

INFANRIX[®]-hexa Datasheet

NAME OF THE MEDICINAL PRODUCT

INFANRIX[®]-hexa

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder and suspension for injection.

1 dose (0.5 ml) contains:

Diphtheria toxoid ¹	not less than 30 International units
Tetanus toxoid ¹	not less than 40 International units
<i>Bordetella pertussis</i> antigens	
Pertussis toxoid ¹	25 micrograms
Filamentous Haemagglutinin ¹	25 micrograms
Pertactin ¹	8 micrograms
Hepatitis B surface antigen ^{2,3}	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain) ⁴	40 D-antigen unit
type 2 (MEF-1 strain) ⁴	8 D-antigen unit
type 3 (Saukett strain) ⁴	32 D-antigen unit
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ³	10 micrograms
conjugated to tetanus toxoid as carrier protein	20 - 40 micrograms

¹adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺

²produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

³adsorbed on aluminium phosphate (AlPO₄) 0.32 milligrams Al³⁺

⁴propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed.

The Hib component is presented as a white powder.

Excipients

Lactose, sodium chloride (NaCl) and water (H₂O) for injections. Medium 199 (as stabiliser containing amino acids, mineral salts, vitamins and other substances), potassium chloride (KCl), disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate and polymyxin B sulphate are present as residuals from the manufacturing process.

PHARMACEUTICAL FORM

Powder and suspension for injection.

CLINICAL PARTICULARS

Therapeutic indications

INFANRIX[®]-*hexa* is indicated for primary immunisation against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b in infants from the age of 6 weeks and may 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[®]-*hexa* according to the EPI schedule (Expanded Program on Immunisation; 6, 10, 14 weeks of age), then the vaccinee must receive a dose of hepatitis B vaccine at birth.

Available data indicate that the vaccine can be given as a fourth dose. However, the data are limited and therefore no recommendation is made for using this combination vaccine as a fourth (i.e. booster) dose during the second year of life.

Infants should receive booster vaccination with other licensed vaccines according to official local recommendations, where available.

Method of administration

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

Contra-indications

INFANRIX[®]-*hexa* should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients or residuals (see Excipients) or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

INFANRIX[®]-*hexa* 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 course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Special warnings and special precautions for use

As with other vaccines, administration of INFANRIX®-hexa 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 $\geq 40.0^{\circ}\text{C}$ 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.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation 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.

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®-hexa 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®-hexa SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVASCULARLY OR INTRADERMALLY.

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

INFANRIX®-hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that

hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see section Pharmacodynamic properties).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of INFANRIX[®]-*hexa*. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered to be a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that INFANRIX[®]-*hexa* can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation 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.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interaction with other medicinal products and other forms of interaction

There are insufficient data with regard to the efficacy and safety of simultaneous administration of INFANRIX[®]-*hexa* and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of INFANRIX[®]-*hexa* with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a three dose primary vaccination.

However, high incidence of fever ($>39.5^{\circ}\text{C}$) was reported in infants receiving INFANRIX[®]-*hexa* and Prevenar compared to infants receiving the hexavalent vaccine alone.

Antipyretic treatment should be initiated according to local treatment guidelines.

INFANRIX[®]-*hexa* 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.

Fertility

No data available.

Pregnancy and lactation

INFANRIX[®]-*hexa* is not intended for use in adults. Information on the safety of the vaccine when used during pregnancy or lactation is not available.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

- Clinical trials:

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with INFANRIX[®]-*hexa* with respect to the primary course.

Frequencies per dose are defined as follows:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1000$ to $< 1/100$

Rare: $\geq 1/10000$ to $< 1/1000$

Very rare: $< 1/10000$

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness

Common: nervousness

Nervous system disorders

Uncommon: somnolence

Very rare: convulsions (with or without fever)

Respiratory, thoracic and mediastinal disorders

Uncommon: cough**

Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus**

Rare: rash

Very rare: dermatitis, urticaria**

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever $\geq 38^\circ\text{C}$, fatigue

Common: local swelling at the injection site (> 50 mm)*, fever $>39.5^\circ\text{C}$, injection site reactions, including induration

Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint*

- Post-MarketingData:

Blood and lymphatic system disorders:

Lymphadenopathy, thrombocytopenia

Immune system disorders:

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders:

Collapse or shock-like state (hypotonic-hyporesponsiveness episode)

Respiratory, thoracic and mediastinal disorders:

Apnoea* [see section “Special Warnings and Special Precautions for use” for apnoea in very premature infants (≤ 28 weeks of gestation)]

Skin and subcutaneous tissue disorders

Angioneurotic oedema**

General disorders and administration site conditions:

Extensive swelling reactions, swelling of the entire injected limb*, vesicles at the injection site

* 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.

**observed with other GSK DTPa-containing vaccines

- Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdose

Insufficient data are available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

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

- DTPa component:
One month after the 3-dose primary vaccination course, 98.5 to 100% of infants vaccinated with INFANRIX[®]-hexa had antibody titers of ≥ 0.1 IU/ml for both tetanus and diphtheria. The overall response rates for each of the three individual pertussis antigens (PT, FHA, pertactin) were 97.2-99.3%, 95.2-100% and 95.9-99.3%, respectively.
- Hepatitis B component:
When the EPI schedule is excluded, then after the primary vaccination course with INFANRIX[®]-hexa, 98.5 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 98.5% was obtained.
- IPV component:
One month after the primary vaccination, the seroprotection rates for each of the three serotypes (type 1, 2 and 3) was 99.2 to 100%, 94.5 to 99.0% and 98.8 to 100% respectively.
- Hib component:
One month after the three-dose primary vaccination course 96.0 to 100% of infants vaccinated with INFANRIX[®]-hexa had antibody titers of ≥ 0.15 $\mu\text{g/ml}$ and 61.9 to 84.0% of infants had titers of ≥ 1.0 $\mu\text{g/ml}$.
The effectiveness of the Hib component of INFANRIX[®]-hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 7 year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was INFANRIX[®]-hexa, was 89.6% for a full primary series

and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

The protective efficacy of Infanrix™ DTPa against WHO-defined typical pertussis (\geq 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 4 years of age.

Infanrix™ DTPa is an integral part of the INFANRIX®-*hexa* 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

Incompatibilities

INFANRIX®-*hexa* 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 date for last use corresponds to the first day of the month mentioned.

The shelf-life is 36 months.

Special precautions for storage

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

During transport, recommended conditions of storage must be respected.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Nature and contents of container

The DTPa-HBV-IPV component is presented as a turbid white suspension in a syringe. Upon storage, a white deposit and clear supernatant can be observed.

The lyophilised Hib vaccine is presented as a white pellet in a glass vial.

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

Vial and syringe with or without needles* in packs of one* orten.

*not currently marketed

Instructions for use and handling

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib pellet should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

INFANRIX[®]-hexa must be reconstituted by adding the entire content of the pre-filled syringe containing DTPa-HBV-IPV to the vial containing the Hib pellet. After the addition of the DTPa-HBV-IPV vaccine to the pellet, the mixture should be well shaken until the pellet is completely dissolved.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least 5 minutes before connecting the pre-filled syringe and reconstituting the vaccine.

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

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C). Withdraw the entire contents of the vial.

MEDICINE CLASSIFICATION

Prescription medicine.

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