Infanrix ™-IPV

1 Name of the Medicinal Product

Infanrix™-IPV

Combined diphtheria-tetanus-acellular pertussis, and inactivated polio vaccine

2 Qualitative And Quantitative Composition

Infanrix™-IPV 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).

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 DTPa-IPV components are formulated in saline.

Infanrix™-IPV meets the World Health Organisation requirements for the manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, and of inactivated poliomyelitis vaccines.

A 0.5 ml dose of vaccine contains not less than 25 Lf (≈ min. 30 IU) of adsorbed diphtheria toxoid, not less than 10 Lf (≈ min. 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.

3 Pharmaceutical Form

Suspension for injection

4 Clinical Particulars

4.1 Therapeutic indications

Infanrix™-IPV is indicated for active immunisation in infants from the age of 2 months against diphtheria, tetanus, pertussis and poliomyelitis.

Infanrix™-IPV is also indicated as a booster dose for children who have previously been immunised with DTP and polio antigens.

4.2 Posology and method of administration

Posology

The primary vaccination schedule consists of three doses in the first year of life and can start from the age of 2 months. An interval of at least 1 month should be respected between subsequent doses.

When the primary course is completed before the age of 6 months, a booster dose can be given in the second year of life. An interval of at least 6 months after completion of primary vaccination schedule should be respected. Data on the use of the vaccine as a booster has been obtained for children up to the age of 13 years.

Method of administration

Infanrix™-IPV is for deep intramuscular injection. For infants, the preferred site of injection is the anterolateral aspect of the thigh; in older children, vaccine should be administered in the deltoid.

It is preferable that each subsequent dose is given at alternate sites.

Infanrix™-IPV 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 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 inactivated polio vaccines.

Infanrix™-IPV 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

As with other vaccines, the administration of ***Infanrix™-IPV*** 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.

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 and/or IPV 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 contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

As with all diphtheria, tetanus, and pertussis vaccines, the vaccine should be given deep intramuscularly.

Infanrix™-IPV 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 should under no circumstances be administered intravenously.

4.5 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 can be administered concomitantly with hepatitis B vaccine, and/or *Haemophilus influenzae* vaccine the injections being applied at different injection sites. Routine simultaneous administration of Hib vaccine and hepatitis B vaccine may be given to children who are at the recommended age to receive these vaccines.

Although data on the concomitant administration of ***Infanrix™-IPV*** and measles, mumps and rubella combined vaccine and varicella vaccine are not available, it is generally accepted that they may be given at the same time if separate injection sites are used.

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:
Adverse reactions associated with vaccination have been evaluated in 11 clinical trials. Adverse event data were actively collected using diary cards and by questioning the parents at clinic visits. Events solicited, and frequently reported, were local reactions (pain/tenderness, redness and swelling) and systemic symptoms (fever, unusual crying, restlessness, irritability, sleeping more or less than usual, malaise, loss of appetite, nausea, vomiting, diarrhoea, headache). The incidence of these symptoms was variable across the trials. As has been observed for other licensed DTPa vaccines, an increase in local reactogenicity and fever > 39.5°C was reported after booster vaccination.
The following events were also commonly reported in the clinical trials in temporal association with vaccination. It should be noted that causality has not necessarily been established for these events.
- Primary vaccination (total number of doses = 1802):
  - Gastrointestinal system: tooth ache
  - Respiratory system: rhinitis, pharyngitis
  - Application site: injection site mass
  - Resistence mechanism: upper respiratory tract infection, otitis media
- Booster vaccination after DTPa-IPV primary course (total number of doses = 216)
  - Vision: conjunctivitis
  - Psychiatric: somnolence, insomnia
  - Gastrointestinal system: tooth ache
  - Respiratory system: rhinitis, bronchitis, pharyngitis
  - Application site: injection site mass
  - Resistence mechanism: upper respiratory tract infection, otitis media
- Booster vaccination after DTPw and IPV (total number of doses = 297)
  - Skin and appendages: puritis
  - Respiratory system: coughing, rhinitis, pharyngitis
  - Body as a whole: asthenia
  - Resistence mechanism: otitis media

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. Local swelling at the injection site (>50 mm) and diffuse swelling may be more frequent (very common and common, respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days.
Post-marketing surveillance:
Very rare allergic reactions, including anaphylactoid reactions, have been reported following vaccination with DTPa containing vaccines.
Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions with 2 to 3 days of vaccination have been reported for infants receiving pertussis containing vaccines. All the subjects recovered totally 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 J07CA02
- Immune response to the DT components:

One month after a primary vaccination course more than 99% of infants vaccinated with ***Infanrix™-IPV*** had antibody titers of ≥ 0.1 IU/ml to both tetanus and diphtheria.
Following administration of a booster dose of ***Infanrix™-IPV***, more than 99.5% of children had antibody titers of ≥ 0.1 IU/ml for both antigens.

- Immune response to the Pa component:

One month after the 3-dose primary vaccination course with ***Infanrix™-IPV*** 100% of infants were seropositive for the three pertussis components (PT, FHA, pertactin), and the overall response rates for each of the three individual pertussis antigens were ≥ 94%.
A booster response was seen in the vast majority of vaccinees against the pertussis antigens; lower response rates were seen in studies where the pre-vaccination levels of antibodies were high. 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*** administration is equivalent to that of ***Infanrix™***, it can be assumed that the protective efficacy of the two vaccines will also be equivalent.
The clinical protection of the DTPa component, 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%.
- a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule) the vaccine eficacy was found to be 84%. In a follow-up of the same cohort, the efficacy was confirmed for up to 4 years of age.

- Immune response to the IPV component :

One month after the primary vaccination, the overall seropositivity for each of the three serotypes (type 1, 2 and 3) was ≥ 99.5%.
Following administration of a booster dose of ***Infanrix™-IPV***, 100% of children were seropositive for the three serotypes.
In all booster trials, vaccination induced a marked increase in antibody levels with respect to pre-booster values.

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

5.3 Preclinical safety data
Not applicable

6 Pharmaceutical Particulars

6.1 List of excipients
Sodium chloride, aluminum salts, M 199 (as stabilizer), 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
Infanrix™-IPV 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
Infanrix™-IPV vaccine has to be stored at +2°C to +8°C.
The DTPa-IPV vaccine should not be frozen. Discard if it has been frozen.

6.5 Nature and content of container
The DTPa-IPV vaccine is a turbid white suspension presented in a pre-filled syringe. Upon storage, a white deposit and clear supernatant can be observed.
The pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

6.6 Instructions for use and handling, and disposal (if appropriate)
Infanrix™-IPV 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, ***Infanrix™-IPV*** suspension should be well shaken.

For further information, please contact the manufacturer.