GLOBAL DATASHEET

Combined diphtheria, tetanus, pertussis (acellular), hepatitis B, poliomyelitis (inactivated) and *Haemophilus influenzae* type b vaccine
GLOBAL PRESCRIBER INFORMATION

TITLE

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

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for 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
- *Bordetella pertussis* 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
- *Haemophilus influenzae* type b polysaccharide\(^3\) 10 micrograms
  - (polyribosylribitol phosphate)\(^3\) conjugated to tetanus toxoid as carrier protein 20 - 40 micrograms

\(^1\)adsorbed on aluminium hydroxide, hydrated (Al(OH)\(_3\)) 0.5 milligrams Al\(^{3+}\)
\(^2\)produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
\(^3\)adsorbed on aluminium phosphate (AlPO\(_4\)) 0.32 milligrams Al\(^{3+}\)
\(^4\)propagated 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

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose
Sodium chloride (NaCl)
Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)
Water for injections

**Residues**

Potassium chloride
Disodium phosphate
Monopotassium phosphate
Polysorbate 20 and 80
Glycine
Formaldehyde
Neomycin sulphate
Polymyxin B sulphate

**CLINICAL INFORMATION**

**Indications**

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenza* type b.

**Dosage and Administration**

**Posology**

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.
After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

**Method of administration**

Infanrix hexa is for deep intramuscular injection.

**Contraindications**

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength, Excipients and Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated 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.

**Warnings and Precautions**

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 ≥ 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 $\geq 3$ 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) 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 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 *Pharmacodynamic Effects*).

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. Vaccinee 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 as a contra-indication. 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 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.

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.

**Interactions**

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 3 dose primary vaccination.

However, high incidence of fever (> 39.5°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.

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

**Pregnancy and Lactation**

**Pregnancy**

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

**Lactation**

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

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

Not relevant.

**Adverse Reactions**

**Clinical Trial Data**

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.

Adverse reactions reported are listed according to the following frequency:
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 ($\leq 50$ mm), fever $\geq 38^\circ$C, fatigue
Common: local swelling at the injection site ($> 50$ mm)**, fever $>39.5^\circ$C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

**Post Marketing Data**

**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 Warnings and Precautions 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

* observed with other GSK DTPa-containing vaccines
** 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.

Experience with hepatitis B vaccine:
Meningitis, 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.

Overdosage
Insufficient data are available.

Clinical Pharmacology
Pharmacodynamics
ATC Code
Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09
Pharmacodynamic Effects
Result obtained in the clinical studies for each of the components are summarised in the tables below:
Percentage of subjects with antibody titres $\geq$ assay cut-off one month after primary vaccination with Infanrix hexa

<table>
<thead>
<tr>
<th>Antibody (cut-off)</th>
<th>Two doses</th>
<th>Three doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-5 months</td>
<td>2-3-4 months</td>
</tr>
<tr>
<td></td>
<td>N= 530 (4 studies)</td>
<td>N= 196 (2 studies)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Anti-diphtheria (0.1 IU/ml) †</td>
<td>98.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-tetanus (0.1 IU/ml) †</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-PT (5 EL.U/ml)</td>
<td>99.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-FHA (5 EL.U/ml)</td>
<td>99.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-PRN (5 EL.U/ml)</td>
<td>99.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-HBs (10 mIU/ml) †</td>
<td>96.8</td>
<td>99.5</td>
</tr>
<tr>
<td>Anti-Polio type 1 (1/8 dilution) †</td>
<td>99.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-Polio type 2 (1/8 dilution) †</td>
<td>96.3</td>
<td>97.8</td>
</tr>
<tr>
<td>Anti-Polio type 3 (1/8 dilution) †</td>
<td>98.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-PRP (0.15 μg/ml) †</td>
<td>91.7</td>
<td>96.4</td>
</tr>
</tbody>
</table>

N=number of subjects
* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres $\geq$ 10 mIU/ml
† cut-off accepted as indicative of protection
Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

<table>
<thead>
<tr>
<th>Antibody (cut-off)</th>
<th>Booster vaccination at 11 months of age following a 3-5 month primary course</th>
<th>Booster vaccination during the second year of life following a three dose primary course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=532 (3 studies)</td>
<td>N= 2009 (12 studies)</td>
</tr>
<tr>
<td>Anti-diphtheria (0.1 IU/ml) †</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-tetanus (0.1 IU/ml) †</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-PT (5 EL.U/ml)</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-FHA (5 EL.U/ml)</td>
<td>100.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-PRN (5 EL.U/ml)</td>
<td>99.2</td>
<td>99.5</td>
</tr>
<tr>
<td>Anti-HBs (10 mIU/ml) †</td>
<td>98.9</td>
<td>98.4</td>
</tr>
<tr>
<td>Anti-Polio type 1 (1/8 dilution) †</td>
<td>99.8</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-Polio type 2 (1/8 dilution) †</td>
<td>99.4</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-Polio type 3 (1/8 dilution) †</td>
<td>99.2</td>
<td>99.9</td>
</tr>
<tr>
<td>Anti-PRP (0.15 μg/ml) †</td>
<td>99.6</td>
<td>99.7</td>
</tr>
</tbody>
</table>

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

The protective efficacy of the pertussis component of Infanrix 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 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.

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are highly efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8
years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven 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).

**Pharmacokinetics**

Evaluation of pharmacokinetic properties is not required for vaccines.

**Clinical Studies**

See *Pharmacodynamic Effects*.

**NON-CLINICAL INFORMATION**

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

**PHARMACEUTICAL INFORMATION**

**Shelf-Life**

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

**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 in a pre-filled syringe or vial.

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

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.
Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

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 powder 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 to the vial containing the Hib powder.

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 five 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.

- Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)

Needle

1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

Syringe
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).

3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.

2. Wording for vial and vial presentation

Upon storage, a white deposit and clear supernatant may be observed in the vial containing the DTPa-HBV-IPV suspension. This does not constitute a sign of deterioration.

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. To do so, draw up the suspension with a syringe and add the suspension to the powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

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.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

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