Infanrix™

1. Name of the medicinal product

Infanrix™

Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa) vaccine

2. Qualitative and quantitative composition

Infanrix™ contains diphtheria toxoid, tetanus toxoid and three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and 69 kiloDalton outer membrane protein (pertactin)] adsorbed onto aluminium salts.

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 treated with formaldehyde; PT is irreversibly detoxified.

The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine components are adsorbed on aluminium salts. The final vaccine is formulated in saline. ***Infanrix™*** meets the World Health Organisation requirements for manufacture of biological substances and for diphtheria and tetanus vaccines. No substances of human origin are used in its manufacture.

A 0.5 ml dose of the vaccine contains not less than 30 International Units (IU) of diphtheria toxoid, 40 IU of tetanus toxoid, 25 mcg of PT, 25 mcg of FHA and 8 mcg of pertactin.

3. Pharmaceutical form

Suspension for injection.

4. Clinical particulars

4.1 Therapeutic indications

Infanrix™ is indicated for active primary immunisation against diphtheria, tetanus and pertussis from the age of 2 months onwards.

Infanrix™ is indicated as a booster dose for children who have previously been immunised with three or four doses of either DTPa vaccine or diphtheria, tetanus and whole-cell pertussis (DTPw) vaccine.

4.2 Posology and method of administration

Posology

The recommended dose (0.5 ml) of the vaccine must be administered. As vaccination schemes vary from country to country, the schedule for each country may be used in accordance with the different national recommendations. The primary immunisation course consists of 3 doses with boosters during the second and sixth year of life.

Method of administration

Infanrix™ is for **deep intramuscular** injection.

Infanrix™ should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects: following injection, firm pressure should be applied to the site (without rubbing) for at least two minutes.

Infanrix™ **should under no circumstances be administered intravenously.**

4.3 Contra-indications

Infanrix™ 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 ***Infanrix™***, diphtheria and tetanus vaccine or DTPw.

Infanrix™ is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

In these circumstances the vaccination course should be continued with diphtheria and tetanus vaccine.

4.4 Special warnings and special precautions for use

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of ***Infanrix™*** should be postponed in subjects suffering from acute severe febrile illness.

The presence of a minor infection, however, is not a contra-indication.

If any of the following events occur in temporal relation to receipt of DTPa or DTPw, 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.

A history of febrile convulsions or a family history of convulsive fits do not constitute contra-indications.

HIV infection is not considered as a contra-indication.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

As for all diphtheria, tetanus and pertussis vaccines, each course of vaccine should be given deep intramuscularly and preferably at alternate injection sites.

Infanrix™ 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™ should under no circumstances be administered intravenously.

4.5 Interaction with other medicaments and other forms of interaction

Infanrix™ can be administered in any temporal relationship with other childhood vaccines.

Infanrix™ can be mixed in the same syringe with the *Haemophilus influenzae* type b (Hib) vaccine ***Hiberix™*** or other PRP-T Hib vaccines.

Other injectable vaccines should always be administered at different injection sites.

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™*** 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

Not applicable.

4.8 Undesirable effects

In controlled clinical studies, signs and symptoms were actively monitored and recorded on diary cards in all vaccinees following the administration of each dose of the vaccine.

The following table, based on the results of comparative studies summarises the local solicited symptoms reported within 48 hours of vaccination as a percentage of doses administered.

Local Solicited symptoms (%)	Primary immunisation		Booster			
	Infanrix ™ (1275 doses)	DTPw (455 doses)	**Infanrix**™ after **Infanrix**™ primary (269 doses)	DTPw after DTPw primary (92 doses)	**Infanrix**™ after DTPw primary (273 doses)	DTPw after DTPw primary (91 doses)
pain	2.5	19.1	15.6	55.4	15.8	59.3
redness (> 2 cm)	0.1	1.1	4.5	3.3	2.2	5.5
swelling (> 2 cm)	0	1.3	3.0	7.6	1.5	5.5

General solicited symptoms which were reported in the same comparative studies and within the same time frame are summarised in the following table.

General solicited symptoms (%)	Primary immunisation		Booster			
	Infanrix™	DTPw	**Infanrix**™ after **Infanrix**™ primary	DTPw after DTPw primary	**Infanrix**™ after DTPw primary	DTPw after DTPw primary
Fever ≥ 38°C (rectal)	9.9	42.2	26.8	64.1	29.3	63.7
Fever ≥ 39.5°C (rectal)	0.2	1.3	0.4	4.3	0.7	4.4
Unusual crying	5.2	11.9	8.6	14.7	2.6	11.0
Vomiting	3.0	4.4	3.3	7.6	2.6	2.2
Diarrhoea	5.9	6.8	11.2	13.0	8.1	16.5
Eating and drinking less than usual	4.2	20.7	7.1	43.5	12.5	29.7
Sleeping more than usual / drowsiness	9.3	13.6	10.4	31.5	10.3	14.3
Sleeping less than usual / restlessness	9.3	16.7	12.3	32.6	7.7	16.5

Additional safety data are available from other studies, which evaluate the primary immunisation course and the booster dose administration. These studies, which include non-comparative studies, confirmed the safety profile of DTPa which is summarised above.
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.
The following unsolicited symptoms have been reported for:

- ***Infanrix™*** primary immunisation (total of 11406 documented doses):
  Skin and appendages (1% or less): dermatitis.
  Respiratory system (3% or less): coughing, rhinitis, bronchitis, other upper respiratory tract infection.
  Resistance mechanism (1% or less): otitis media.
- ***Infanrix™*** booster following ***Infanrix™*** primary immunisation (total of 2363 documented doses):
  Respiratory system (4% or less): coughing, pharyngitis, bronchitis, other upper respiratory tract infection, rhinitis, respiratory disorder.
  Resistance mechanism (3% or less): viral infection, otitis media.
- ***Infanrix™*** booster following DTPw primary immunisation (total of 606 documented doses):
  Respiratory system (3% or less): coughing, pharyngitis, upper respiratory tract infection, bronchitis.
  Resistance mechanism (2% or less): otitis media.

Post-marketing surveillance:
Very rare allergic reactions, including anaphylactoid reactions have been reported.
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.
Swelling of the entire injected limb.

4.9 Overdose
Not applicable.

5. Pharmacological particulars

5.1. Pharmacodynamic properties.
Pharmaco-therapeutic group: Bacterial vaccines, ATC code J07AJ52.

Immune response of Infanrix *TM* primary immunisation:
One month after a three-dose primary vaccination course in the first 6 months of life more than 99% of infants vaccinated with ***Infanrix™*** had antibody titers of more than 0.1 IU/ml to both diphtheria and tetanus.
The vaccine contains PT, FHA and pertactin, antigens which are considered to play an important role in protection against pertussis disease. In clinical studies, the vaccine response to these pertussis antigens was more than 95%.

Immune response of *Infanrix™* booster immunisation:
Following administration of an ***Infanrix™*** booster in the second year of life (13-24 months) all ***Infanrix™*** primed infants had antibody titers of more than 0.1 IU/ml to both diphtheria and tetanus. The booster response to the pertussis antigens was seen in more than 96% of these children.

Protective efficacy of *Infanrix™*:
The protective efficacy of ***Infanrix™*** against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough with laboratory confirmation) 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.
- an NIH 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.

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
Aluminium hydroxide, sodium chloride, water for injections.
Formaldehyde and Polysorbate 80 are present as residuals from the manufacturing process.

6.2 Incompatibilities
Infanrix™ should not be mixed with other vaccines in the same syringe, with the exception of ***Hiberix™*** or other PRP-T Hib vaccines.

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

6.4 Special precautions for storage
Infanrix™ should be stored at +2°C to +8°C.
Do not freeze. Discard if the vaccine has been frozen.

6.5 Nature and contents of container
Infanrix™ is presented as a turbid white suspension in a glass vial or glass prefilled syringe. Upon storage a white deposit and clear supernatant is observed.
The vials and prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

6.6 Instructions for use, handling and disposal (if appropriate)
*How to use **Infanrix™***
Infanrix™ is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant is observed. The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.
*To mix **Infanrix™** and **Hiberix™***
Infanrix™ may be used to reconstitute ***Hiberix™*** vaccine for simultaneous administration via one injection. ***Hiberix™*** is presented as a white Hib pellet in a vial, with a clear and colourless sterile diluent (saline) in either a second vial or a prefilled syringe. Discard the diluent.
The combined DTPa-Hib vaccine must be reconstituted by adding the entire contents of a monodose ***Infanrix™*** prefilled syringe to the monodose vial containing the white ***Hiberix™*** pellet. After the addition of ***Infanrix™*** to the ***Hiberix™*** pellet, the mixture should be well shaken until the ***Hiberix™*** pellet is completely dissolved in the ***Infanrix™*** suspension.
The reconstituted combined vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to administration. In the event of either being observed, discard the reconstituted vaccine.
A new needle should be used to administer the vaccine.
After reconstitution, the vaccine should be injected promptly.

For further information, refer to manufacturer.

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