

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in July 2009

## Infanrix<sup>®</sup> – Hib

### TITLE

Diphtheria-tetanus-acellular pertussis and *Haemophilus influenzae* type b (Hib) vaccine.

### SCOPE

#### Trade Name

*INFANRIX<sup>®</sup>-Hib*

#### Formulation and Strength

Powder and suspension for suspension for injection

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid	≥ 30 IU
Tetanus toxoid	≥ 40 IU
Pertussis antigens	
Pertussis toxoid	25 micrograms
Filamentous Haemagglutinin	25 micrograms
Pertactin	8 micrograms
<i>Haemophilus influenzae</i> type b polysaccharide	10 micrograms of Hib
conjugated to tetanus toxoid	30-50 micrograms

The diphtheria, tetanus, acellular pertussis component is a turbid white suspension.

The lyophilised *Haemophilus influenzae* type b (Hib) component is a white powder.

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 irreversibly detoxified.

The diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine components are adsorbed on aluminium salts. The final vaccine is formulated in saline.

The Hib polysaccharide is prepared from Hib, strain 20,752 and coupled to tetanus toxoid. After purification the conjugate is lyophilised in the presence of lactose as stabiliser.

**INFANRIX<sup>®</sup>-Hib** meets the World Health Organisation requirements for manufacture of biological substances, of Hib conjugate vaccines and of diphtheria, tetanus, pertussis and combined vaccines.

## **Excipients**

Lyophilised Hib vaccine: Lactose

DTPa vaccine: Aluminium hydroxide, sodium chloride, water for injections

Residues: Formaldehyde, Polysorbate 80.

## **CLINICAL INFORMATION**

### **Indications**

INFANRIX-Hib is indicated for active immunisation of all infants from the age of 2 months to 7 years of age against diphtheria, tetanus, pertussis (DTP) and Hib.

INFANRIX -Hib does not protect against diseases due to other types of *H. influenzae* nor against meningitis caused by other organisms.

### **Dosage and 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. As vaccination schemes vary from country to country, the schedule for each country may be used in accordance with the different national recommendations.

To ensure long term protection, a booster dose is recommended for DTP and Hib in the second year of life. Further booster doses with Hib after the age of 2 years are generally not recommended.

#### **Method of administration**

The reconstituted vaccine is for deep intramuscular injection preferably at alternate sites for each injection.

### **Contraindications**

INFANRIX-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 or Hib vaccines.

INFANRIX-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. In these circumstances pertussis vaccination course should be discontinued and the vaccination course should be continued with diphtheria tetanus and Hib vaccines.

As with other vaccines, the administration of INFANRIX<sup>®</sup>-Hib should be postponed in subjects suffering from any severe febrile illness or acute infection. The presence of a minor infection, however, is not a contraindication.

## **Warnings and Precautions**

It is good clinical practice that vaccination should be preceded by a review of 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 vaccines, 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  $\geq 40.5$  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  $\geq 3$  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.

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

INFANRIX -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.

As with all diphtheria, tetanus and pertussis vaccines, the vaccine should be administered by deep intramuscular injection and preferably at alternate sites for each injection.

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 -Hib should under no circumstances be administered intravascularly.

A history of febrile convulsions, a family history of convulsive fits, a family history of SIDS and a family history of an adverse event following INFANRIX-Hib do not constitute contra-indications.

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

## **Interactions**

INFANRIX -Hib can be administered either simultaneously or at any time before or after a different inactivated or live vaccine.

Different injectable vaccines should always 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 immunologic response may not be achieved.

## **Pregnancy and Lactation**

### **Fertility**

No data available.

### **Pregnancy**

As INFANRIX-Hib is not intended for use in adults, adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

### **Lactation**

As INFANRIX-Hib is not intended for use in adults, adequate human data on use during lactation and adequate animal reproduction studies are not available.

## **Ability to perform tasks that require judgement, motor or cognitive skills**

INFANRIX -Hib has no or negligible influence on the ability to drive and use machines.

## **Adverse Reactions**

- **Clinical studies:**

### **Primary vaccination**

- a) In controlled clinical studies, local (injection site) and systemic adverse events were actively monitored and recorded on diary cards following administration of the vaccine as a primary course. (3,933 doses administered)

Most adverse events were reported within 48 hours of vaccination. All symptoms resolved without any sequelae.

Adverse events are defined by WHO preferred terms and reported with the following frequencies:

Very common:  $\geq 10\%$

Common:  $\geq 1\%$  and  $< 10\%$

Uncommon:  $\geq 0.1\%$  and  $< 1\%$

Rare:  $\geq 0.01\%$  and  $< 0.1\%$

Very rare:  $< 0.01\%$

**Application site:**

Very common: swelling ( $< 2$  cm), redness ( $< 2$  cm), pain (minor or cried / protested on touch).

Uncommon: swelling ( $> 2$  cm), redness ( $> 2$  cm), pain (infant cried when limb moved / spontaneously painful).

**Body as a whole:**

Very common: unusual crying.

Common: fever ( $\geq 38.0$  rectal).

Uncommon: fever ( $\geq 39.5$  °C rectal).

**Central and peripheral nervous system:**

Very common: restlessness.

**Gastrointestinal system:**

Very common: diarrhoea, loss of appetite.

Common: vomiting.

**Psychiatric:**

Very common: somnolence.

- b) In controlled clinical studies, unsolicited adverse events were actively monitored for 31 days (day 0-30) following administration of the vaccine as a primary course (12,218 doses administered).

Unsolicited adverse events considered at least possibly related by the investigator were as follows:

**Autonomic nervous system:**

Rare: sweating increased.

**Body as a whole:**

Uncommon: fatigue.

Rare: malaise.

Very rare: abdomen enlarged, edema, granulomatous lesion, pain.

**Central and peripheral nervous system:**

Very rare: gait abnormal, hypokinesia.

**Gastrointestinal system:**

Uncommon: enteritis, flatulence, gastroenteritis.

Very rare: abdominal pain, saliva increased, toothache.

**Metabolic and nutritional:**

Rare: thirst.

**Platelet bleeding and clotting:**

Rare: hematoma.

**Psychiatric:**

Common: nervousness.

Uncommon: agitation, insomnia.

Very rare: apathy

**Resistance mechanism:**

Uncommon: upper respiratory tract infection.

Rare: infection, otitis media.

**Respiratory system:**

Uncommon: bronchitis.

Rare: coughing, dyspnea, pneumonia, rhinitis.

Very rare: pharyngitis, stridor.

**Skin and appendages:**

Rare: rash erythematous.

Very rare: bullous eruption, eczema.

**Vision:**

Very rare: conjunctivitis.

**Booster vaccination**

- a) In controlled clinical studies, local (injection site) and systemic adverse events were actively monitored and recorded on diary cards following administration of the booster dose of vaccine (2,196 doses administered)

Most adverse events were reported within 48 hours of vaccination. All symptoms resolved without any sequelae.

**Application site:**

Very common: redness (>2 cm), swelling (<2 cm), pain (minor or cried / protested on touch), redness (<2cm), local swelling at the injection site ( $\leq$  50 mm).

Common: swelling (>2 cm), local swelling at the injection site (> 50 mm).\*

Uncommon: pain (infant cries when limb is moved / spontaneously painful) diffuse swelling of the injected limb, sometimes involving the adjacent joint\*

**Body as a whole:**

Very common: fever (> 38 °C rectal), unusual crying.

Uncommon: fever (> 39.5°C rectal).

**Central and peripheral nervous system:**

Very common: restlessness.

**Gastrointestinal system:**

Very common: loss of appetite, diarrhoea.

Common: vomiting.

**Psychiatric:**

Very common: somnolence.

b) In controlled clinical studies, unsolicited adverse events were actively monitored for 31 days (day 0-30) following administration of the booster dose of vaccine (2,087 doses administered).

Unsolicited adverse events considered at least possibly related by the investigator were as follows:

**Body as a whole:**

Rare: edema legs, fatigue.

**Central and peripheral nervous system:**

Rare: dizziness, gait abnormal, hyperkinesia.

**Gastrointestinal system:**

Rare: constipation, gastroenteritis.

**Hearing and vestibular:**

Rare: ear disorder.

**Musculoskeletal system:**

Rare: arthritis.

**Psychiatric:**

Uncommon: insomnia.

Rare: agitation, emotional lability, nervousness.

**Resistance mechanism:**

Uncommon: upper respiratory tract infection.

Rare: infection viral.

**Skin and appendages:**

Uncommon: rash erythematous.

Rare: dermatitis.

c) Following administration of booster vaccine (2,087 doses administered), convulsions and febrile convulsions were uncommonly reported. No causal link between these adverse events and either component of the vaccine has been established.

**Post-Marketing Surveillance:**

Post-marketing surveillance data includes reports for both primary and booster vaccination schedules.

**Application site:**

Extensive swelling reactions, swelling of the entire injected limb\*

**Body as a whole:**

Very rare: allergic reactions including anaphylactoid reactions

**Central and peripheral nervous system:**

Very rare: convulsions within 2 to 3 days of vaccination, collapse or shock-like state (hypotonic-hyporesponsiveness episode).

\* 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.

**Overdosage**

Occasional reports of overdose have been received. Overdose has not resulted in ill effect.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

**ATC Code**

Pharmaco-therapeutic group: Bacterial vaccines, ATC code J07AG52

## **Pharmacodynamic Effects**

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

- **DTPa component**

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*Immunological data:*

One month after the 3-dose primary vaccination course, 98.9 to 99.9% of infants vaccinated with INFANRIX-Hib had antibody titres of  $\geq 0.1$  IU/ml to tetanus and diphtheria.

Following administration of a 4<sup>th</sup> dose of Infanrix<sup>TM</sup>-Hib in the second year of life, 99.0 to 100 % of infants had antibody titres of  $\geq 0.1$  IU/ml for both diphtheria and tetanus.

One month after the 3-dose primary vaccination course, the overall response rate for each of the three individual pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin) was between 97.1 to 98.9 %, 96.1 to 98.3 % and 96.2 to 98.2 %, respectively.

Following administration of a 4<sup>th</sup> dose of Infanrix-Hib in the second year of life, a booster response was seen in at least 96.1 %, 95.8 % and 97.6 % of vaccinated infants against the respective pertussis antigens.

*Protective efficacy data:*

The clinical protection of the DTPa component, 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 %.
- 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 was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

- **Hib component:**

One month after the 3-dose primary vaccination course, 92.5 to 95.6 % of infants vaccinated with Infanrix-Hib had antibody titres of  $\geq 0.15$   $\mu\text{g/ml}$  against Hib.

Following administration of a 4<sup>th</sup> dose of Infanrix-Hib in the second year of life, 99.0 to 100 % of infants had antibody titres of  $\geq 0.15$   $\mu\text{g/ml}$ , and 97.6 to 99.6 % of infants had antibody titres of  $\geq 1.0$   $\mu\text{g/ml}$  against Hib.

## **Pharmacokinetics**

Evaluation of pharmacokinetic properties is not required for vaccines.

**Absorption**

Not relevant for vaccines.

**Distribution**

Not relevant for vaccines.

**Metabolism**

Not relevant for vaccines.

**Elimination**

Not relevant for vaccines.

**Special Patient Populations**

Not relevant for vaccines.

**Clinical Studies**

See section “Pharmacodynamic effects”.

**NON-CLINICAL INFORMATION**

**Animal toxicology and/or pharmacology**

Preclinical data reveal no special hazard for humans based on general safety studies.

**PHARMACEUTICAL INFORMATION**

**Chemical Structure**

Not relevant for vaccines.

**Shelf-life**

3 years.

After reconstitution, INFANRIX-Hib should be injected promptly.

## **Storage**

Store at 2°C – 8°C (in a refrigerator).

Do not freeze.

Keep the container in the outer carton in order to protect from light.

## **Nature and contents of container**

Powder in vial (Type I glass) with stopper (butyl).

0.5 ml of suspension for injection in vial (Type I glass) with a stopper (rubber butyl).

0.5 ml of suspension for injection in pre-filled syringe (Type I glass) with a plunger stopper (rubber butyl).

Pack size of 1,10 with or without needles.

## **Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **Use and Handling**

Upon storage, a white deposit and clear supernatant may be observed. This does not constitute a sign of deterioration.

The syringe should be well shaken in order to obtain a homogeneous turbid white suspension.

The DTPa suspension should be inspected visually for any Foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccines.

The vaccine is reconstituted by adding the entire contents of the syringe to the vial containing the Hib powder. After the addition of the DTPa vaccine to powder, the mixture should be well shaken until the powder is completely dissolved.

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.

Any unused product or waste material should be disposed of in accordance with local requirements.

## **MANUFACTURER**

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## **LICENSE HOLDER**

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## **LICENSE NUMBER**

121-41-30018

**INFHIB20.4.09**