ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Synflorix suspension for injection in pre-filled syringe
Synflorix suspension for injection
Synflorix suspension for injection in multidose container (2 doses)
Synflorix suspension for injection in multidose container (4 doses)

Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Pneumococcal polysaccharide serotype 1[1,2]	1 microgram
Pneumococcal polysaccharide serotype 4[1,2]	3 micrograms
Pneumococcal polysaccharide serotype 5[1,2]	1 microgram
Pneumococcal polysaccharide serotype 6B[1,2]	1 microgram
Pneumococcal polysaccharide serotype 7F[1,2]	1 microgram
Pneumococcal polysaccharide serotype 9V[1,2]	1 microgram
Pneumococcal polysaccharide serotype 14[1,2]	1 microgram
Pneumococcal polysaccharide serotype 18C1,3	3 micrograms
Pneumococcal polysaccharide serotype 19F1,4	3 micrograms
Pneumococcal polysaccharide serotype 23F[1,2]	1 microgram

[1] adsorbed on aluminium phosphate	0.5 milligram Al^{3+} in total
[2] conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein	9–16 micrograms
[3] conjugated to tetanus toxoid carrier protein	5–10 micrograms
[4] conjugated to diphtheria toxoid carrier protein	3–6 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (injection).
The vaccine is a turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact on pneumococcal diseases in different age groups as well as the variability of the epidemiology in different geographical areas.

4.2 Posology and method of administration

Posology

The immunisation schedules for Synflorix should be based on official recommendations.

Infants from 6 weeks to 6 months of age

Three-dose primary series
The recommended immunisation series to ensure optimal protection consists of four doses, each of 0.5 ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. A booster (fourth) dose is recommended at least 6 months after the last primary dose and may be given from the age of 9 months onwards (preferably between 12 and 15 months of age) (see sections 4.4 and 5.1).

Two-dose primary series
Alternatively, when Synflorix is given as part of a routine infant immunisation programme, a series consisting of three doses, each of 0.5 ml may be given. The first dose may be given as early as 6 weeks of age with a second dose administered 2 months later. A booster (third) dose is recommended at least 6 months after the last primary dose and may be given from the age of 9 months onwards (preferably between 12 and 15 months of age) (see section 5.1).

Preterm newborn infants (born between 27–36 weeks gestation)

In preterm infants born after at least 27 weeks of gestational age, the recommended immunisation series consists of four doses, each of 0.5 ml. The primary infant series consists of three doses with the first dose given at 2 months of age and with an interval of at least 1 month between doses. A booster (fourth) dose is recommended at least 6 months after the last primary dose (see sections 4.4 and 5.1).

Unvaccinated infants and children ≥ 7 months of age

– infants aged 7–11 months: The vaccination schedule consists of two primary doses of 0.5 ml with an interval of at least 1 month between doses. A booster (third) dose is recommended in the second year of life with an interval of at least 2 months after the last primary dose.

– children aged 12 months –5 years: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

It is recommended that subjects who receive a first dose of Synflorix complete the full vaccination course with Synflorix.

Special populations

In individuals who have underlying conditions predisposing them to invasive pneumococcal disease (such as Human Immunodeficiency Virus (HIV) infection, sickle cell disease (SCD) or splenic dysfunction), Synflorix may be given according to the above mentioned schedules except that a 3-dose schedule should be given as primary vaccination in infants starting vaccination from 6 weeks to 6 months of age (see sections 4.4 and 5.1).

Paediatric population

The safety and efficacy of Synflorix in children over 5 years of age have not been established.

Method of administration

The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in young children.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to any of the carrier proteins.

As with other vaccines, the administration of Synflorix should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

4.4 Special warnings and precautions for use

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.

Prior to immunisation

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

The potential risk of apnoea and the need for respiratory monitoring for 48–72 h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Synflorix should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Synflorix.

In children as of 2 years of age, syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As for other vaccines administered intramuscularly, Synflorix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Information on protection conferred by the vaccine

Official recommendations for the immunisation against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

There is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine except the cross-reactive serotype 19A (see section 5.1) or against non-typeable *Haemophilus influenzae*. Synflorix does not provide protection against other micro-organisms.

As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease, pneumonia or otitis media caused by the serotypes in the vaccine and the cross-reactive serotype 19A. In addition, as otitis media and pneumonia are caused by many micro-organisms other than the *Streptococcus pneumoniae* serotypes represented by the vaccine, the overall protection against these diseases is expected to be limited and substantially lower than protection against invasive disease caused by the serotypes in the vaccine and serotype 19A (see section 5.1).

In clinical trials, Synflorix elicited an immune response to all ten serotypes included in the vaccine, but the magnitude of the responses varied between serotypes. The functional immune response to serotypes 1 and 5 was lower in magnitude than the response against all other vaccine serotypes. It is not known whether this lower functional immune response against serotypes 1 and 5 will result in

lower protective efficacy against invasive disease, pneumonia or otitis media caused by these serotypes (see section 5.1).

Children should receive the dose regimen of Synflorix that is appropriate to their age at the time of commencing the vaccination series (see section 4.2).

Immunosuppressive therapy and immunodeficiency

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, prenatal exposure to anti-retroviral therapy and/or to HIV, or other causes, may have reduced antibody response to vaccination.

Safety and immunogenicity data are available for HIV infected infants (asymptomatic or with mild symptoms according to WHO classification), HIV negative infants born from HIV positive mothers, children with sickle cell disease and children with splenic dysfunction (see sections 4.8 and 5.1). Safety and immunogenicity data for Synflorix are not available for individuals in other specific immunocompromised groups and vaccination should be considered on an individual basis (see section 4.2).

The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 2 years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who have other immunocompromising conditions) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Synflorix should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.

Prophylactic use of antipyretics

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 clinical data suggest that paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.

The use of prophylactic antipyretic medicinal products is recommended:
- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.

Antipyretic treatment should be initiated according to local treatment guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines

Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM_{197} and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). In addition when the meningococcal serogroups A, C, W-135 and Y vaccine (TT conjugate) was co-administered with a booster dose of Synflorix during the second year of life in children primed with 3 doses of Synflorix, lower antibody geometric mean concentration (GMC) and opsonophagocytic assay geometric mean titre (OPA GMT) were observed for one pneumococcal serotype (18 C). There was no impact of co-administration on the other nine pneumococcal serotypes. Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed. The clinical relevance of the above observations is unknown.

Use with systemic immunosuppressive medicinal products

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

Use with prophylactic administration of antipyretics

Clinical data suggest that prophylactic administration of paracetamol, used to reduce the rate of possible post-vaccination febrile reactions, might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known. See section 4.4.

4.6 Fertility, pregnancy and lactation

Synflorix is not intended for use in adults. Human data on the use during pregnancy or breast-feeding and 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

Safety assessment of Synflorix was based on clinical trials involving the administration of 63,905 doses of Synflorix to 22,429 healthy children and 137 preterm infants as primary vaccination. Furthermore, 19,466 children and 116 preterm infants received a booster dose of Synflorix in the second year of life.
Safety was also assessed in 435 previously unvaccinated children from 2 to 5 years old of which 285 subjects received 2 doses of Synflorix.
In all trials, Synflorix was administered concurrently with the recommended childhood vaccines.

In infants, the most common adverse reactions observed after primary vaccination were redness at the injection site and irritability which occurred after approximately 41% and 55% of all doses respectively. Following booster vaccination, the most common adverse reactions were pain at the injection site and irritability, which occurred at approximately 51% and 53% respectively. The majority of these reactions were of mild to moderate severity and were not long lasting.

No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the primary vaccination series.

Local reactogenicity of primary vaccination course was similar in infants < 12 months of age and in children > 12 months of age except for injection site pain for which the incidence increased with increasing age: pain was reported by more than 39% of the infants < 12 months of age and by more than 58% of the children > 12 months of age.

Following booster vaccination, children > 12 months of age are more likely to experience injection site reactions compared to the rates observed in infants during the primary series with Synflorix.

Following catch-up vaccination in children 12 to 23 months of age, urticaria was reported more frequently (uncommon) compared to the rates observed in infants during primary and booster vaccination.

Reactogenicity was higher in children receiving whole cell pertussis vaccines concomitantly. In a clinical study children received either Synflorix (N=603) or 7-valent Prevenar (N=203) concomitantly with a DTPw containing vaccine. After the primary vaccination course, fever ≥38 °C and >39 °C was reported respectively in 86.1% and 14.7% of children receiving Synflorix and in 82.9% and 11.6% of children vaccinated with 7-valent Prevenar.

In comparative clinical studies, the incidence of local and general adverse events reported within 4 days after each vaccination dose was within the same range as after vaccination with 7-valent Prevenar.

Tabulated list of adverse reactions
Adverse reactions (for all age groups)have been categorised by frequency.

Frequencies are reported as:
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)

Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Immune system disorders	Rare	Allergic reactions (such as eczema, allergic dermatitis, atopic dermatitis)
	Very rare	Angioedema
Metabolism and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Crying abnormal
Nervous system disorders	Very common	Drowsiness
	Rare	Convulsions (including febrile convulsions)
Vascular disorders	Very rare	Kawasaki disease
Respiratory, thoracic and mediastinal disorders	Uncommon	Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)
Gastrointestinal disorders	Uncommon	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Urticaria
General disorders and administration site conditions	Very common	Fever ≥ 38 °C rectally (age < 2 years), pain, redness, swelling at the injection site.
	Common	Fever > 39 °C rectally (age < 2 years), injection site reactions like injection site induration
	Uncommon	Injection site reactions like injection site haematoma, haemorrhage and nodule
Adverse reactions additionally reported after booster vaccination of primary series and/or catch-up vaccination:		

Nervous system disorders	Uncommon	Headache (age 2 to 5 years)
Gastrointestinal disorders	Uncommon	Nausea (age 2 to 5 years)
General disorders and administration site conditions	Common	Fever ≥ 38 °C rectally (age 2 to 5 years)
	Uncommon	Fever > 40 °C rectally (age < 2 years), fever > 39 °C rectally (age 2 to 5 years), injection site reactions like diffuse swelling of the injected limb, sometimes involving the adjacent joint, pruritus.
Post-marketing experience		
Immune system disorders	Very rare	Anaphylaxis
Nervous system disorders	Rare	Hypotonic-hyporesponsive episode

Special populations

Safety of Synflorix was assessed in 83 HIV positive (HIV+/+) infants (asymptomatic or with mild symptoms according to WHO classification), 101 HIV negative infants born from HIV positive mothers (HIV+/-) and 50 infants with sickle cell disease (SCD), receiving primary vaccination. Of these, 76, 96 and 49 infants, respectively, received a booster dose. Safety of Synflorix was also assessed in 50 children with SCD starting vaccination at 7–11 months of age, all of them receiving the booster vaccination, and in 50 children with SCD starting vaccination at 12–23 months of age. Results suggest comparable reactogenicity and safety profile of Synflorix between these high risk groups and healthy children.

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: vaccines, pneumococcal vaccines, ATC code: J07AL52

Epidemiological data

The 10 pneumococcal serotypes included in this vaccine represent the major disease-causing serotypes in Europe covering approximately 56% to 90% of invasive pneumococcal disease (IPD) in children <5 years of age. In this age group, serotypes 1, 5 and 7F account for 3.3% to 24.1% of IPD depending on the country and time period studied.

Pneumonia of different aetiologies is a leading cause of childhood morbidity and mortality globally. In prospective studies, *Streptococcus pneumoniae* was estimated to be responsible for 30-50% of pneumonia cases.

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and Non-Typeable *Haemophilus influenzae* (NTHi) are the most common causes of bacterial AOM worldwide.

Efficacy and effectiveness in clinical trials

In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), children were randomised into 4 groups according to the two infant vaccination schedules [2-dose (3, 5 months of age) or 3-dose (3, 4, 5 months of age) primary schedule followed by a booster dose as of 11 months of age] to receive either Synflorix (2/3rd of clusters) or hepatitis vaccines as control (1/3rd of clusters). In the catch-up cohorts, children between 7–11 months of age at first vaccine dose received Synflorix or hepatitis B control vaccine according to a 2-dose primary schedule followed by a booster dose and children between 12–18 months of age at first vaccine dose received 2 doses of either Synflorix or hepatitis A control vaccine. Average follow-up, from first vaccination, was 24 to 28 months for invasive disease and hospital-diagnosed pneumonia. In a nested study, infants were followed up till approximately 21 months of age to assess impact on nasopharyngeal carriage and physician-diagnosed AOM reported by parents.

In a large-scale phase III, randomized, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS) conducted in Argentina, Panama and Colombia, healthy infants aged 6 to 16 weeks received either Synflorix or hepatitis B control vaccine at 2, 4 and 6 months of age followed respectively by either Synflorix or hepatitis A control vaccine at 15 to 18 months of age.

Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

Effectiveness/efficacy in infant cohort below 7 months of age at enrolment

Vaccine effectiveness or efficacy (VE) was demonstrated in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes when Synflorix was given to infants in either 2+1 or 3+1 schedules in FinIP or 3+1 schedule in COMPAS (see Table 1).

Table 1: Number of vaccine serotype IPD cases and vaccine effectiveness (FinIP) or efficacy (COMPAS) in infants below 7 months of age at enrolment receiving at least one vaccine dose (Infant total vaccinated cohort)

Type of IPD	FinIP					COMPAS		
	No. of IPD cases			VE (95% CI)		No. of IPD cases		VE (95% CI)
	Synflorix 3+1 schedule	Synflorix 2+1 schedule	Control[2]	3+1 schedule	2+1 schedule	Synflorix 3+1 schedule	Control	3+1 schedule
	N 10,273	N 10,054	N 10,200			N 11,798	N 11,799	
Vaccine serotype IPD[1]	0	1	12	100%[3] (82.8; 100)	91.8%[4] (58.3; 99.6)	0	18	100%[5] (77.3; 100)
Serotype 6B IPD	0	0	5	100% (54.9; 100)	100% (54.5; 100)	0	2	-
Serotype 14 IPD	0	0	4	100% (39.6; 100)	100% (43.3; 100)	0	9	100% (49.5; 100)

IPD Invasive Pneumococcal Disease
VE Vaccine effectiveness (FinIP) or efficacy (COMPAS)
N number of subjects per group
CI Confidence Interval
(1) In FinIP apart from serotypes 6B and 14, culture-confirmed vaccine serotype IPD cases included 7F (1 case in the Synflorix 2+1 clusters), 18C, 19F and 23F (1 case of each in the control clusters). In COMPAS, serotypes 5 (2 cases), 18C (4 cases) and 23F (1 case) were detected in control group in addition to serotypes 6B and 14.
(2) the 2 groups of control clusters of infants were pooled
(3) p-value<0.0001
(4) p-value=0.0009
(5) in the ATP cohort VE was 100% (95% CI: 74.3; 100; 0 versus 16 cases)

In FinIP the overall observed VE against culture-confirmed IPD was 100% (95% CI: 85.6; 100; 0 versus 14 cases) for the 3+1 schedule, 85.8% (95% CI: 49.1; 97.8; 2 versus 14 cases) for the 2+1 schedule and 93.0% (95% CI: 74.9; 98.9; 2 versus 14 cases) regardless of the primary vaccination schedule. In COMPAS it was 66.7% (95% CI: 21.8; 85.9; 7 versus 21 cases).

Effectiveness following catch-up immunisation

Among the 15,447 children in the catch-up vaccinated cohorts, there were no culture-confirmed IPD cases in the Synflorix groups while 5 vaccine serotype IPD cases were observed in the control groups (serotypes 4, 6B, 7F, 14 and 19F).

Pneumonia

Efficacy against pneumonia was assessed in COMPAS. The mean duration follow-up from 2 weeks post-dose 3 in the ATP cohort was 23 months (range from 0 to 34 months) for the interim analysis (IA) and 30 months (range from 0 to 44 months) for the end-of-study analysis. At the end of this IA or end-of-study ATP follow-up period, the mean age was 29 months (range from 4 to 41 months) and 36 months (range from 4 to 50 months), respectively. The proportion of subjects who received the booster dose in the ATP cohort was 92.3% in both analyses.

Efficacy of Synflorix against first episodes of likely bacterial Community Acquired Pneumonia (CAP) occurring from 2 weeks after the administration of the 3rd dose was demonstrated in the ATP cohort (P value ≤ 0.002) in the interim analysis (event-driven; primary objective).
Likely bacterial CAP (B–CAP) is defined as radiologically confirmed CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray, or with non-alveolar infiltrates but with C reactive protein (CRP) ≥ 40 mg/l.

The vaccine efficacy against B–CAP observed at the interim analysis is presented below (table 2).

Table 2: Numbers and percentages of subjects with first episodes of B–CAP occurring from 2 weeks after the administration of the 3rd dose of Synflorix or control vaccine and vaccine efficacy (ATP cohort)

Synflorix N=10,295		Control vaccine N=10,201		Vaccine efficacy
n	% (n/N)	n	% (n/N)	
240	2.3%	304	3.0%	22.0% (95% CI: 7.7; 34.2)

N number of subjects per group
n/% number/percentage of subjects reporting a first episode of B–CAP anytime from 2 weeks after the administration of the 3rd dose
CI Confidence Interval

In the interim analysis (ATP cohort), the vaccine efficacy against first episodes of CAP with alveolar consolidation or pleural effusion (C–CAP, WHO definition) was 25.7% (95% CI: 8.4; 39.6) and against first episodes of clinically suspected CAP referred for X-ray was 6.7% (95% CI: 0.7; 12.3).

At the end-of-study analysis (ATP cohort), the vaccine efficacy (first episodes) against B–CAP was 18.2% (95% CI: 4.1; 30.3), against C–CAP 22.4% (95% CI: 5.7; 36.1) and against clinically suspected CAP referred for X-ray 7.3% (95% CI: 1.6; 12.6). Efficacy was 100% (95% CI: 41.9; 100) against bacteraemic pneumococcal pneumonia or empyema due to vaccine serotypes. The protection against B–CAP before booster dose and at the time or after booster dose was 13.6% (95% CI: -11.3; 33.0) and 21.7% (95% CI: 3.4; 36.5) respectively. For C–CAP it was 15.1% (95% CI: -15.5; 37.6) and 26.3% (95% CI: 4.4; 43.2) respectively.
The reduction in B–CAP and C–CAP was greatest in children < 36 months of age (vaccine efficacy of 20.6% (95% CI: 6.5; 32.6) and 24.2% (95% CI: 7.4; 38.0) respectively). Vaccine efficacy results in

children > 36 months of age suggest a waning of protection. The persistence of protection against B–CAP and C–CAP beyond the age of 36 months is currently not established.

The results of the COMPAS study, which was performed in Latin America, should be interpreted with caution due to possible differences in epidemiology of pneumonia in different geographical locations.

In the FinIP study, vaccine effectiveness in reducing hospital-diagnosed pneumonia cases (identified based on the ICD 10 codes for pneumonia) was 26.7% (95% CI: 4.9; 43.5) in the 3+1 infant schedule and 29.3% (95% CI: 7.5; 46.3) in the 2+1 infant schedule. For catch-up vaccination, vaccine effectiveness was 33.2% (95% CI: 3.0; 53.4) in the 7–11 month cohort and 22.4% (95% CI: -8.7; 44.8) in the 12–18 month cohort.

Acute Otitis Media (AOM)

Two efficacy studies, COMPAS and POET (Pneumococcal Otitis Media Efficacy Trial), were conducted with pneumococcal conjugate vaccines containing protein D: Synflorix and an investigational 11-valent conjugate vaccine (which in addition contained serotype 3), respectively.

In COMPAS, 7,214 subjects [Total Vaccinated cohort (TVC)] were included in the AOM efficacy analysis of which 5,989 subjects were in the ATP cohort (Table 3).

Table 3: Vaccine efficacy against AOM(1) in COMPAS

Type or cause of AOM	Vaccine efficacy (95% CI)
	ATP(2)
Clinical AOM	16.1% (-1.1; 30.4)(3)
Any pneumococcal serotype	56.1% (13.4; 77.8)
10 pneumococcal vaccine serotypes	67.1% (17.0; 86.9)
Non-typeable *Haemophilus influenzae* (NTHi)	15.0%(4) (-83.8; 60.7)

CI Confidence Interval
(1) First episode
(2) Follow up period for a maximum of 40 months from 2 weeks after third primary dose
(3) Not statistically significant by pre-defined criteria (One sided p=0.032). However, in TVC cohort, vaccine efficacy against first clinical AOM episode was 19% (95% CI: 4.4; 31.4).
(4) Not statistically significant.

In another large randomised double-blind trial (POET) conducted in the Czech Republic and in Slovakia, 4,907 infants (ATP cohort) received either the 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of Synflorix (along with serotype 3 for which efficacy was not demonstrated) or a control vaccine (hepatitis A vaccine) according to a 3, 4, 5 and 12-15 months vaccination schedule.

Efficacy of the 11 Pn-PD vaccine against the first occurrence of vaccine serotype AOM episode was 52.6% (95% CI: 35.0; 65.5). Serotype specific efficacy against the first AOM episode was demonstrated for serotypes 6B (86.5%, 95% CI: 54.9; 96.0), 14 (94.8%, 95% CI: 61.0; 99.3), 19F (43.3%, 95% CI: 6.3; 65.4) and 23F (70.8%, 95% CI: 20.8; 89.2). For other vaccine serotypes, the number of AOM cases was too limited to allow any efficacy conclusion to be drawn. Efficacy against any AOM episode due to any pneumococcal serotype was 51.5% (95% CI: 36.8; 62.9). The vaccine efficacy against the first episode of NTHi AOM was 31.1% (95% CI: -3.7; 54.2, not significant). Efficacy against any NTHi AOM episode was 35.3% (95% CI: 1.8; 57.4). The estimated vaccine efficacy against any clinical episodes of otitis media regardless of aetiology was 33.6% (95% CI: 20.8; 44.3).

Based on immunological bridging of the functional vaccine response (OPA) of Synflorix with the 11-valent formulation used within POET, it is expected that Synflorix provides similar protective efficacy against pneumococcal AOM.

No increase in the incidence of AOM due to other bacterial pathogens or non-vaccine/non-vaccine related serotypes was observed in either COMPAS (based on the few cases reported) or POET trial.

Effectiveness against physician-diagnosed AOM reported by parents was studied in the nested study within the FinIP trial. Vaccine effectiveness was 6.1% (95% CI: -2.7; 14.1) for the 3+1 schedule and 7.4% (95% CI -2.8; 16.6) for 2+1 schedule for this AOM endpoint in the infant vaccinated cohort.

Impact on nasopharyngeal carriage (NPC)

The effect of Synflorix on nasopharyngeal carriage was studied in 2 double-blind randomised studies using an inactive control: in the nested study of FinIP in Finland (5,023 subjects) and in COMPAS (1,700 subjects).

In both COMPAS and the nested Finnish study, Synflorix reduced vaccine type carriage with an apparent increase in non-vaccine (excluding vaccine-related) serotypes observed after booster. The results were not statistically significant across all analyses in COMPAS. However, taken together there was a trend for decrease in overall pneumococcal carriage.

In both studies there were significant decrease of individual serotypes 6B and 19F. In the nested Finnish study, a significant reduction was also observed for individual serotypes 14, 23F and, in the 3 dose primary schedule, for the cross-reactive serotype 19A.

In a clinical study NPC was assessed in HIV positive infants (N = 83) and HIV negative infants born from HIV positive mothers (N = 101) and compared to HIV negative infants born from HIV negative mothers (N = 100). The HIV exposure or infection did not appear to alter the effect of Synflorix on pneumococcal carriage up to 24–27 months of age, i.e. up to 15 months following booster vaccination.

Effectiveness in post-marketing surveillance

In Brazil, Synflorix was introduced into the national immunisation programme (NIP) using a 3+1 schedule in infants (2, 4, 6 months of age and a booster dose at 12 months) with a catch-up campaign in children up to 2 years of age. Based on almost 3 years of surveillance following Synflorix introduction, a matched case-control study reported a significant decrease in culture or PCR confirmed IPD due to any vaccine serotype, and IPD due to individual serotypes 6B, 14 and 19A.

Table 4: Summary of effectiveness of Synflorix for IPD in Brazil

Types of IPD[1]	**Adjusted Effectiveness[2] % (95% CI)**
Any vaccine serotype IPD[3]	83.8% (65.9; 92.3)
- Invasive pneumonia or bacteraemia	81.3% (46.9; 93.4)
- Meningitis	87.7% (61.4; 96.1)
IPD due to individual serotypes[4]	
- 6B	82.8% (23.8; 96.1)
- 14	87.7% (60.8; 96.1)
- 19A	82.2% (10.7; 96.4)

(1) Culture or PCR confirmed IPD

(2) The adjusted effectiveness represents the percent reduction in IPD in the Synflorix vaccinated group compared to the unvaccinated group, controlling for confounding factors.
(3) Culture or PCR confirmed cases for serotypes 4, 6B, 7F, 9V, 14, 18C, 19F and 23F contributed to the analysis.
(4) Individual serotypes for which statistical significance was reached in the effectiveness analysis controlling for confounding factors (no adjustment for multiplicity performed).

In Finland, Synflorix was introduced into NIP with a 2+1 schedule in infants (3, 5 months of age and a booster dose at 12 months) without catch-up campaign. Before and after NIP comparison suggests a significant decrease in the incidence of any culture confirmed IPD, any vaccine serotype IPD and IPD due to serotype 19A.

Table 5: Rates of IPD and the corresponding rate reductions in Finland

IPD	**Incidence per 100,000 person years**		**Relative rate reduction[(1)] % (95% CI)**
	Before NIP	**After NIP**	
Any culture confirmed	62.9	12.9	80% (72; 85)
Any vaccine serotype[(2)]	49.1	4.2	92% (86; 95)
Serotype 19A	5.5	2.1	62% (20; 85)

(1) The relative rate reduction indicates how much the incidence of IPD in children of ≤5 years of age was reduced in the Synflorix cohort (followed for 3 years after NIP introduction) versus age and season matched non-vaccinated historical cohorts (each followed for 3 year periods before introduction of Synflorix into NIP).
(2) Culture confirmed cases for serotypes 1, 4, 6B, 7F, 9V, 14, 18C, 19F and 23F contributed to the analysis.

In Quebec, Canada, Synflorix was introduced into the infant immunisation programme (2 primary doses to infants less than 6 months of age and a booster dose at 12 months) following 4.5 years of use of 7-valent Prevenar. Based on 1.5 years of surveillance following Synflorix introduction, with over 90% coverage in the vaccine-eligible age group, a decrease in vaccine serotype IPD incidence (largely due to changes in serotype 7F disease) was observed with no concomitant increase in non-vaccine serotype IPD incidence. Overall, the incidence of IPD was 35/100,000 person-years in those cohorts exposed to Synflorix, and 64/100,000 person-years in those exposed to 7-valent Prevenar, representing a statistically significant difference (p = 0.03). No direct cause-and-effect can be inferred from observational studies of this type.

Immunogenicity data

Immunologic non-inferiority to 7-valent Prevenar

The assessment of potential efficacy against IPD pre-licensure was based on a comparison of immune responses to the seven serotypes shared between Synflorix and another pneumococcal conjugate vaccine for which protective efficacy was evaluated previously (i.e. 7-valent Prevenar), as recommended by the WHO. Immune responses to the extra three serotypes in Synflorix were also measured.

In a head-to-head comparative trial with 7-valent Prevenar, non-inferiority of the immune response to Synflorix measured by ELISA was demonstrated for all serotypes, except for 6B and 23F (upper limit of the 96.5% CI around the difference between groups >10%) (Table 6). For serotypes 6B and 23F, respectively, 65.9% and 81.4% of infants vaccinated at 2, 3 and 4 months reached the antibody threshold (i.e. 0.20 µg/ml) one month after the third dose of Synflorix versus 79.0% and 94.1% respectively, after three doses of 7-valent Prevenar. The clinical relevance of these differences is unclear, as Synflorix was observed to be effective against IPD caused by serotype 6B in a double-blind, cluster-randomized clinical study (see Table 1).

The percentage of vaccinees reaching the threshold for the three additional serotypes in Synflorix (1, 5 and 7F) was respectively 97.3%, 99.0% and 99.5% and was at least as good as the aggregate 7-valent Prevenar response against the 7 common serotypes (95.8%).

Table 6: Comparative analysis between 7-valent Prevenar and Synflorix in percentage of subjects with antibody concentrations ≥ 0.20 µg/ml one month post-dose 3

Antibody	Synflorix		7-valent Prevenar		Difference in % ≥ 0.20µg/ml (7-valent Prevenar minus Synflorix)		
	N	%	N	%	%	96.5% CI	
Anti-4	1106	97.1	373	100	2.89	1.71	4.16
Anti-6B	1100	65.9	372	79.0	13.12	7.53	18.28
Anti-9V	1103	98.1	374	99.5	1.37	-0.28	2.56
Anti-14	1100	99.5	374	99.5	-0.08	-1.66	0.71
Anti-18C	1102	96.0	374	98.9	2.92	0.88	4.57
Anti-19F	1104	95.4	375	99.2	3.83	1.87	5.50
Anti-23F	1102	81.4	374	94.1	12.72	8.89	16.13

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by 7-valent Prevenar. Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines. After the booster dose the GMCs elicited by Synflorix were lower for most serotypes in common with 7-valent Prevenar.

In the same study, Synflorix was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87.7% to 100% of Synflorix vaccinees and 92.1% to 100% of 7-valent Prevenar vaccinees reached an OPA titre ≥ 8 one month after the third dose. The difference between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was <5% for all serotypes in common, including 6B and 23F. Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by Synflorix were lower than those elicited by 7-valent Prevenar for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre ≥ 8 were respectively 65.7%, 90.9% and 99.6% after the primary vaccination course and 91.0%, 96.3% and 100% after the booster dose. The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

It has also been demonstrated that Synflorix induces an immune response to the cross-reactive serotype 19A with 48.8% (95% CI: 42.9; 54.7) of vaccinees reaching an OPA titre ≥ 8 one month after a booster dose.

The administration of a fourth dose (booster dose) in the second year of life elicited an anamnestic antibody response as measured by ELISA and OPA for the vaccine serotypes and the cross-reactive serotype 19A demonstrating the induction of immune memory after the three-dose primary course.

Additional immunogenicity data

Infants from 6 weeks to 6 months of age:

3-dose primary schedule

In clinical studies the immunogenicity of Synflorix was evaluated after a 3-dose primary vaccination series (6941 subjects) according to different schedules (including 6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age) and after a fourth (booster) dose (5645 subjects) given at least 6 months after the last primary dose and from the age of 9 months onwards. In general, comparable vaccine responses were

observed for the different schedules, although somewhat higher immune responses were noted for the 2-4-6 month schedule.

2-dose primary schedule

In clinical studies the immunogenicity of Synflorix was evaluated after a 2-dose primary vaccination series (470 subjects) according to different schedules (including 6–14 weeks, 2–4 or 3–5 months of age) and after a third (booster) dose (470 subjects) given at least 6 months after the last primary dose and from the age of 9 months onwards.

A clinical study evaluated the immunogenicity of Synflorix in 2-dose or 3-dose primed subjects in four European countries. Although there was no significant difference between the two groups in the percentages of subjects with antibody concentration ≥ 0.20 μg/ml (ELISA), the percentages of subjects for serotypes 6B and 23F were lower than for the other vaccine serotypes (Table 7 and Table 8). The percentage of subjects with OPA titres ≥ 8 in 2-dose primed subjects compared to 3-dose primed subjects were lower for serotypes 6B, 18C and 23F (74.4%, 82.8%, 86.3% respectively for the 2-dose schedule and 88.9%, 96.2%, 97.7% respectively for the 3-dose schedule). Overall, the persistence of the immune response until the booster at 11 months of age was lower in the 2-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed for each vaccine serotype (Table 7 and Table 8). After the booster dose a lower percentage of subjects with OPA titres ≥ 8 was observed in the 2-dose schedule for serotypes 5 (87.2% versus 97.5% for the 3-dose primed subjects) and 6B (81.1% versus 90.3%), all other responses were comparable.

Table 7: Percentage of 2-dose primed subjects with antibody concentrations ≥ 0.20 μg/ml one month post-primary and one month post-booster

Antibody	≥ 0.20 μg/ml (ELISA)					
	Post-primary			Post-booster		
	%	95% CI		%	95% CI	
Anti-1	97.4	93.4	99.3	99.4	96.5	100
Anti-4	98.0	94.4	99.6	100	97.6	100
Anti-5	96.1	91.6	98.5	100	97.6	100
Anti-6B	55.7	47.3	63.8	88.5	82.4	93.0
Anti-7F	96.7	92.5	98.9	100	97.7	100
Anti-9V	93.4	88.2	96.8	99.4	96.5	100
Anti-14	96.1	91.6	98.5	99.4	96.5	100
Anti-18C	96.1	91.6	98.5	100	97.7	100
Anti-19F	92.8	87.4	96.3	96.2	91.8	98.6
Anti-23F	69.3	61.3	76.5	96.1	91.7	98.6

Table 8: Percentage of 3-dose primed subjects with antibody concentrations ≥ 0.20 μg/ml one month post-primary and one month post-booster

Antibody	≥ 0.20 μg/ml (ELISA)					
	Post-primary			Post-booster		
	%	95% CI		%	95% CI	
Anti-1	98.7	95.3	99.8	100	97.5	100
Anti-4	99.3	96.4	100	100	97.5	100
Anti-5	100	97.6	100	100	97.5	100
Anti-6B	63.1	54.8	70.8	96.6	92.2	98.9
Anti-7F	99.3	96.4	100	100	97.5	100
Anti-9V	99.3	96.4	100	100	97.5	100
Anti-14	100	97.6	100	98.6	95.2	99.8
Anti-18C	99.3	96.4	100	99.3	96.3	100
Anti-19F	96.1	91.6	98.5	98.0	94.2	99.6
Anti-23F	77.6	70.2	84.0	95.9	91.3	98.5

For the cross-reactive serotype 19A, similar ELISA antibody GMCs were observed post-primary and post-booster for the 2-dose schedule [0.14 µg/ml (95% CI: 0.12; 0.17) and 0.73 µg/ml (95% CI: 0.58; 0.92)] and the 3-dose schedule [0.19 µg/ml (95% CI: 0.16; 0.24) and 0.87 µg/ml (95% CI: 0.69; 1.11)]. The percentage of subjects with OPA titres ≥ 8 and GMTs observed post-primary and post-booster were lower in the 2-dose schedule than that in the 3-dose schedule. In both schedules, a booster response indicative of immunological priming was observed.

The clinical consequences of the lower post-primary and post-booster immune responses observed after the 2-dose primary schedule are not known.

A clinical study conducted in South Africa assessed the immunogenicity of Synflorix after 3-dose (6-10-14 weeks of age) or 2-dose (6-14 weeks of age) priming followed by a booster dose at 9-10 months of age. After primary vaccination, for the vaccine serotypes the percentages of subjects reaching antibody threshold and with OPA titres ≥ 8 were similar after 2-dose compared to 3-dose except lower OPA percentage for serotype 14. The antibody GMCs and OPA GMTs were lower after 2-dose for most vaccine serotypes.

For the cross-reactive serotype 19A, similar percentages of subjects reaching antibody threshold and OPA titres ≥ 8 and similar antibody GMC and OPA GMT were observed post-primary in both groups. Overall, the pre-booster persistence of immune responses was lower in the 2-dose compared to the 3-dose priming group for most vaccine serotypes and was similar for serotype 19A.

Booster dose at 9–10 months of age

In the study conducted in South Africa, the booster dose given at 9-10 months of age induced marked increases in antibody GMCs and OPA GMTs for each vaccine serotype and serotype 19A in both 2-dose and 3-dose priming groups indicative of immunological priming.

Booster dose at 9–12 versus 15–18 months of age

A clinical study conducted in India assessing a booster dose given at 9-12 or 15-18 months of age in 66 and 71 children, respectively, following primary vaccination at 6, 10 and 14 weeks of age, did not suggest differences between groups in terms of antibody GMCs. Higher OPA GMTs in the group boosted at 15-18 months of age were observed for most of the vaccine serotypes and serotype 19A. However, the clinical relevance of this observation is not known.

Immune memory

In the follow-up of the European study evaluating the 2-dose and 3-dose primary vaccination schedules, the persistence of antibodies at 36–46 months of age was demonstrated in subjects that had received a 2-dose primary series followed by a booster dose with at least 83.7% of subjects remaining seropositive for vaccine serotypes and the cross-reactive serotype 19A. In subjects that had received a 3-dose primary series followed by a booster dose, at least 96.5% of the subjects remained seropositive for vaccine serotypes and 86.4% for serotype 19A. After a single dose of Synflorix, administered during the 4th year of life, as a challenge dose, the fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, was similar in 2-dose primed subjects to that in 3-dose primed subjects. These results are indicative of immunological memory in primed subjects for all vaccine serotypes and the cross-reactive serotype 19A.

Unvaccinated infants and children ≥ 7 months of age:

The immune responses elicited by Synflorix in previously unvaccinated older children were evaluated in three clinical studies.

The first clinical study evaluated the immune responses for vaccine serotypes and the cross-reactive serotype 19A in children aged 7–11 months, 12–23 months and 2 to 5 years:

- Children aged 7–11 months received 2 primary doses followed by a booster dose in the second year of life. The immune responses after the booster dose in this age group were generally similar to those observed after the booster dose in infants who had been primed with 3 doses below 6 months of age.
- In children aged 12–23 months, the immune responses elicited after two doses were comparable to the responses elicited after three doses in infants below 6 months of age, except for vaccine serotypes 18C and 19F as well as serotype 19A for which responses were higher in the 12–23 months children.
- In children aged 2 to 5 years that received 1 dose, the ELISA antibody GMCs were similar for 6 vaccine serotypes as well as serotype 19A than those achieved following a 3-dose vaccination schedule in infants below 6 months of age while they were lower for 4 vaccine serotypes (serotypes 1, 5, 14 and 23F). The OPA GMTs were similar or higher following a single dose than a 3-dose primary course in infants below 6 months of age, except for serotype 5.

In the second clinical study, a single dose administered four months after two catch-up doses at 12–20 months of age elicited a marked increase of ELISA GMCs and OPA GMTs (when comparing the responses pre and post the last dose), indicating that two catch-up doses provide adequate priming.

The third clinical study showed that the administration of 2 doses with a 2 month interval starting at 36–46 months of age resulted in higher ELISA antibody GMCs and OPA GMTs than those observed one month after a 3-dose primary vaccination for each vaccine serotype and the cross-reactive serotype 19A. The proportion of subjects with an ELISA antibody concentration ≥ 0.20 µg/ml or an OPA titre ≥ 8 for each vaccine serotype was comparable or higher in the catch-up group than in the 3-dose primed infants.

Long-term persistence of antibodies has not been investigated after administration of a primary series in infants plus booster or after a 2-dose priming in older children.

In a clinical study, it has been demonstrated that Synflorix can be safely administered as a booster dose in the second year of life to children who had received 3 primary doses of 7-valent Prevenar. This study has shown that the immune responses against the 7 common serotypes were comparable to those elicited by a booster dose of 7-valent Prevenar. However, children who received 7-valent Prevenar for the primary series would not be primed against the additional serotypes contained in Synflorix (1, 5, 7F). Therefore the degree and duration of protection against invasive pneumococcal disease and otitis media due to these three serotypes in children of this age group following a single dose of Synflorix cannot be predicted.

Immunogenicity data in preterm infants

Immunogenicity of Synflorix in very preterm (gestation period of 27-30 weeks) (N=42), preterm (gestation period of 31-36 weeks) (N=82) and full term (gestation period > 36 weeks) (N=132) infants was evaluated following a 3-dose primary vaccination course at 2, 4, 6 months of age. Immunogenicity following a fourth dose (booster dose) at 15 to 18 months of age was evaluated in 44 very preterm, 69 preterm and 127 full term infants.

One month after primary vaccination (i.e. after the third dose), for each vaccine serotype at least 92.7% of subjects achieved ELISA antibody concentrations ≥ 0.20 µg/ml and at least 81.7% achieved OPA titres ≥ 8 except serotype 1 (at least 58.8% with OPA titres ≥ 8). Similar antibody GMCs and OPA GMTs were observed for all infants except lower antibody GMCs for serotypes 4, 5, 9V and the cross-reactive serotype 19A in very preterms and serotype 9V in preterms and lower OPA GMT for serotype 5 in very preterms. The clinical relevance of these differences is not known.

One month after the booster dose increases of ELISA antibody GMCs and OPA GMTs were seen for each vaccine serotype and the cross-reactive serotype 19A, indicative of immunological memory. Similar antibody GMCs and OPA GMTs were observed for all infants except a lower OPA GMT for

serotype 5 in very preterm infants. Overall, for each vaccine serotype at least 97.6% of subjects achieved ELISA antibody concentrations ≥ 0.20 µg/ml and at least 91.9% achieved OPA titres ≥ 8.

Immunogenicity in special population

HIV positive (HIV+/+) infants and HIV negative infants born from HIV positive mothers (HIV+/-)

In a clinical study conducted in South Africa the immunogenicity of Synflorix administered as a 3-dose primary vaccination course (at 6, 10 and 14 weeks of age) followed by a booster dose (at 9 to 10 months of age) was assessed in 70 HIV positive (HIV+/+) infants, 91 HIV negative infants born from HIV positive mothers (HIV+/-) and 93 HIV negative infants born from HIV negative mothers (HIV-/-). Only HIV+/+ infants with WHO classification stage 1 (asymptomatic) or 2 (mild symptoms) were to be enrolled.

For most vaccine serotypes, group comparisons did not suggest any differences in post-primary immune responses between the HIV+/+ and HIV-/- groups, or the HIV+/- and HIV-/- groups, except for a trend towards a lower percentage of subjects reaching OPA titres ≥ 8 and lower OPA GMTs in the HIV+/+ group. The clinical relevance of this lower post-primary OPA response is not known. For the cross-reactive serotype 19A, the results did not suggest any differences in ELISA antibody GMCs and OPA GMTs between groups.

The booster dose of Synflorix in HIV+/+ and HIV+/- infants induced robust increases in ELISA antibody GMCs and OPA GMTs for each vaccine serotype and serotype 19A indicative of immunological priming. For most vaccine serotypes and serotype 19A, group comparisons did not suggest any differences post-booster dose in ELISA antibody GMCs and OPA GMTs between the HIV+/+ and HIV-/- groups, or the HIV+/- and HIV-/- groups.

The results for protein D suggested comparable post-primary and post-booster immune responses between groups.

In each group, persistence of the immune responses was observed at 24–27 months of age, i.e. up to 15 months following booster vaccination.

Children with sickle cell disease

A clinical study conducted in Burkina Faso assessed the immunogenicity of Synflorix administered to 146 children with SCD (haemoglobin SS disease, haemoglobin SC disease or with β-thalassemia) compared to 143 age-matched children without SCD. Among children with SCD, 48 children <6 months of age received primary vaccination at 8, 12 and 16 weeks of age, followed by a booster dose at 9–10 months of age, 50 children aged 7–11 months and 48 aged 12–23 months started catch-up vaccination according to their age. The immune response to Synflorix for each of the vaccine serotypes and serotype 19A, as well as for protein D, did not appear to be influenced by SCD.

Children with splenic dysfunction

Immunogenicity and safety of Synflorix were assessed in a limited number of primed or unprimed subjects with congenital or acquired asplenia, splenic dysfunction or complement deficiencies: 6 subjects 2–5 years of age and 40 subjects 6–17 years of age (Synflorix is indicated up to 5 years of age). Synflorix was shown to be immunogenic and no new safety concerns were observed in this study.

Immunogenicity of Synflorix containing the preservative 2-phenoxyethanol (2-PE)

Immunogenicity of Synflorix containing the preservative 2-PE (presented in a 4-dose container) was assessed in healthy infants vaccinated at 6, 10 and 18 weeks of age and compared to those receiving Synflorix without added preservative (160 enrolled subjects per group).

Immune responses were compared using non-inferiority criteria in terms of antibody GMC ratio (GMC from group of subjects receiving Synflorix without 2-PE over GMC from group of subjects receiving Synflorix with 2-PE) for each of the 10 vaccine serotypes and for the cross-reactive serotype 19A.

Non-inferiority was demonstrated as the upper limit of the 2-sided 95% CI of the antibody GMC ratios was below 2 for each of the 10 vaccine serotypes and for serotype 19A. In addition, OPA GMTs were in same ranges for both groups.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Studies with an 11-valent vaccine formulation representative for Synflorix revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1-dose and 2-dose containers
Sodium chloride
Water for injections

4-dose container
Sodium chloride
2-phenoxyethanol
Water for injections

For adsorbent, 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

1-dose and 2-dose containers
4 years

4-dose container
3 years

After first opening of multidose vial:

2-dose vial
After first opening of the 2-dose vial, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2 °C – 8 °C). If not used within 6 hours it should be discarded.

4-dose vial
After first opening of the 4-dose vial, the vaccine may be stored for a maximum of 28 days in a refrigerator (2 °C – 8 °C). If not used within 28 days it should be discarded.

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.

Multidose vial
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pre-filled syringe
0.5 ml of suspension in a pre-filled syringe (type I glass) for 1 dose with a plunger stopper (butyl rubber) with or without needles. Pack size of 1, 10 or 50.

Vial
0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (butyl rubber). Pack size of 1, 10 or 100.

Multidose vial
1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (butyl rubber). Pack size of 100.
2 ml of suspension in a vial (type I glass) for 4 doses with a stopper (butyl rubber). Pack size of 10 or 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Pre-filled syringe
A fine white deposit with a clear colourless supernatant may be observed upon storage of the pre-filled syringe. This does not constitute a sign of deterioration.

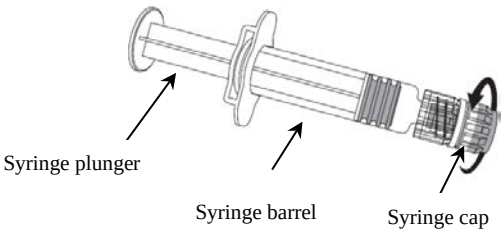
The content of the pre-filled syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

The vaccine should be allowed to reach room temperature before use.

The vaccine should be well shaken before use.

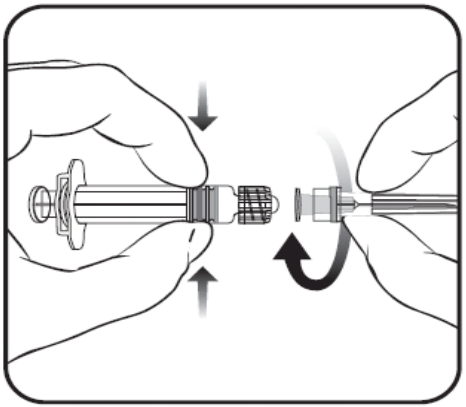
Instructions for administration of the vaccine

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.

3. Remove the needle protector, which on



occasion can be a little stiff.

Needle protector

Vial
A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

The vaccine should be allowed to reach room temperature before use.

The vaccine should be well shaken before use.

Multidose vial
A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

The vaccine should be allowed to reach room temperature before use.

The vaccine should be well shaken before use.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

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)

Pre-filled syringe
EU/1/09/508/001
EU/1/09/508/002
EU/1/09/508/003
EU/1/09/508/004
EU/1/09/508/005
EU/1/09/508/010

Vial
EU/1/09/508/006

EU/1/09/508/007
EU/1/09/508/008

Multidose vial
2-dose vial
EU/1/09/508/009
4-dose vial
EU/1/09/508/012
EU/1/09/508/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 March 2009
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

22 November 2018

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