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INFANRIX[®] -IPV+Hib

TITLE

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

SCOPE

Trade Name

INFANRIX[®] -IPV+Hib

Formulation and Strength

Powder and suspension for suspension for injection.

Hib vaccine (lyophilised) for reconstitution with the DTPa-IPV vaccine (suspension).

INFANRIX[®]-IPV+Hib contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN/69 kiloDalton outer membrane protein)] adsorbed on aluminium salts. It contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain) and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid.

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 and purified. FHA and pertactin are treated with formaldehyde, PT is treated with glutaraldehyde and formaldehyde, and irreversibly inactivated.

The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

The Hib polysaccharide is prepared from *Haemophilus influenzae* type b, strain 20,752 and is coupled to tetanus toxoid. After purification the conjugate is lyophilised in the presence of lactose as stabiliser.

INFANRIX-IPV+Hib meets the World Health Organisation requirements for the manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of inactivated poliomyelitis vaccines and Hib conjugate vaccines.

A 0.5 ml dose of vaccine contains not less than 25 Lf { $\approx$ min. 30 International Units (IU)} of adsorbed diphtheria toxoid, not less than 10 Lf ($\approx$ min. 40 IU) of adsorbed tetanus toxoid, 25 μ g of PT, 25 μ g of FHA, 8 μ g of pertactin, 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 μ g of purified capsular polysaccharide of Hib covalently bound to approximately 30 μ g tetanus toxoid.

Excipients

Lactose, Sodium chloride, Aluminum hydroxide, Medium 199, Water for injections.

Residues

Potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 80, glycine, formaldehyde, neomycin sulfate, polymyxin sulphate.

CLINICAL INFORMATION

Indications

INFANRIX[®]-IPV+Hib is indicated for active immunisation in infants from the age of 2 months to 5 years, 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 DTP, polio and Hib antigens.

The Hib component of the vaccine does not protect against diseases due to other serotypes 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 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 aspect of the 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 contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

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.

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 possible occurrence of undesirable events) and a clinical examination.

If any of the following events occur in temporal relation to receipt of DTP-containing vaccine, 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 the events are not associated with permanent sequelae. According to available clinical data, the risk benefit ratio of acellular pertussis vaccine is better than the risk benefit ratio of whole cell pertussis vaccine. The following events were previously considered contra-indications for DTPw and can now be considered precautions :

- 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.

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) and 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.

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

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.

INFANRIX-IPV+Hib contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

The use of INFANRIX-IPV+Hib in persons over five year of age is not recommended.

As with all diphtheria, tetanus, and pertussis vaccines, the vaccine should be given deep intramuscularly. The vaccine should be given in the anterolateral aspect of the 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.

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.

Administration of INFANRIX-IPV+Hib should be recorded in the patient's International Vaccination Certificate.

Interactions

It is current practice in paediatric vaccination to coadminister different vaccines during the same session, where injectable vaccines should always be given at different injection sites.

INFANRIX-IPV+Hib can be administered concomitantly with hepatitis B vaccine, the injections being applied 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

- **Pregnancy**

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

- **Lactation**

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not applicable.

Adverse Reactions

- **Clinical trials**

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.

Frequencies per dose are defined as follows:

Very common: $\geq 10\%$

Common: $\geq 1\%$ and $< 10\%$

Uncommon: $\geq 0.1\%$ and $< 1\%$

Rare: $\geq 0.01\%$ and $< 0.1\%$

Very rare: $< 0.01\%$

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 ($\geq 38.0^{\circ}\text{C}$)

Common: injection site reactions including induration, local swelling at the injection site (> 50 mm)¹

Uncommon: fever² $> 39.5^{\circ}\text{C}$, fatigue, diffuse swelling of the injected limb, sometimes involving the adjacent joint¹

Post-marketing surveillance

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-hyporesponsiveness episode)

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

⁴ reported with D and T vaccines

Overdosage

Not applicable.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA06

Pharmacodynamics Effects

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

Percentage of subjects with antibody titres $\geq$ 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

* cut-off accepted as indicative of protection

** Post dose 2 results from studies where DTPa-HB-IPV/Hib was administered in a schedule 3, 5 and 11 Months of age.

Percentage of subjects with antibody titres $\geq$ 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

* cut-off accepted as indicative of protection

** Post dose 3 results from studies where DTPa-HB-IPV/Hib was administered in a schedule 3, 5 and 11 Months of age.

The effectiveness of the GlaxoSmithKline Biologicals' Hib component (when combined with DTPa, DTPa-IPV or DTPa-HBV-IPV) has been and continues to be 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 3 year follow-up period, the effectiveness of hexavalent vaccines was 92.8% for a full primary series and 100% for a booster dose.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See section “*Pharmacodynamic effects*”.

PHARMACEUTICAL INFORMATION

Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.
The shelf-life of the vaccine components before reconstitution is 36 months.

Storage

The lyophilised Hib vaccine and the DTPa-IPV vaccine have to be stored at +2°C to +8°C.

The DTPa-IPV vaccine should not be frozen. Discard if it has been frozen.

Nature and content of container

The lyophilised Hib vaccine is presented as a white powder in a glass vial.

The DTPa-IPV vaccine is a turbid white suspension presented in a prefilled syringe and glass vial. Upon storage, a white deposit and clear supernatant can be observed.

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

Incompatibilities

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

Use and Handling

The Hib powder the DTPa-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 DTPa-IPV suspension should be shaken before reconstitution.

The vaccine is reconstituted by adding the entire contents of the supplied container of the DTPa-IPV vaccine to the vial containing the 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 DTPa-IPV vaccine to the powder, the mixture should be well shaken.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. In the event of other variation being observed, discard the vaccines. This does not impair the performance of the vaccine. After reconstitution, the vaccine should be injected promptly.

MANUFACTURER

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