

INFANRIX HEXA

1. Name of the Medicinal Product

Infanrix hexa, Powder and suspension for suspension for injection in a pre-filled syringe. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed).

2. Qualitative And Quantitative Composition

After reconstitution, 1 dose (0.5 ml) contains:

| | |
|----------------------------------------------------------------------------------------------|----------------------------|
| Pertussis toxoid, adsorbed (PT) | 25 µg |
| Filamentous haemagglutinin, adsorbed (FHA) | 25 µg |
| Pertactin (69kDa Outer Membrane Protein – PRN) | 8 µg |
| Diphtheria toxoid, adsorbed (D) | Not less than 30 IU |
| Tetanus toxoid, adsorbed (T) | Not less than 40 IU |
| rDNA Hepatitis B surface antigen (HbsAg) | 10 µg |
| Inactivated Polio Virus (IPV) Type 1 | 40 DU |
| Inactivated Polio Virus (IPV) Type 2 | 8 DU |
| Inactivated Polio Virus (IPV) Type 3 | 32 DU |
| Conjugate of Haemophilus influenzae type b capsular polysaccharide (PRP) and Tetanus toxoid. | 10 µg of PRP and ~ 25 µg T |

The vaccine may contain traces of formaldehyde, neomycin and polymyxin which are used during the manufacturing process (see section 4.3).

Excipients with known effect

The vaccine contains para-aminobenzoic acid 0.057 nanograms per dose and phenylalanine 0.0298 micrograms per dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Powder and suspension for suspension for injection in a pre-filled syringe.

The diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis (DTPa-HBV-IPV) component is a turbid white suspension.

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

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 disease caused by Haemophilus influenzae type b for infants between 6 weeks and 36 months of age.

4.2 Posology and method of administration

Posology

The immunisation schedules for Infanrix hexa should be based on official recommendations.

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). 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 six weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

Booster vaccination:

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 must 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, but, as a minimum, a dose of Hib conjugate vaccine must be administered. Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Paediatric population

The safety and efficacy of Infanrix hexa in children over 36 months of age have not been established.
No data are available.

Method of administration

Infanrix hexa is for deep intramuscular injection, preferably at alternating sites for subsequent injections.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or formaldehyde, neomycin and polymyxin.

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

Infanrix hexa is contraindicated if the infant or toddlers 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, polio and Hib vaccines.

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 contraindication.

4.4 Special warnings and precautions for use

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.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis 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 any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1).

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.

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 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 ≥ 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.

As for any vaccination, the risk-benefit of immunising with Infanrix hexa or deferring this vaccination should be weighed carefully in an infant or in a child suffering from a new onset or progression of a severe neurological disorder.

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.

Do not administer the vaccine intravascularly or intradermally.

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute a contraindication 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.

The physician should be aware that the rate of febrile reactions is higher when Infanrix hexa is co-administered with a pneumococcal conjugate vaccine (PCV7, PCV10, PCV13), or with a measles-mumps-rubella-varicella (MMRV) vaccine, compared to that occurring following the administration of Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient (see sections 4.5 and 4.8).

Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see section 4.8).

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with paracetamol and ibuprofen suggest that the prophylactic use of paracetamol might reduce the fever rate, while prophylactic use of ibuprofen showed a limited effect in reducing fever rate. The use of prophylactic antipyretic medicinal products is recommended for children with seizure disorders or with a prior history of febrile seizures.

Antipyretic treatment should be initiated according to local treatment guidelines.

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.

Special populations

HIV infection is not considered as a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Clinical data indicate that Infanrix hexa can be given to preterm infants, however, as expected in this population, a lower immune response has been observed for some antigens (see section 4.8 and section 5.1)

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 preterm infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

As the benefit of the vaccination is high in these infants, vaccination should not be withheld or delayed.

Interference with laboratory testing

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.

Excipients with known effect

Infanrix hexa contains para-aminobenzoic acid. It may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

The vaccine contains 0.0298 microgram phenylalanine in each dose. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

The vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

The vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

4.5 Interaction with other medicinal products and other forms of interaction

Infanrix hexa can be given concomitantly with pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13), meningococcal serogroup C conjugate vaccine (CRM₁₉₇ and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), meningococcal serogroup B vaccine (MenB), oral rotavirus vaccine and measles-mumps-rubella-varicella (MMRV) vaccine.

Data have shown no clinically relevant interference in the antibody response to each of the individual antigens, although inconsistent antibody response to poliovirus type 2 in co-administration with Synflorix was observed (seroprotection ranging from 78% to 100%) and the immune response rates to the PRP (Hib) antigen of Infanrix hexa after 2 doses given at 2 and 4 months of age were higher if co-administered with a tetanus toxoid conjugate pneumococcal or meningococcal vaccine (see section 5.1). The clinical relevance of these observations remains unknown.

When Infanrix hexa was co-administered with MenB and pneumococcal conjugate vaccines, inconsistent results were seen across studies for responses to inactivated poliovirus type 2, pneumococcal conjugate serotype 6B antigen and to the pertussis pertactin antigen but these data do not suggest clinically significant interference. Data from clinical studies indicate that, when Infanrix hexa is co-administered with pneumococcal conjugate vaccines, the rate of febrile reactions is higher compared to that occurring following the administration of Infanrix hexa alone. Data from one clinical study indicate that when Infanrix hexa is co-administered with MMRV vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of Infanrix hexa alone and similar to that occurring following the administration of MMRV vaccine alone (see sections 4.4 and 4.8). The immune responses were unaffected.

Due to an increased risk of fever, pain at the injection site, appetite lost and irritability when Infanrix hexa was co-administered with MenB vaccine and 7-valent pneumococcal conjugate vaccine, separate vaccinations can be considered when possible.

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

4.6 Fertility, 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 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactivity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Tabulated summary of adverse reactions

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies per dose are defined as follows:

- Very common: ($\geq 1/10$)
- Common: ($\geq 1/100$ to $< 1/10$)
- Uncommon: ($\geq 1/1,000$ to $< 1/100$)
- Rare: ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare: ($< 1/10,000$)

The following drug-related adverse reactions were reported in clinical studies (data from more than 16,000 subjects) and during post-marketing surveillance.

| System Organ Class | Frequency | Adverse reactions |
|--------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infections and infestations | Uncommon | Upper respiratory tract infection |
| Blood and lymphatic system disorders | Rare | Lymphadenopathy ² , thrombocytopenia ² |
| Immune system disorders | Rare | Anaphylactic reactions ² , anaphylactoid reactions (including urticaria) ² Allergic reactions (including pruritus) ² |
| Metabolism and nutrition disorders | Very common | Appetite lost |
| Psychiatric disorders | Very common | Crying abnormal, irritability, restlessness |
| | Common | Nervousness |
| Nervous system disorders | Very common | Somnolence |
| | Rare | Collapse or shock-like state (hypotonic- hyporesponsive episode) ² |
| | Very rare | Convulsions (with or without fever) |
| | Uncommon | Cough |

| | | |
|------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Respiratory, thoracic and mediastinal disorders | Rare | Bronchitis, Apnoea ² [see section 4.4 for apnoea in very preterm infants (≤ 28 weeks of gestation)] |
| Gastrointestinal disorders | Common | Diarrhoea, vomiting |
| Skin and subcutaneous tissue disorders | Rare | Rash, Angioedema ² |
| | Very rare | Dermatitis |
| General disorders and administration site conditions | Very common | Fever $\geq 38^{\circ}\text{C}$, pain, redness, local swelling at the injection site (≤ 50 mm) |
| | Common | Fever $>39.5^{\circ}\text{C}$, injection site reactions, including induration, local swelling at the injection site (> 50 mm) ¹ |
| | Uncommon | Diffuse swelling of the injected limb, sometimes involving the adjacent joint ¹ , fatigue |
| | Rare | Swelling of the entire injected limb ^{1, 2} , extensive swelling reactions ² , injection site mass ² , injection site vesicles ² |

¹ 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.

² Adverse reactions from spontaneous reporting.

- Experience in co-administration:

Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.

In clinical studies in which some of the vaccinees received Infanrix hexa concomitantly with Prevenar (PCV7) as a booster (4th) dose of both vaccines, fever $\geq 38.0^{\circ}\text{C}$ was reported in 43.4% of infants receiving Prevenar and Infanrix hexa at the same time as compared to 30.5% of infants receiving the hexavalent vaccine alone. Fever $\geq 39.5^{\circ}\text{C}$ was observed in 2.6% and 1.5% of infants receiving Infanrix hexa with or without Prevenar, respectively (see sections 4.4 and 4.5). The incidence and severity of fever following co-administration of the two vaccines in the primary series was lower than that observed after the booster dose.

Data from clinical studies show similar incidences of fever when Infanrix hexa is co-administered with other pneumococcal saccharide conjugated vaccine.

In a clinical study in which some of the vaccinees received a booster dose of Infanrix hexa concomitantly with measles-mumps-rubella-varicella (MMRV) vaccine, fever $\geq 38.0^{\circ}\text{C}$ was reported in 76.6% of children receiving MMRV vaccine and Infanrix hexa at the same time, as compared to 48% of children receiving Infanrix hexa alone and 74.7% of children receiving MMRV vaccine alone. Fever of greater than 39.5°C was reported in 18% of children receiving Infanrix hexa with MMRV vaccine, as compared to 3.3% of children receiving Infanrix hexa alone and 19.3% of children receiving MMRV alone (see sections 4.4 and 4.5).

- Safety in preterm infants:

Infanrix hexa has been administered to more than 1000 preterm infants (born after a gestation period of 24 to 36 weeks) in primary vaccination studies and in more than 200 preterm infants as a booster dose in the second year of life. In comparative clinical studies, similar rates of symptoms were observed in preterm and full-term infants (refer to section 4.4 for information on apnoea).

- Experience with hepatitis B vaccine:

In extremely rare cases, allergic reactions mimicking serum sickness, paralysis, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness, Guillain-Barré syndrome, encephalopathy, encephalitis and meningitis have been reported. The causal relationship to the vaccine has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>. Additionally, you should also report to GSK Israel, (il.safety@gsk.com).

4.9 Overdose

No case of overdose has been reported.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial and viral vaccines combined, ATC code: J07CA09

Immunogenicity

The immunogenicity of Infanrix hexa has been evaluated in clinical studies from 6 weeks of age. The vaccine was assessed in 2-dose 3-dose priming schedules, including the schedule for the Expanded Program on Immunisation, and as a booster dose. The results of these clinical studies are summarised in the tables below.

After a 3-dose primary vaccination schedule, at least 95.7% of infants had developed seroprotective or seropositive antibody levels against each of the vaccine antigens. After booster vaccination (post-dose 4), at least 98.4% of children had developed seroprotective or seropositive antibody levels against each of the vaccine antigens.

Percentage of subjects with antibody titres indicative of seroprotection / seropositivity one month after 3-dose primary and booster vaccination with Infanrix hexa

| Antibody (cut-off) | Post-dose 3 | Post-dose 4 (Booster vaccination during the second year of life following a 3-dose primary course) |
|---------------------------|--------------------|-----------------------------------------------------------------------------------------------------------|
| | | |

| | 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) | N=2009 (12 studies) |
|----------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------|
| | % | % | % | % | % |
| Anti-diphtheria (0.1 IU/ml) † | 100.0 | 99.8 | 99.7 | 99.2 | 99.9 |
| Anti-tetanus (0.1 IU/ml) † | 100.0 | 100.0 | 100.0 | 99.6 | 99.9 |
| Anti-PT (5 EL.U/ml) | 100.0 | 100.0 | 99.8 | 99.6 | 99.9 |
| Anti-FHA (5 EL.U/ml) | 100.0 | 100.0 | 100.0 | 100.0 | 99.9 |
| Anti-PRN (5 EL.U/ml) | 100.0 | 100.0 | 99.7 | 98.9 | 99.5 |
| Anti-HBs (10 mIU/ml) † | 99.5 | 98.9 | 98.0 | 98.5* | 98.4 |
| Anti-Polio type 1 (1/8 dilution) † | 100.0 | 99.9 | 99.7 | 99.6 | 99.9 |
| Anti-Polio type 2 (1/8 dilution) † | 97.8 | 99.3 | 98.9 | 95.7 | 99.9 |
| Anti-Polio type 3 (1/8 dilution) † | 100.0 | 99.7 | 99.7 | 99.6 | 99.9 |
| Anti-PRP (0.15 µg/ml) † | 96.4 | 96.6 | 96.8 | 97.4 | 99.7** |

N = number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

** Post booster, 98.4% of subjects had anti-PRP concentration ≥ 1 µg/ml indicative of long-term protection

† cut-off accepted as indicative of protection

Serological correlates of protection have been established for diphtheria, tetanus, polio, Hepatitis B and Hib. For pertussis there is no serological correlate of protection. However, 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.

Efficacy in protecting against pertussis

The clinical protection of the pertussis component of Infanrix (DTPa), against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated after 3-dose primary immunisation in the studies tabulated below:

| Study | Country | Schedule | Vaccine efficacy | Considerations |
|--------------|----------------|-----------------|-------------------------|-----------------------|
|--------------|----------------|-----------------|-------------------------|-----------------------|

| | | | | |
|-----------------------------------------------|---------|--------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Household contact study (prospective blinded) | Germany | 3,4,5 months | 88.7% | Based on data collected from secondary contacts in households where there was an index case with typical pertussis |
| Efficacy study (NIH sponsored) | Italy | 2,4,6 months | 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. |

Persistence of the immune response

The persistence of the immune response to a 3-dose primary (at 2-3-4, 3-4-5 or 2-4-6 months of age) and booster (in the second year of life) schedule with Infanrix hexa was evaluated in children 4-8 years of age. Protective immunity against the three poliovirus types and PRP was observed in at least 91.0% of children and against diphtheria and tetanus in at least 64.7% of children. At least 25.4% (anti-PT), 97.5% (anti-FHA) and 87.0% (anti-PRN) of children were seropositive against the pertussis components.

Percentage of subjects with antibody titres indicative of seroprotection / seropositivity after primary and booster vaccination with Infanrix hexa

| Antibody (cut-off) | Children at 4-5 years of age | | Children at 7-8 years of age | |
|-----------------------------------------|------------------------------|-------|------------------------------|------|
| | N | % | N | % |
| Anti-diphtheria (0.1 IU/ml) | 198 | 68.7* | 51 | 66.7 |
| Anti-tetanus (0.1 IU/ml) | 198 | 74.7 | 51 | 64.7 |
| Anti-PT (5 EL.U/ml) | 197 | 25.4 | 161 | 32.3 |
| Anti-FHA (5 EL.U/ml) | 197 | 97.5 | 161 | 98.1 |
| Anti-PRN (5 EL.U/ml) | 198 | 90.9 | 162 | 87.0 |
| Anti-HBs (10 mIU/ml) | 250§ | 85.3 | 207§ | 72.1 |
| | 171§ | 86.4 | 149§ | 77.2 |
| Anti-Polio type 1 (1/8 dilution) | 185 | 95.7 | 145 | 91.0 |
| Anti-Polio type 2 (1/8 dilution) | 187 | 95.7 | 148 | 91.2 |
| Anti-Polio type 3 (1/8 dilution) | 174 | 97.7 | 144 | 97.2 |
| Anti-PRP (0.15 µg/ml) | 198 | 98.0 | 193 | 99.5 |

N = number of subjects

* Samples tested by ELISA to have anti-diphtheria antibody concentrations < 0.1 IU/ml were re-tested using Vero-cell neutralisation assay (seroprotection cut-off ≥ 0.016 IU/ml): 96.5% of the subjects were seroprotected

§ Number of subjects from 2 clinical studies

With regards to hepatitis B, seroprotective antibody concentrations (≥ 10 mIU/ml) following a 3-dose primary and booster schedule with Infanrix hexa have been shown to persist in $\geq 85\%$ of subjects 4-5 years of age, in $\geq 72\%$ of subjects 7-8 years of age, in $\geq 60\%$ of subjects 12-13 years of age and in 53.7% of subjects 14-15 years of age.

Hepatitis B immunological memory was confirmed in children 4 to 15 years of age. These children had received Infanrix hexa as primary and booster vaccination in infancy, and when an additional dose of monovalent HBV vaccine was administered, protective immunity was observed in at least 93% of subjects.

Immunogenicity in preterm infants

The immunogenicity of Infanrix hexa was evaluated across three studies including approximately 300 preterm infants (born after a gestation period of 24 to 36 weeks) following a 3-dose primary vaccination course at 2, 4 and 6 months of age. The immunogenicity of a booster dose at 18 to 24 months of age was evaluated in approximately 200 preterm infants.

One month after primary vaccination at least 98.7% of subjects were seroprotected against diphtheria, tetanus and poliovirus types 1 and 2; at least 90.9% had seroprotective antibody levels against the hepatitis B, PRP and poliovirus type 3 antigens; and all subjects were seropositive for antibodies against FHA and PRN while 94.9% were seropositive for anti-PT antibodies.

One month after the booster dose at least 98.4% of subjects had seroprotective or seropositive antibody levels against each of the antigens except against PT (at least 96.8%) and hepatitis B (at least 88.7%). The response to the booster dose in terms of fold increases in antibody concentrations (15- to 235-fold), indicate that preterm infants were adequately primed for all the antigens of Infanrix hexa.

In a follow-up study conducted in 74 children, approximately 2.5 to 3 years after the booster dose, 85.3% of the children were still seroprotected against hepatitis B and at least 95.7% were seroprotected against the three poliovirus types and PRP.

Post marketing experience

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).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical 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

Hib powder:

Lactose

DTPa-HBV-IPV suspension:

Sodium chloride
Medium 199
(as stabilizer containing amino acids (including phenylalanine), mineral salts (including sodium and potassium), vitamins (including para-aminobenzoic acid) and other substances)

Water for injections

Adjuvant:

Aluminium -
as aluminium hydroxide ($\text{Al}(\text{OH})_3$)
as aluminium phosphate (AlPO_4)

6.2 Incompatibilities

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

6.3 Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.

After reconstitution: an immediate use is recommended. However, the stability has been demonstrated for 8 hours at 21°C after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package, in order to protect from light.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period Infanrix hexa should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only. Do not store the vaccine routinely under these extreme storage conditions, based on this information.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) containing 1 dose with a stopper (butyl rubber) and 0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are made with synthetic rubber.

Pack sizes of 1, 10, 20 and 50 with or without needles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Upon storage, a clear liquid and white deposit may be observed in the pre-filled syringe containing the DTPa-HBV-IPV suspension. This is a normal observation.

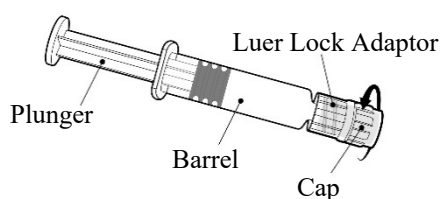
The pre-filled syringe should be well shaken in order to obtain a homogeneous turbid, white suspension.

The vaccine is reconstituted by adding the entire contents of the pre-filled syringe to the vial containing the powder. The mixture should be well shaken until the powder is completely dissolved prior to administration.

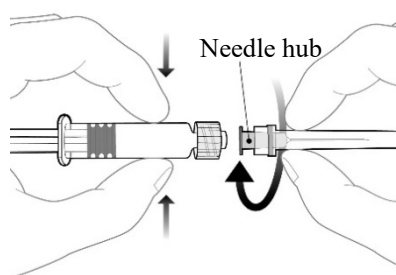
The reconstituted vaccine appears as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The vaccine suspension should be inspected visually before and after reconstitution for any foreign particulate matter and/or abnormal physical appearance. If either is observed, do not administer the vaccine.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.
Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Reconstitute the vaccine as described above.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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

7. Manufacturer

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium

8. License Holder

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva, Israel

9. LICENSE NUMBER

133-20-30676

Inf Hex DR V8

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