent 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 outweigh possible risks, particularly since these events are not associated with permanent sequelae.
The following events were previously considered contra-indications for DTPw and can now be considered general precautions:

- temperature of ≥ 40.5°C within 48 hours of vaccination, 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.

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.
As with all injectable vaccines, appropriate medical treatment should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.
Infanrix™-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.
As with all diphtheria, tetanus and pertussis vaccines, the vaccine should be administered by deep intramuscular injection and preferably at alternate sites for each injection.
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-Hib should under no circumstances be administered intravascularly.
A history of febrile convulsions, a family history of convulsive fits, a family history of SIDS and a family history of an adverse event following ***Infanrix™-Hib*** do not constitute contra-indications.
Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication.

4.5 Interaction with other medicaments and other forms of interaction
Infanrix™-Hib can be administered either simultaneously or at any time before or after a different inactivated or live vaccine.
Different injectable vaccines should always 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 immunologic response may not be achieved.

4.6 Use during pregnancy and lactation
As ***Infanrix™-Hib*** is not intended for use in adults, adequate human data on use during pregnancy or lactation and adequate animal reproduction studies are not available.

4.7 Effect on ability to drive and use machines
Infanrix™-Hib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Clinical Trials: In controlled clinical studies, signs and symptoms were actively monitored and recorded on diary cards following the administration of the vaccine.
Local and general solicited symptoms reported within 48 hours of vaccination (following primary immunisation or booster dose) are listed below.

Adverse events are defined by WHO preferred terms and reported with the following frequencies:
Very common: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%

Application site:
Very common: swelling (<2 cm), redness (<2 cm), pain (minor or cried / protested on touch), local swelling at the injection site (≤ 50 mm).

Common: swelling (>2 cm), redness (>2 cm), local swelling at the injection site (> 50 mm)*
Uncommon: pain (infant cried when limb moved / spontaneously painful), diffuse swelling of the injected limb, sometimes involving the adjacent joint*

Body as a whole:
Very common: unusual crying.

Uncommon: fever (≥38.0°C rectal), fever (≥39.5 °C rectal).

Central and peripheral nervous system:
Very common: restlessness.

Gastrointestinal system:
Very common: diarrhoea, loss of appetite.
Common: vomiting.

Psychiatric:
Very common: somnolence.

The following unsolicited symptoms have been reported with a frequency of > 1% (total of 2336 documented doses); these are not necessarily related to the vaccine:

- gastro-intestinal system (1.1% or less): gastroenteritis, enteritis; resistance mechanism (2.5% or less): viral infection, otitis media; respiratory system (5.7% or less): pharyngitis, coughing, rhinitis, respiratory disorder, bronchitis, upper respiratory tract infection;
- vision (1.3% or less): conjunctivitis.

Following administration of booster vaccine, convulsions and febrile convulsions were uncommonly reported. No causal link between these adverse events and either component of the vaccine has been established.

Post-Marketing Surveillance:
Post-marketing surveillance data includes reports for both primary and booster vaccination schedules.

Application site:
Extensive swelling reactions, swelling of the entire injected limb*

Body as a whole:
Allergic reactions including anaphylactoid reactions

Central and peripheral nervous system:
Convulsions within 2 to 3 days of vaccination, collapse or shock-like state (hypotonic-hyporesponsiveness episode).

* 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.

4.9 Overdose
Occasional reports of overdose have been received. Overdose has not resulted in ill effect.

5. Pharmacological particulars

5.1. Pharmacodynamic properties.
Pharmaco-therapeutic group: Bacterial vaccines, ATC code J07AG52
DTPa component:
One month after the primary vaccination course more than 99.6% of infants vaccinated with ***Infanrix™-Hib*** had antibody titers of ≥ 0.1 IU/ml to tetanus and diphtheria. The mean vaccine response to the pertussis antigens (PT, FHA, pertactin) was 97.7%.
Following administration of ***Infanrix™-Hib*** booster in the second year of life, 100% of infants had antibody titers of ≥ 0.1 IU/ml to both diphtheria and tetanus.
The booster response to the pertussis antigens was seen in 100% of these infants.
The protective efficacy of a primary vaccination course of ***Infanrix™*** against typical pertussis (as defined by World Health Organisation) was assessed up until the time of booster in a prospective blinded household contact study. 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 88.7%, with a two-sided 95% confidence interval of 76.6% to 94.6%.

Hib component:
A titre of ≥ 0.15 µg/ml was obtained in 95-100% of infants one month after the completion of the primary vaccination course.
A titre of ≥ 0.15 µg/ml was obtained in 100% of infants one month after the booster dose and all infants had a titre of ≥ 1 µg/ml with 95.5% over 10 µg/ml.

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

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on general safety studies.

6. Pharmaceutical particulars

6.1 List of excipients
Lyophilised Hib vaccine: lactose
DTPa vaccine: Aluminium hydroxide, sodium chloride, water for injections
Formaldehyde and polysorbate 80 are present as residuals from the manufacturing process.

6.2 Incompatibilities
In the absence of compatibility studies, ***Infanrix™-Hib*** must not be mixed with other medicinal products.

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

6.4 Special precautions for storage
The lyophilised Hib vaccine and the DTPa vaccine have to be stored at +2°C to +8°C and be protected from light.
The DTPa vaccine should not be frozen. Discard if it has been frozen.
The lyophilised Hib vaccine is not affected by freezing.

6.5 Nature and contents of container
Powder in vial (Type I glass) with stopper (butyl).
0.5 ml of suspension for injection in vial (Type I glass) with a stopper (rubber butyl).
0.5 ml of suspension for injection in pre-filled syringe (Type I glass) with a plunger stopper (rubber butyl).

6.6 Instructions for use, handling and disposal (if appropriate)
The lyophilised Hib vaccine is presented as a white pellet and the DTPa vaccine is a suspension.
The DTPa vaccine and 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 vaccines.
The vaccine must be reconstituted by adding the entire contents of the container of the DTPa vaccine to the vial containing the pellet.
After the addition of the DTPa vaccine to the pellet, the mixture should be well shaken. The reconstituted vaccine must not be injected before complete dissolution of the pellet.
After reconstitution, ***Infanrix™-Hib*** should be injected promptly.

For further information, refer to manufacturer.

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