

NAME OF THE MEDICINAL PRODUCT

INFANRIX™ -IPV+Hib

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

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 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.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Therapeutic indications

INFANRIX™-IPV+Hib is indicated as a booster dose for children aged 15 months and older 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.

Posology and method of administration

Posology

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

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

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.

Special warnings and special precautions for use

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.

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.

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 by deep intramuscular injection. 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.

The vaccination should be recorded in the patient's immunisation record.

Interaction with other medicinal products and other forms of interaction

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.

Use during pregnancy and lactation

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

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

In controlled clinical studies, the most common reactions reported were those at the site of injection. They included pain, redness and swelling. All symptoms resolved without any sequelae.

Systemic adverse events reported were fever, unusual crying, vomiting, diarrhoea, loss of appetite and restlessness. Fever of >39.5°C, considered as related/possibly related to vaccination, has been infrequently reported.

Other symptoms which have been reported during the studies are nervousness, anorexia, somnolence and fatigue.

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported. All the subjects recovered totally and spontaneously without sequelae.

Allergic reactions, including anaphylactoid reactions have been reported very rarely with Infanrix-IPV+Hib.

Overdose

Not applicable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA02 + J07AG01

Immune response to the DT components:

One month after a primary vaccination course more than 99% of infants vaccinated with INFANRIX™-IPV+Hib had antibody titers of ≥ 0.1 IU/mL to both tetanus and diphtheria.

Following administration of a 4th dose of INFANRIX™-IPV+Hib in the second year of life, more than 99.5 % of infants had antibody titers of ≥ 0.1 IU/mL for both tetanus and diphtheria.

Immune response to the Pa component:

One month after the 3-dose primary vaccination course with INFANRIX™-IPV+Hib 100% of infants were seropositive for the three pertussis components (PT, FHA, pertactin), and the overall response rate for each of the three individual pertussis antigens was 98.4%, 97.7% and 97.3% respectively.

A booster response was seen in 97.6% - 99.0% - 98.5% of vaccinees against the respective pertussis antigens. All subjects were seropositive one month after this dose.

Protective efficacy of the Pa component:

As the immune response to pertussis antigens following INFANRIX™-IPV+Hib administration is equivalent to that of Infanrix™, it can be assumed that the protective efficacy of the two vaccines will also be equivalent.

The protective efficacy of pertussis component of Infanrix™, against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule).
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%. Protection against laboratory confirmed mild disease, defined as 14 days or more of cough of any type was 73% and 67% when defined as 7 days or more of cough of any type.
- a NIH (National Institute of Health - USA) sponsored efficacy study performed in Italy (2,4,6 months schedule). The vaccine efficacy was found to be 84%. When the definition of pertussis was expanded to include clinically milder cases with respect to type and duration of cough, the efficacy of Infanrix™ was calculated to be 71% against >7 days of any cough and 73% against >14 days of any cough.

Immune response to the IPV component:

One month after the primary vaccination, the overall response rate for each of the three serotypes (type 1, 2 and 3) were 99.4%, 97.5% and 100% respectively. More than 99.5% of infants were seropositive for the three serotypes. Following administration of a fourth dose of INFANRIX™-IPV+Hib in the second year of life, 100 % of infants were seropositive for the three serotypes.

Immune response to the Hib component:

A titre of ≥ 0.15 $\mu\text{g/mL}$ was obtained in $\geq 95\%$ of infants one month after the primary vaccination course.

A titre of ≥ 1.0 $\mu\text{g/mL}$ was obtained in all infants one month after the booster dose, and in 87.4% of them, a titre of ≥ 10 $\mu\text{g/mL}$ was reached.

Induction of immunological memory was shown to be an intrinsic part of the mechanism of action of Hib conjugates vaccines. It was shown, with this vaccine, that the primed vaccinee responds with an anamnestic response to a subsequent exposure to the antigen (regardless of the level of measurable antibodies).

In a randomised comparative study, it was shown that INFANRIX™-IPV+Hib was at least as immunogenic as a DTPw-IPV-Hib vaccine.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Not applicable.

Pharmaceutical Particulars

List of excipients

Lactose, sodium chloride, potassium chloride, disodium phosphate, monopotassium phosphate, 2-phenoxyethanol (as preservative), aluminum salts (as adjuvant), polysorbate 80, glycine, formaldehyde, M 199 (as stabilizer), neomycin sulfate, polymyxin sulfate, water for injections.

Incompatibilities

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.

The shelf life of the vaccine components before reconstitution is 24 months.

Special precautions for storage

The lyophilised Hib vaccine and the DTPa-IPV vaccine have to be stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$.

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 pellet 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.

Instructions for use and handling, and disposal (if appropriate)

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

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

After reconstitution, the vaccine should be injected promptly.

MARKETING AUTHORISATION HOLDER

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