

INFANRIX[®]-*penta* Datasheet

NAME OF THE MEDICINE

INFANRIX[®]-*penta*

Combined diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio vaccine.

QUALITATIVE AND QUANTITATIVE COMPOSITION

INFANRIX[®]-*penta* contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN; 69 kiloDalton outer membrane protein)] and the purified major surface antigen (HBsAg) of the hepatitis B virus (HBV), adsorbed on aluminium salts. It also contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain).

The tetanus and diphtheria toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment, and formaldehyde treatment of FHA and PRN. The diphtheria toxoid, tetanus toxoid and acellular pertussis components are adsorbed onto aluminium salts. The DTPa-HBV-IPV components are formulated in saline and contain 2-phenoxyethanol.

The surface antigen of the HBV is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptide and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of the natural HBsAg.

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

INFANRIX[®]-*penta* meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of hepatitis B vaccines made by recombinant DNA techniques and of inactivated poliomyelitis vaccines.

A 0.5 ml dose of vaccine contains not less than 30 IU of adsorbed diphtheria toxoid, not less than 40 IU of adsorbed tetanus toxoid, 25 mcg of adsorbed PT, 25 mcg of adsorbed FHA, 8 mcg of adsorbed pertactin, 10 mcg of adsorbed recombinant HBsAg protein, 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.

For excipients, see “List of Excipients” section.

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

Therapeutic indications

INFANRIX[®]-*penta* is indicated for immunisation against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis in infants from the age of 6 weeks and may also be given to infants who received a first dose of hepatitis B vaccine at birth.

Posology and method of administration

Posology

The primary vaccination schedule (such as 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months; 3, 5 and 11 or 12 months; 6, 10, 14 weeks) consists of three doses of 0.5 ml. An interval of at least 1 month should be respected between doses.

If it is intended to administer INFANRIX[®]-*penta* according to the EPI schedule (Expanded Program on Immunisation; at 6, 10, 14 weeks of age), then the vaccinee must receive a dose of hepatitis B vaccine at birth.

Children previously immunized with three doses of INFANRIX[®]-*penta* within the first 6 months of life may be given a fourth (booster dose) 6-12 months after the third dose. Clinical data for a booster dose are available with the following alternative combinations of antigens : DTPa, DTPa and Hib, DTPa-HBV-IPV and DTPa-IPV and Hib.

The choice of the immunization schedule and the booster dose should be based on official local recommendations, where available.

Method of administration

INFANRIX[®]-*penta* is for deep intramuscular injection.

Contra-indications

INFANRIX[®]-*penta* should not be administered to subjects with known hypersensitivity to any component of the vaccine (see 6.1), or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, Hepatitis B or polio vaccines.

INFANRIX[®]-*penta* 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 pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus, hepatitis B and inactivated polio vaccines.

Special warnings and special precautions for use

As with other vaccines, administration of INFANRIX[®]-*penta* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

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 are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsiveness 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.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

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[®]-*penta* 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[®]-*penta* SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY.

INFANRIX[®]-*penta* contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

The hepatitis B component of the vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

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 INFANRIX[®]-*penta* 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.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born \leq 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Interaction with other medicinal products and other forms of interaction

Clinical studies have demonstrated that INFANRIX[®]-*penta* can be administered simultaneously with *Haemophilus influenzae* type b vaccines. In these clinical studies, the injectable vaccines were given at different injection sites.

INFANRIX[®]-*penta* should not be mixed in the same syringe with any other vaccine.

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

As INFANRIX[®]-*penta* is not intended for use in adults, 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

Primary vaccination:

Clinical trials involved the administration of 22,430 doses of Infanrix penta to 7,568 healthy infants from 6 weeks of age as primary vaccination. Of these infants, 7,488 had received Infanrix penta concomitantly with a licensed *Haemophilus influenzae* type b vaccine while the remaining 80 subjects were given a single injection of Infanrix penta.

In one large open randomised comparative study, infants were enrolled to receive a three dose primary series of Infanrix penta (N = 4,668) concomitantly at separate sites along with one of four Hib vaccines, or separate injections of commercially available vaccines (DTPa + Hib + oral polio vaccine; N = 768). Infanrix penta coadministered with a licensed Hib vaccine was shown to be as safe as the commercial vaccines administered separately. The incidences of undesirable events after vaccination with Infanrix penta + Hib were not higher than the incidences after vaccination with the commercial vaccines administered separately. For both groups, solicited local reactions were reported in 51 to 59% of subjects. Fever of $>39.5^{\circ}\text{C}$ was reported for 1.4% of infants administered Infanrix penta +

Hib; fever of $>40^{\circ}\text{C}$ was reported for 0.2% (values for infants administered licensed vaccines separately were respectively 1.0% and 0.3%).

Adverse events reported following primary vaccination with Infanrix penta + Hib in this study were categorised by frequency. No increase in the incidence or severity of these undesirable events was seen with subsequent doses of the primary vaccination series. In many instances the causal relationship to the vaccine has not been established.

Very common

Local reactions: pain, redness and swelling at the injection site.

Systemic reactions: diarrhoea, loss of appetite, restlessness, fever, unusual crying, irritability.

Common

Vomiting, pruritus

Uncommon

Enteritis, gastro-enteritis, infection, viral infection, otitis media, upper respiratory tract infection, bronchitis, respiratory disorder, sinusitis, dermatitis, eczema, nervousness, conjunctivitis and somnolence.

Very rare

Convulsions, allergic reactions, urticaria

In two smaller randomised comparative trials, severe undesirable events after Infanrix penta were reported with a lower frequency as compared to a commercial diphtheria, tetanus, pertussis (DTP) whole cell vaccine.

Booster vaccination:

A total of 1,028 infants 12 to 24 months of age received a booster dose of Infanrix penta; 839 of these subjects received Infanrix penta for both the primary and booster doses (for a total of 4 doses of vaccine).

As has been observed for DTPa and DTPa-containing combinations, an increase in reactogenicity was reported after booster vaccination with Infanrix penta with respect to the primary course; however, the incidence of symptoms graded as severe was low.

Irrespective of the vaccine used for the primary course, fever $>39.5^{\circ}\text{C}$ was reported for overall 3.3% of infants administered Infanrix penta as a booster dose. The incidence of fever $>39.5^{\circ}\text{C}$ in a control group of infants boosted with commercially-available DTPa-IPV/Hib + HBV vaccines was 2.9%. The incidences of fever $> 40^{\circ}\text{C}$ were respectively 0.6% for Infanrix penta and 0.8% for the licensed vaccines.

In a randomised comparative trial, infants primed with Infanrix penta were boosted with the same vaccine (N = 375) or received a booster dose with commercially-available DTPa-IPV/Hib (N = 396). The incidences of the solicited general and local symptoms following the booster dose were not significantly different between groups. However, slightly higher levels of fever were observed in the group which received Infanrix penta with fever of $>39.5^{\circ}\text{C}$ being reported for 3.9% of infants administered Infanrix penta and fever of $>40^{\circ}\text{C}$ reported for 1.7% (values for infants administered licensed vaccines were respectively 2.1% and 0.8%).

Adverse events reported following booster vaccination with Infanrix penta in this trial were categorised by frequency. In many instances the causal relationship to the vaccine has not been established.

Very common

Local reactions: pain, redness, swelling at the injection site

Systemic reactions: diarrhoea, loss of appetite, fever $\geq 38^{\circ}\text{C}$, restlessness, sleepiness.

Common

Swelling at the injection site ($> 50\text{ mm}$)*, injection site reactions, including induration, vomiting, enteritis, gastro-enteritis, dermatitis, influenza-like symptoms, infection, viral infection, moniliasis, upper respiratory tract infection, otitis media, bronchitis, coughing, rhinitis, pharyngitis, stridor, eczema, rash

Uncommon

Diffuse swelling of the injected limb, sometimes involving the adjacent joint*

Although not reported following either primary or booster vaccination with Infanrix penta during clinical trials, collapse or shock-like state (hypotonic-hyporesponsiveness episode) and anaphylactoid reactions have been reported infrequently with other DTPa containing vaccines during post-marketing surveillance.

Swelling of the entire injected limb has been observed very rarely during post-marketing surveillance*. Other events observed during post-marketing surveillance include Lymphadenopathy, thrombocytopenia and Apnoea [see Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)].

Nearly 100 million doses of Engerix B 10 μg , GlaxoSmithKline Biologicals' hepatitis B vaccine, have been distributed for infants < 2 years old. In extremely rare cases, paralysis, neuropathy, Guillain-Barré syndrome, encephalopathy, encephalitis and meningitis have been reported. The causal relationship to the vaccine has not been established.

* 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.

Overdose

Not applicable

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code JO7CA.

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

DTPa component:

One month after the 3-dose primary vaccination course, 98.4 to 100% of infants vaccinated with INFANRIX[®]-*penta* had antibody titers of ≥ 0.1 IU/ml for both tetanus and diphtheria. The overall response rate for each of the three individual pertussis antigens (PT, FHA, pertactin) was between 97.0-100%, 86.4-100% and 89.0-100% respectively.

Following administration of a 4th dose of INFANRIX[®]-*penta* in the second year of life, 98.8 to 100% of infants had antibody titers of ≥ 0.1 IU/ml for both tetanus and diphtheria. A booster response was seen in 95.3-100%, 93.2-100% and 91.9-100% of vaccinees against the respective pertussis antigens.

Hepatitis B component:

When the EPI schedule is excluded, then after the primary vaccination course with INFANRIX[®]-*penta*, 95.7 to 100% of infants developed protective antibody titers of ≥ 10 mIU/ml. In order to ensure an adequate response to the hepatitis B component children who will be vaccinated in the EPI schedule must receive a dose of hepatitis B vaccine at birth. In a study in which the EPI schedule was applied after a dose of hepatitis B vaccine at birth, one month after the third dose, a seroprotection rate of 98.7% was obtained.

By one month after the booster dose, 96.5 to 100% of these subjects developed protective titers of ≥ 10 mIU/ml.

IPV component:

One month after the primary vaccination, the seroprotection rate for each of the three serotypes (type1, 2 and 3) was between 96.0-100%, 94.8-100% and 96.0-100% respectively. Following administration of the booster dose, 94.4 to 100%, 100% and 100% of infants were seroprotected for the three serotypes respectively.

The protective efficacy of Infanrix[™] DTPa, 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%, which was not statistically different from the DTPw vaccine.

- a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%.

In a follow-up of the same cohort, the efficacy for GlaxoSmithKline's Infanrix[™] DTPa vaccine was found to be 84% up to four years of age.

Infanrix[™] DTPa is an integral part of the INFANRIX[®]-*penta* combination vaccine.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride (NaCl), 2-phenoxyethanol, aluminium hydroxide (Al(OH)₃), aluminium phosphate (AlPO₄), water (H₂O) for injections. Medium 199 (as stabilizer containing amino acids, mineral salts, vitamins and other substances) (M 199), potassium chloride (KCl), disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate, polymyxin B sulphate are present as residuals from the manufacturing process.

Incompatibilities

INFANRIX[®]-*penta* 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 data for last use corresponds to the first day of the month mentioned.

The shelf-life is 36 months.

Special precautions for storage

INFANRIX[®]-*penta* should be stored at +2°C to +8°C. Protect from light.

During transport, recommended conditions of storage must be respected.

Do not freeze. Discard if the vaccine has been frozen.

Nature and contents of container

INFANRIX[®]-*penta* is presented as a turbid white suspension in a syringe. Upon storage, a white deposit and clear supernatant can be observed.

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

Package Quantities

Syringe with or without needle in packs of 1 or 10.

Instructions for use and handling

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.

Upon removal from refrigerator and prior to administration, the vaccine may be kept for up to 8 hours at room temperature (21°C).

MEDICINE CLASSIFICATION

Prescription medicine.

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