Infanrix™ -IPV+Hib

1 Name of The Medicinal Product

Infanrix™-IPV+Hib

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

2 Qualitative and Quantitative Composition

Infanrix™-IPV+Hib contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (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, purified and treated with formaldehyde; PT is 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 the reconstituted vaccine contains not less than 30 International Units (IU) of adsorbed diphtheria toxoid, not less than 40 IU of adsorbed tetanus toxoid, 25 µg of PT, 25 µg of FHA, 8 µg 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 µg of purified capsular polysaccharide of Hib covalently bound to approximately 30 µg tetanus toxoid.

3 Pharmaceutical Form

Powder and suspension for suspension for injection

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

4 Clinical Particulars

4.1 Therapeutic 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 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.

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. 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.

4.3 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.

4.4 Special warnings and special precautions for use

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 contra-indication.

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.

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) 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 contra-indications.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication.

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.**

4.5 Interaction with other medicaments and other forms of interaction

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.

4.6 Use during pregnancy and lactation

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

Not applicable.

4.8 Undesirable effects

Clinical trials

In controlled clinical studies, the most common reactions reported were local reactions at the site of injection.

The symptoms included pain, redness and swelling; all of which 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 study period are nervousness, anorexia, somnolence and fatigue.

Studies have been conducted to evaluate the incidence of local swelling reactions after booster administration.

The frequency of these reactions was as follows:

Very common (≥ 10%): local swelling at the injection site (≤50 mm)

Common (≥1/100, <1/10): local swelling at the injection site (>50 mm)*

Uncommon (≥1/1,000, <1/100): diffuse swelling of the injected limb, sometimes involving the adjacent joint.*

*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.

In a randomised comparative study, it was shown that after primary vaccination with ***Infanrix™-IPV+Hib*** the local reactions and fever were significantly lower compared to vaccination with a whole cell pertussis combined (DTPw-IPV-Hib) vaccine. Local reactions such as redness, swelling or pain were observed in 21.3% of cases after ***Infanrix™-IPV+Hib*** versus 44.2% after DTPw-IPV-Hib. A significant reduction in the number of cases and severity of fever was reported following administration of ***Infanrix™-IPV+Hib*** compared to the whole cell pertussis combined vaccine. Rectal temperature ≥ 38°C was reported in 22% of cases after administration of ***Infanrix™-IPV+Hib*** vaccine versus 48.2% after the whole cell pertussis combined vaccine; fever > 39.5°C was reported in 1.9% of cases versus 5.4% respectively.

After the booster dose, local reactions (e.g., redness, swelling or pain) were observed in 23.9% of cases after ***Infanrix™-IPV+Hib*** versus 69.0% after DTPw-IPV-Hib. Rectal temperature ≥ 38°C was reported in 16.3% of vaccinees after administration of ***Infanrix™-IPV+Hib*** vaccine versus 62.1% after the whole cell pertussis combined vaccine; fever > 39.5°C was reported in 2.2% of cases versus 4.6% respectively.

Post-marketing surveillance

Very rare allergic reactions, including anaphylactoid reactions, have been reported following vaccination with DTPa containing vaccines including ***Infanrix™-IPV+Hib***.

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported in pertussis containing vaccines including ***Infanrix™-IPV+Hib***. All the subjects recovered without sequelae.

Swelling of the entire injected limb.

4.9 Overdose

Not applicable

5 Pharmacological Properties

5.1 Pharmacodynamic properties

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

Immune response to the DT components:

One month after a 3-dose primary vaccination course with ***Infanrix™-IPV+Hib*** more than 99% of infants vaccinated had antibody titers of ≥ 0.1 IU/ml to both tetanus and diphtheria. Following administration of a booster 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 a 3-dose primary vaccination course with ***Infanrix™-IPV+Hib*** 100% of infants vaccinated 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% and 98.5% of vaccinees versus the respective pertussis antigens. All subjects were seropositive one month after the booster dose.

Protective efficacy of the Pa component:

As the immune response to the pertussis antigens following ***Infanrix™-IPV+Hib*** administration is equivalent to that of ***Infanrix™*** it can be assumed that the protective efficacy of ***Infanrix™-IPV+Hib*** and ***Infanrix™*** will also be equivalent for this component.

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

- 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 clinically confirmed mild disease which is defined as ≥14 days of cough of any type was 73% and when defined as ≥ 7 days of cough of any type was 67%.
- 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 3 dose primary vaccination course with ***Infanrix™-IPV+Hib***, the overall response rate for each of the three polio serotypes (type 1, 2 and 3) was 99.4%, 97.5% and 100% respectively. More than 99.5% of infants were seropositive for the three polio serotypes. The level of seropositivity for the three polio serotypes increased to 100% of infants following administration of a booster dose of ***Infanrix™-IPV+Hib*** in the second year of life.

Immune response to the Hib component:

One month after the 3 dose primary vaccination course with ***Infanrix™-IPV+Hib*** a titre of ≥ 0.15 µg/ml was obtained in ≥ 95 % of infants. A titre of ≥ 1.0 µg/ml was obtained in all infants one month after the booster dose. In 87.4% of these infants, a titre of ≥ 10 µg/ml was reached.

Induction of immunological memory has been shown to be an intrinsic feature of the mechanism of action of Hib conjugated vaccines. With ***Infanrix™-IPV+Hib***, the primed vaccinee was demonstrated to respond 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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Appropriate safety tests have been performed.

6 Pharmaceutical Particulars

6.1 List of excipients

Lactose, sodium chloride, aluminum salts, M 199, water for injections. Potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 80, glycine, formaldehyde, neomycin sulfate, polymyxin sulfate are present as residuals from the manufacturing process.

6.2 Incompatibilities

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

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-IPV vaccine should be stored at between +2°C to +8°C.

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

6.5 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 pre-filled syringe or a glass vial. Upon storage, a white deposit and clear supernatant can be observed.

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

6.6 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 it is used.

The vaccine must be reconstituted by adding the entire contents of the supplied container of the vaccine to the vial containing the Hib pellet. After the addition of the DTPa-IPV suspension to the Hib pellet, 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 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.

For further information, please contact the manufacturer.

Infanrix is a trademark.

GlaxoSmithKline

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