SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Infanrix hexa, Powder and suspension for suspension for injection.
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:

Diphtheria toxoid[1]	not less than 30 International Units (IU)
Tetanus toxoid[1]	not less than 40 International Units (IU)
Bordetella pertussis antigens	
Pertussis toxoid (PT)[1]	25 micrograms
Filamentous Haemagglutinin (FHA)[1]	25 micrograms
Pertactin (PRN)[1]	8 micrograms
Hepatitis B surface antigen (HBs)[2,3]	10 micrograms
Poliovirus (inactivated) (IPV)	
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 (polyribosylribitol phosphate, PRP) [3] conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 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 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.
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 from the age of 6 weeks and toddlers against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b.

The use of Infanrix hexa should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination

The primary vaccination schedule consists of two or three doses (of 0.5 ml) which should be administered according to official recommendations (see the table below in this section and section 5.1 for schedules evaluated in clinical trials).

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.

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.
- Infanrix hexa can be used for a mixed pentavalent/hexavelent vaccine primary immunisation schedule in accordance with official recommendations.

Locally established immunoprophylactic measures against hepatitis B should be maintained.

Infanrix hexa can be replaced by the adminstration of a pentavalent vaccine co-adminsitered with hepatitis B vaccine.

Booster vaccination
After a 2-dose or a 3-dose primary series vaccination with Infanrix hexa, a booster dose with Infanrix hexa should be given at least 6 months after the last priming dose (see the table below in this section and section 5.1 for schedules evaluated in clinical trials).
Infanrix hexa may be used as a booster in individuals who have previously been vaccinated with another hexavalent vaccine or a pentavalent DTPa-IPV+Hib vaccine associated with a monovalent hepatitis B vaccine for their primary series.

When a booster dose with a hexavalent DTPa (diphtheria, tetanus, and acellular pertussis) containing vaccine is not available, a dose of Hib vaccine must be administered, as a minimum.

Paediatric population

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

Primary vaccination	**Booster vaccination**	**General considerations**
Full-term infants		
3-dose	A booster dose must be given.	• There should be an interval of at least 1 month between primary doses. • The booster dose should be given at least 6 months after the last priming dose and preferably before 18 months of age.
2-dose	A booster dose must be given.	• There should be an interval of at least 2 months between primary doses.

		• The booster dose should be given at least 6 months after the last priming dose and preferably between 11 and 13 months of age.
Preterm infants born after at least 24 weeks of gestational age		
3-dose	A booster dose must be given.	• There should be an interval of at least 1 month between primary doses. • The booster dose should be given at least 6 months after the last priming dose and preferably before 18 months of age.

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.

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 ≥ 40.0°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.

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 and the batch number of the administered product should be clearly recorded.

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 (CRM_{197} 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, loss of appetite 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 reactogenicity 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:	(≥1/10)
Common:	(≥1/100 to <1/10)
Uncommon:	(≥1/1 000 to <1/100)
Rare:	(≥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	Loss of appetite
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)
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
	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 ≥ 38°C, pain, redness, local swelling at the injection site (≤ 50 mm)
	Common	Fever >39.5°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 ≥ 38.0°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 ≥39.5°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 ≥ 38.0°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).

- Safety in infants and toddlers born to mothers vaccinated with dTpa during pregnancy

In two clinical studies, Infanrix hexa has been administered to more than 500 subjects born to mothers vaccinated with dTpa (n=341) or placebo (n=346) during the third trimester of pregnancy (see section 5.1). The safety profile of Infanrix hexa was similar regardless of exposure/non-exposure to dTpa during pregnancy.

- 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. Healthcare professionals are asked to report any suspected adverse reactions via (see details below)

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

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 and 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

After a 2-dose primary vaccination schedule, at least 84.3% of infants had developed seroprotective or seropositive antibody levels against each of the vaccine antigens. After a complete vaccination according to a 2-dose primary and booster schedule with Infanrix hexa, at least 97.9% of the subjects had developed seroprotective or seropositive antibody levels against each of the vaccine antigens.

According to different studies, immune response to the PRP antigen of Infanrix hexa after 2 doses given at 2 and 4 months of age will vary if co-administered with a tetanus toxoid conjugate vaccine. Infanrix hexa will confer an anti-PRP immune response (cut-off ≥ 0.15µg/ml) in at least 84% of the infants. This

rises to 88% in case of concomitant use of pneumococcal vaccine containing tetanus toxoid as carrier and to 98% when Infanrix hexa is co-administered with a TT conjugated meningococcal vaccine (see section 4.5).

Percentage of subjects with antibody titres indicative of seroprotection / seropositivity one month after 2-dose primary and booster vaccination with Infanrix hexa

Antibody (cut-off)	Post-dose 2		Post-dose 3	
	2-4-12 months of age N=223 (1 study)	3-5-11 months of age N=530 (4 studies)	2-4-12 months of age N=196 (1 study)	3-5-11 months of age N=532 (3 studies)
	%	%	%	%
Anti-diphtheria (0.1 IU/ml) †	99.6	98.0	100.0	100.0
Anti-tetanus (0.1 IU/ml) †	100	100.0	100.0	100.0
Anti-PT (5 EL.U/ml)	100	99.5	99.5	100.0
Anti-FHA (5 EL.U/ml)	100	99.7	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.6	99.0	100.0	99.2
Anti-HBs (10 mIU/ml) †	99.5	96.8	99.8	98.9
Anti-Polio type 1 (1/8 dilution) †	89.6	99.4	98.4	99.8
Anti-Polio type 2 (1/8 dilution) †	85.6	96.3	98.4	99.4
Anti-Polio type 3 (1/8 dilution) †	92.8	98.8	97.9	99.2
Anti-PRP (0.15 µg/ml) †	84.3	91.7	100.0*	99.6*

N = number of subjects
† cut-off accepted as indicative of protection
* Post booster, 94.4% of subjects in the 2-4-12 months schedule and 97.0% of subjects in the 3-5-11 months schedule had anti-PRP concentration ≥ 1 µg/ml indicative of long-term 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 (DTPa), 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§ 171§	85.3 86.4	207§ 149§	72.1 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 ≥ 85% of subjects 4-5 years of age, in ≥72% of subjects 7-8 years of age, in ≥60% of subjects 12-13 years of age and in 53.7% of subjects 14-15 years of age. Additionally, following a 2-dose primary and booster schedule, seroprotective antibody concentrations against hepatitis B persisted in ≥ 48% of subjects 11-12 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 infants and toddlers born to mothers vaccinated with dTpa during pregnancy

The immunogenicity of Infanrix hexa in infants and toddlers born to healthy mothers vaccinated with dTpa at 27-36 weeks of pregnancy was evaluated in two clinical studies.
Infanrix hexa was co-administered with a 13-valent pneumococcal conjugate vaccine to infants at 2, 4 and 6 months or 2, 3 and 4 months in three-dose primary vaccination schedules (n=241), or at 3 and 5 months or 2 and 4 months in two-dose primary vaccination schedules (n=27); and to the same infants/toddlers from 11 to 18 months as booster dose (n=229).

Post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with dTpa on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system. In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.

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

Results of long-term follow-up in Sweden demonstrate that acellular pertussis vaccines are 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 with this 3-5-12 month's schedule. 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 particular schedule.

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).

Results of ongoing routine national surveillance in Italy demonstrate that Infanrix hexa is effective in controlling Hib disease in infants when the vaccine is administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 11 months. Over a six year period starting in 2006, where Infanrix hexa was the principal Hib-containing vaccine in use with vaccination coverage exceeding 95%, Hib invasive disease continued to be well controlled, with four confirmed Hib cases reported in Italian children aged less than 5 years through passive surveillance.

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 anhydrous

DTPa-HBV-IPV suspension:
Sodium chloride (NaCl)
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

For adjuvants, see section 2.

6.2 Incompatibilities

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

6.3 Shelf-life

4 years.

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.

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 and 10, with or without needles and a multipack of 5 packs, each containing 10 vials and 10 pre-filled syringes, 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.

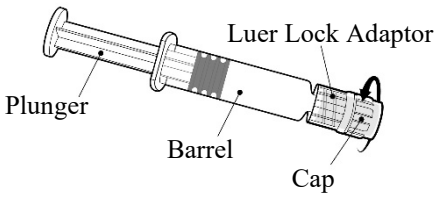
The pre-filled syringe should be well shaken in order to obtain a homogeneous turbid white suspension.

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.

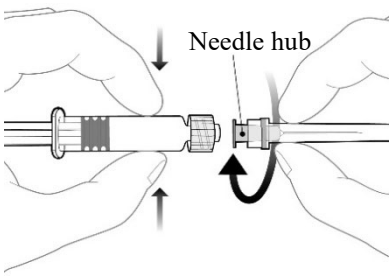
The vaccine suspension should be inspected visually before and after reconstitution for any foreign particulate matter and/or abnormal physical appearance. If either is observed, do not administer the vaccine.

<u>Instructions for the pre-filled syringe</u>



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. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/152/001
EU/1/00/152/002
EU/1/00/152/005
EU/1/00/152/006
EU/1/00/152/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2000
Date of latest renewal: 31 August 2010

10. DATE OF REVISION OF THE TEXT

01/08/2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu