Infanrix *hexa*™

1. Name of the medicinal product
Infanrix hexa™
Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

2. Qualitative and quantitative composition
Infanrix hexa™ 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) and purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid, adsorbed onto 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.
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 poliovirues are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.
The Hib polysaccharide is prepared from Hib, strain 20,752 and after activation with cyanogen bromide and derivatisation with an adipic hydrazide spacer is coupled to tetanus toxoid via carbodiimide condensation. After purification the conjugate is adsorbed on aluminium salt, and then lyophilised in the presence of lactose as stabiliser.
Infanrix hexa™ 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, of inactivated poliomyelitis vaccines and of Hib conjugate vaccines.
A 0.5 ml dose of the 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. It also contains 10 mcg of adsorbed purified capsular polysaccharide of Hib (PRP) covalently bound to 20-40 mcg tetanus toxoid (T).
For excipients, see **Section 6.1**.

3. Pharmaceutical form
Powder and suspension for injection.

4. Clinical particulars
4.1 Therapeutic indications
Infanrix hexa™ is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

4.2 Posology and method of administration
• Primary vaccination
The primary vaccination schedule consists of three doses of 0.5 ml (such as 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months or two doses (such as 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 vaccination 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).
Infanrix hexa™ is for deep intramuscular injection.

4.3 Contra-indications
Hypersensitivity to the active substances or to any of the excipients or residues (see **Section 6.1**).
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.

4.4 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 ≥ 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.
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 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 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 ≤ 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.

4.5 Interaction with other medicaments 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 *Prevnar(14) Prevenar13*™ (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 *Prevnar(14) Prevenar13*™ 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.

4.6 Use during pregnancy and lactation
As ***Infanrix hexa™*** 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
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 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: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%
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 ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever ≥39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**
• Post-Marketing Surveillance:
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 4.4** 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:
Paralysis, neuropathy, encephalopathy, encephalitis, meningitis, mimicking serum sickness, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and 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.

4.9 Overdose
Insufficient data are available.

5. Pharmacological particulars
5.1 Pharmacodynamic properties.
Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09.
Result obtained in the clinical studies for each of the components are summarised in the tables below :

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with *Infanrix hexa™*

Antibody (cut-off)	Two doses	Three doses			
	3-5 months N= 530 (4 studies)	2-3-4 months N= 196 (2 studies)	2-4-6 months N= 1693 (6 studies)	3-4-5 months N= 1055 (6 studies)	6-10-14 weeks N= 265 (1 study)
	%	%	%	%	%
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 µg/ml) †	91.7	96.4	96.6	96.8	97.4

* in a subgroup of infants not administered given hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 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™*

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

† 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 GlaxoSmithKline Biologicals'Hib component (when combined with DTPa, DTPa-IPV or DTPa-HBV-IPV) has been and continues to be investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 4.5 year follow-up period, the effectiveness of DTPa/Hib or DTPa-IPV/Hib vaccines was 96.7% for a full primary series and 98.5% for a booster dose (irrespective of priming). Over a three year follow-up period, the effectiveness of hexavalent vaccines was 92.8% for a full primary series and 100% for a booster dose.

5.2 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 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.

6. Pharmaceutical particulars
6.1 List of excipients
Lactose, sodium chloride (NaCl), Medium 199 (as stabilizer containing amino acids, mineral salts, vitamins and other substances) aluminium hydroxide, aluminium phosphate, water for injections. Potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate, polymyxin B sulphate are present as residuals from the manufacturing process.

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

6.3 Shelf life
The expiry date of the vaccine is indicated on the label and packaging. The date for last use corresponds to the last day of the month mentioned.

6.4 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.

6.5 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.

6.6 Instructions for use, handling and disposal (if appropriate)
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 container.
The vaccine is reconstituted by adding the contents of the 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 ± 1 °C) for at least five minutes before connecting the 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 promptly. However the vaccine may be kept for up to 8 hours at room temperature (21°C).
For further information, please contact the manufacturer.
Infanrix hexa is a trademark.

Infanrix *hexa*™

870 mm