

ANNEX I
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)
<i>Bordetella pertussis</i> 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
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate, PRP) ³	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

¹adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺

²produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

³adsorbed on aluminium phosphate (AlPO₄) 0.32 milligrams Al³⁺

⁴propagated 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 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

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 and section 5.1 for schedules evaluated in clinical trials).

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 antigen composition is in accordance with the official recommendations.

Primary vaccination	Booster vaccination	General considerations
Full-term infants		
3-dose	A booster dose must be given.	<ul style="list-style-type: none"> • 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.	<ul style="list-style-type: none"> • 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.	<ul style="list-style-type: none"> • 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.

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.

Locally established immunoprophylactic measures against hepatitis B should be maintained.

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.

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.

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 \leq 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 (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 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: ($\geq 1/10$)
Common: ($\geq 1/100$ to $< 1/10$)
Uncommon: ($\geq 1/1,000$ 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	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)
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 $\geq 38.0^{\circ}\text{C}$ 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).

- 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 the national reporting system listed in [Appendix V](#).

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 \geq 10 mIU/ml

** Post booster, 98.4% of subjects had anti-PRP concentration \geq 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 \geq 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	Italy	2,4,6 months	84%	In a follow-up of the same cohort, the

(NIH sponsored)				efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.
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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 \geq 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 (\geq 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. Additionally, following a 2-dose primary and booster schedule, seroprotective antibody concentrations against hepatitis B persisted in \geq 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

3 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) with a stopper (butyl).

0.5 ml of suspension in a pre-filled syringe (type I glass) with plunger stopper (butyl).

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.

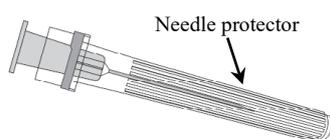
The reconstituted vaccine appears as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

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.

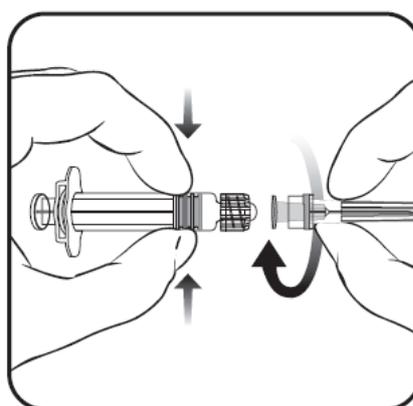
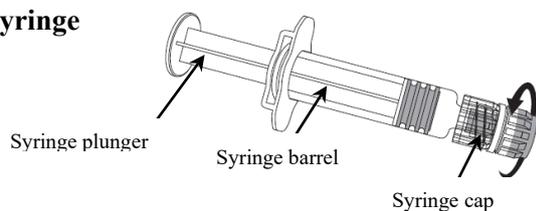
The pre-filled syringe can be supplied with either a ceramic coated treatment (CCT) of the luer tip or with a plastic rigid tip cap (PRTC) luer lock adaptor.

- *Instructions for use of pre-filled syringe if supplied with a PRTC luer lock adaptor*

Needle



Syringe



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.

4. Reconstitute the vaccine as described above.

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

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

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

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

GlaxoSmithKline Biologicals s.a.
Parc de la Noire Epine 20, rue Fleming,
1300 Wavre
Belgium

GlaxoSmithKline Biologicals s.a.
10, Tuas South Avenue 8
Singapore 637421
Singapore

GSK Vaccines GmbH
Emil-von-Behring-Str. 76,
D-35041 Marburg
Germany

GlaxoSmithKline Biologicals Kft
Homoki Nagy István utca 1.
H-2100 Gödöllő
Hungary

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
1 VIAL AND 1 PRE-FILLED SYRINGE WITHOUT NEEDLE
1 VIAL AND 1 PRE-FILLED SYRINGE WITH 2 NEEDLES

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. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml):

Diphtheria toxoid ¹	≥ 30 IU
Tetanus toxoid ¹	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis toxoid ¹ , Filamentous haemagglutinin ¹ , Pertactin ¹)	25, 25, 8 micrograms
Hepatitis B surface antigen ²	10 micrograms
Poliovirus (inactivated) type 1, 2, 3	40, 8, 32 DU
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ²	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

¹adsorbed on Al(OH)₃ 0.5 milligrams Al³⁺

²adsorbed on AlPO₄ 0.32 milligrams Al³⁺

3. LIST OF EXCIPIENTS

Lactose anhydrous
Sodium chloride
Medium 199 containing principally amino acids, mineral salts, vitamins
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

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

Vial: powder

Pre-filled syringe: suspension

1 vial and 1 pre-filled syringe

1 dose (0.5 ml)

1 vial and 1 pre-filled syringe + 2 needles

1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Intramuscular use

Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/152/001 - 1 vial and 1 pre-filled syringe without needle
EU/1/00/152/005 - 1 vial and 1 pre-filled syringe with 2 needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
10 VIALS AND 10 PRE-FILLED SYRINGES WITHOUT NEEDLES
10 VIALS AND 10 PRE-FILLED SYRINGES WITH 20 NEEDLES

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. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml):

Diphtheria toxoid ¹	≥ 30 IU
Tetanus toxoid ¹	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis toxoid ¹ , Filamentous haemagglutinin ¹ , Pertactin ¹)	25, 25, 8 micrograms
Hepatitis B surface antigen ²	10 micrograms
Poliovirus (inactivated) type 1, 2, 3	40, 8, 32 DU
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ²	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

¹adsorbed on Al(OH)₃ 0.5 milligrams Al³⁺

²adsorbed on AlPO₄ 0.32 milligrams Al³⁺

3. LIST OF EXCIPIENTS

Lactose anhydrous
Sodium chloride
Medium 199 containing principally amino acids mineral salts, vitamins
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

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

Vial: powder

Pre-filled syringe: suspension

10 vials and 10 pre-filled syringes

10 x 1 dose (0.5 ml)

10 vials and 10 pre-filled syringes + 20 needles

10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

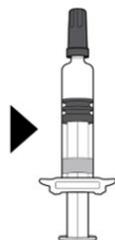
Intramuscular use

Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY



Powder and suspension to be reconstituted before administration



8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/152/002 - 10 vials and 10 pre-filled syringes without needles
EU/1/00/152/006 - 10 vials and 10 pre-filled syringes with 20 needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PACK OF 10 VIALS AND 10 PRE-FILLED SYRINGES WITHOUT NEEDLES FOR
MULTIPACK OF 50 (5 X 10) (WITHOUT BLUE BOX)**

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. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml):

Diphtheria toxoid ¹	≥ 30 IU
Tetanus toxoid ¹	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis toxoid ¹ , Filamentous haemagglutinin ¹ , Pertactin ¹)	25, 25, 8 micrograms
Hepatitis B surface antigen ²	10 micrograms
Poliovirus (inactivated) type 1, 2, 3	40, 8, 32 DU
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ² conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 micrograms
¹ adsorbed on Al(OH) ₃	0.5 milligrams Al ³⁺
² adsorbed on AlPO ₄	0.32 milligrams Al ³⁺

3. LIST OF EXCIPIENTS

Lactose anhydrous
Sodium chloride
Medium 199 containing principally amino acids, mineral salts, vitamins
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection in a pre-filled syringe
Vial: powder
Pre-filled syringe: suspension

Component of a multipack comprising 5 packs, each containing 10 vials and 10 pre-filled syringes
without needles

10 vials and 10 pre-filled syringes
10 x 1 dose (0.5 ml)

Each individual pack cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

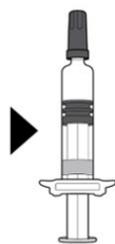
Read the package leaflet before use
Intramuscular use

Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY



Powder and suspension to be reconstituted before administration



8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/152/021 - pack of 50 (5 X 10) without needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACK OF 50 (5 X 10) (OUTER WRAPPER LABEL TO BE APPLIED ON
TRANSPARENT FOIL, INCLUDING BLUE BOX)**

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. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml):

Diphtheria toxoid ¹	≥ 30 IU
Tetanus toxoid ¹	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis toxoid ¹ , Filamentous haemagglutinin ¹ , Pertactin ¹)	25, 25, 8 micrograms
Hepatitis B surface antigen ²	10 micrograms
Poliovirus (inactivated) type 1, 2, 3	40, 8, 32 DU
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ² conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 micrograms
¹ adsorbed on Al(OH) ₃	0.5 milligrams Al ³⁺
² adsorbed on AlPO ₄	0.32 milligrams Al ³⁺

3. LIST OF EXCIPIENTS

Lactose anhydrous
Sodium chloride
Medium 199 containing principally amino acids, mineral salts, vitamins
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection in a pre-filled syringe
Vial: powder
Pre-filled syringe: suspension

Multipack comprising 5 packs, each containing 10 vials and 10 pre-filled syringes without needles
50 x 1 dose (0.5 ml)

Each individual pack cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/152/021 - pack of 50 (5 X 10) without needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH HIB POWDER**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hib for Infanrix hexa
Powder for suspension for injection
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE WITH DTPA HBV IPV SUSPENSION**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

DTPa HBV IPV for Infanrix hexa
Suspension for suspension for injection
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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).

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for your child only. Do not pass it on to others.
- If your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Infanrix hexa is and what it is used for
2. What you need to know before your child receives Infanrix hexa
3. How Infanrix hexa is given
4. Possible side effects
5. How to store Infanrix hexa
6. Contents of the pack and other information

1. What Infanrix hexa is and what it is used for

Infanrix hexa is a vaccine used to protect your child against six diseases:

- **Diphtheria:** a serious bacterial infection that mainly affects the airways and sometimes the skin. The airways become swollen causing serious breathing problems and sometimes suffocation. The bacteria also release a poison. This can cause nerve damage, heart problems, and even death.
- **Tetanus:** tetanus bacteria enter the body through cuts, scratches or wounds in the skin. Wounds that are more likely to get tetanus infection are burns, fractures, deep wounds or wounds that have soil, dust, horse manure or wood splinters in them. The bacteria release a poison. This can cause muscle stiffness, painful muscle spasms, fits and even death. The muscle spasms can be strong enough to cause bone fractures of the spine.
- **Whooping cough (Pertussis):** a highly infectious illness that affects the airways. It causes severe coughing that may lead to problems with breathing. The coughing often has a “whooping” sound. The cough may last for one to two months or longer. Whooping cough can also cause ear infections, chest infections (bronchitis) which may last a long time, lung infections (pneumonia), fits, brain damage and even death.
- **Hepatitis B:** is caused by the hepatitis B virus. It makes the liver swollen. The virus is found in body fluids such as in the vagina, blood, semen or spit (saliva) of infected people.
- **Polio:** a viral infection. Polio is often only a mild illness. However, sometimes it can be very serious and cause permanent damage or even death. Polio can make the muscles unable to move (paralysis). This includes the muscles needed for breathing and walking. The arms or legs affected by the disease may be painfully twisted (deformed).
- ***Haemophilus influenzae* type b (Hib):** can cause brain swelling (inflammation). This can lead to serious problems such as mental slowness (retardation), cerebral palsy, deafness, epilepsy or partial

blindness. It can also cause swelling of the throat. This can cause death by suffocation. Less commonly, the bacteria can also infect the blood, heart, lungs, bones, joints, and tissues of the eyes and mouth.

How Infanrix hexa works

- Infanrix hexa helps your child's body make its own protection (antibodies). This will protect your child against these diseases.
- As with all vaccines, Infanrix hexa may not fully protect all children who are vaccinated.
- The vaccine cannot cause the diseases that it protects your child from.

2. What you need to know before your child receives Infanrix hexa

Infanrix hexa should not be given

- if your child is allergic to:
 - Infanrix hexa or any of the ingredients of this vaccine (listed in section 6).
 - formaldehyde.
 - neomycin or polymyxin (antibiotics).

Signs of an allergic reaction may include itchy skin, rash, shortness of breath and swelling of the face or tongue.

- if your child has had an allergic reaction to any vaccine against diphtheria, tetanus, whooping cough, hepatitis B, polio or *Haemophilus influenzae* type b.
- if your child has had problems of the nervous system within 7 days after previous vaccination with a vaccine against whooping cough
- if your child has a severe infection with a high temperature (over 38°C).
A minor infection such as a cold should not be a problem, but talk to your doctor first.

Infanrix hexa should not be given if any of the above apply to your child. If you are not sure, talk to your doctor or pharmacist before your child is given Infanrix hexa.

Warnings and precautions

Talk to your doctor or pharmacist before your child is given Infanrix hexa:

- if after previously having Infanrix hexa or another vaccine against whooping cough, your child had any problems, especially:
 - a high temperature (over 40°C) within 48 hours of vaccination
 - a collapse or "shock-like" state within 48 hours of vaccination
 - persistent crying lasting 3 hours or more within 48 hours of vaccination
 - fits with or without a high temperature within 3 days of vaccination
- if your child has an undiagnosed or progressive disease of the brain or epilepsy which is not controlled. After control of the disease the vaccine can be given.
- if your child has a bleeding problem or bruises easily
- if your child tends to have fits when they have a fever, or if there is a history of this in the family.
- if your child should become unresponsive or experience seizures (fits) after the vaccination, please contact your doctor immediately. See also section 4 Possible side effects.
- if your baby was born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination. These babies may require respiratory monitoring for 48-72h following the administration of the first two or three doses of Infanrix hexa.

If any of the above apply to your child (or you are not sure), talk to your doctor or pharmacist before your child is given Infanrix hexa.

Other medicines and Infanrix hexa

Your doctor may ask you to give your child a medicine that lowers fever (such as paracetamol) before or immediately after Infanrix hexa is given. This can help to lower some of the side effects (febrile reactions) of Infanrix hexa.

Tell your doctor or pharmacist if your child is taking, has recently taken, might take any other medicines or has recently received any other vaccine.

Infanrix hexa contains neomycin, polymyxin, para-aminobenzoic acid, phenylalanine, sodium and potassium

This vaccine contains neomycin and polymyxin (antibiotics). Tell your doctor if your child has had an allergic reaction to these ingredients.

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'.

3. How Infanrix hexa is given

How much is given

- Your child will have a total of two or three injections with respectively at least 2 or 1 month(s) between each injection.
- You will be told by the doctor or nurse when your child should come back for their next injections.
- If additional injections (boosters) are necessary, the doctor will tell you.

How the vaccine is given

- Infanrix hexa will be given as an injection into a muscle.
- The vaccine should never be given into a blood vessel or into the skin.

If your child misses a dose

- If your child misses an injection which is due, it is important that you make another appointment.
- **Make sure your child finishes the complete vaccination course. If not, your child may not be fully protected against the diseases.**

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. The following side effects may happen with this vaccine:

Allergic reactions

If your child has an allergic reaction, see your doctor straight away. The signs may include:

- rashes that may be itchy or blistering
- swelling of the eyes and face
- difficulty in breathing or swallowing
- a sudden drop in blood pressure and loss of consciousness.

These signs usually start very soon after the injection has been given. Talk to a doctor straight away if they happen after leaving the doctor's surgery.

See your doctor straight away if your child has any of the following serious side effects:

- collapse
- times when they lose consciousness or have a lack of awareness
- fits – with or without fever

These side effects have happened very rarely with Infanrix hexa as with other vaccines against whooping cough. They usually happen within 2 to 3 days after vaccination.

Other side effects include:

Very common (these may occur with more than 1 in 10 doses of the vaccine): sleepiness, loss of appetite, high temperature of 38°C or higher, swelling, pain, redness where the injection was given, unusual crying, feeling irritable or restless.

Common (these may occur with up to 1 in 10 doses of the vaccine): diarrhoea, being sick (vomiting), high temperature of more than 39.5°C, swelling larger than 5 cm or hard lump where the injection was given, feeling nervous.

Uncommon (these may occur with up to 1 in 100 doses of the vaccine): upper respiratory tract infection, tiredness, cough, large swelling at the injected limb.

Rare (these may occur with up to 1 in 1,000 doses of the vaccine): bronchitis, rash, swollen glands in the neck, armpit or groin (lymphadenopathy), bleeding or bruising more easily than normal (thrombocytopenia), in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination, temporarily stopping breathing (apnoea), swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema), swelling of the whole injected limb, blisters.

Very rare (these may happen with up to 1 in 10,000 doses of the vaccine): itching (dermatitis).

Experience with hepatitis B vaccine

In extremely rare cases the following side effects have been reported with hepatitis B vaccine: paralysis, numbness or weakness of the arms and legs (neuropathy), inflammation of some nerves, possibly with pins and needles or loss of feeling or normal movement (Guillain-Barré syndrome), swelling or infection of the brain (encephalopathy, encephalitis), infection around the brain (meningitis). The causal relationship to the vaccine has not been established. Bleeding or bruising more easily than normal (thrombocytopenia) has been reported with hepatitis B vaccines.

Reporting of side effects

If your child gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Infanrix hexa

- Keep this vaccine out of the sight and reach of children.
- Do not use this vaccine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- Store in the original package in order to protect from light.
- Do not freeze. Freezing destroys the vaccine.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines your child no longer uses. These measures will help protect the environment.

6. Contents of the pack and other information

What Infanrix hexa contains

The active substances are:

Diphtheria toxoid ¹	not less than 30 International Units (IU)
Tetanus toxoid ¹	not less than 40 International Units (IU)
<i>Bordetella pertussis</i> antigens	
Pertussis toxoid ¹	25 micrograms
Filamentous Haemagglutinin ¹	25 micrograms
Pertactin ¹	8 micrograms
Hepatitis B surface antigen ^{2,3}	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain) ⁴	40 D-antigen unit
type 2 (MEF-1 strain) ⁴	8 D-antigen unit
type 3 (Saukett strain) ⁴	32 D-antigen unit
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) ³	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

¹adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺

²produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

³adsorbed on aluminium phosphate (AlPO₄) 0.32 milligrams Al³⁺

⁴propagated in VERO cells

The other ingredients are:

Hib powder: lactose anhydrous

DTPa-HBV-IPV suspension: sodium chloride (NaCl), medium 199 (containing amino acids (including phenylalanine), mineral salts (including sodium and potassium), vitamins (including para-aminobenzoic acid) and other substances) and water for injections

What Infanrix hexa looks like and contents of the pack

- The diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis (DTPa-HBV-IPV) component is a white, slightly milky liquid presented in a pre-filled syringe (0.5 ml).
- The Hib component is a white powder presented in a glass vial.
- Both components are mixed together just before your child receives the injection. The mixed appearance is a white, slightly milky liquid.
- Infanrix hexa is available in packs 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.

Marketing Authorisation Holder and Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals SA/NV
Tél/Tel: + 32 10 85 52 00

Lietuva

GlaxoSmithKline Biologicals SA
Tel: +370 80000334

България

GlaxoSmithKline Biologicals SA
Тел.: +359 80018205

Česká republika

GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
cz.info@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti

GlaxoSmithKline Biologicals SA
Tel: +372 8002640

Ελλάδα

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε.
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Hrvatska

GlaxoSmithKline Biologicals SA
Tel: +385 800787089

Ireland

GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 495 5000

Ísland

Vistor hf.
Sími: +354 535 7000

Italia

GlaxoSmithKline S.p.A.
Tel:+ 39 (0)45 7741 111

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals SA/NV
Tél/Tel: + 32 10 85 52 00

Magyarország

GlaxoSmithKline Biologicals SA
Tel.: +36 80088309

Malta

GlaxoSmithKline Biologicals SA
Tel: +356 80065004

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal

Smith Kline & French Portuguesa - Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline Biologicals SA
Tel: +40 800672524

Slovenija

GlaxoSmithKline Biologicals SA
Tel: +386 80688869

Slovenská republika

GlaxoSmithKline Biologicals SA.
Tel: +421 800500589

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Κύπρος
GlaxoSmithKline Biologicals SA
Τηλ: +357 80070017

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

Latvija
GlaxoSmithKline Biologicals SA
Tel: +371 80205045

United Kingdom (Northern Ireland)
GlaxoSmithKline Biologicals SA
Tel: +44(0)800 221441
customercontactuk@gsk.com

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

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 then be well shaken until the powder is completely dissolved prior to administration.

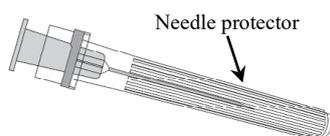
The reconstituted vaccine appears as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

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.

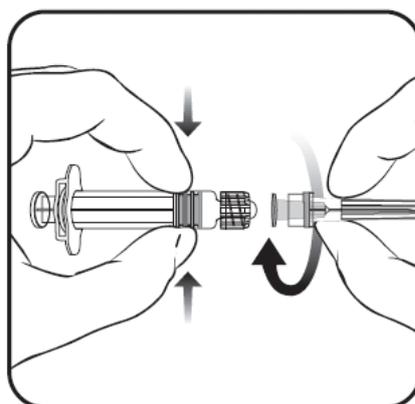
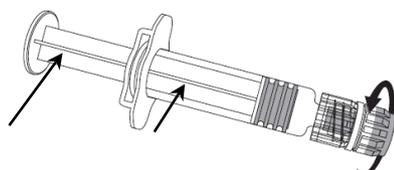
The pre-filled syringe can be supplied with either a ceramic coated treatment (CCT) of the luer tip or with a plastic rigid tip cap (PRTC) luer lock adaptor.

- ***Instructions for use of pre-filled syringe if supplied with a PRTC luer lock adaptor***

Needle



Syringe



Syringe plunger

Syringe barrel



Syringe cap

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Reconstitute the vaccine as described above.

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