

SYNFLORIX® PRODUCT INFORMATION

Pneumococcal polysaccharide conjugate vaccine, 10 valent adsorbed

NAME OF THE MEDICINE

Synflorix

Pneumococcal polysaccharide conjugate vaccine, 10 valent adsorbed

DESCRIPTION

Synflorix is a pneumococcal polysaccharide conjugate vaccine using Protein D as the main carrier protein. Protein D is a highly conserved surface protein from Non-Typeable *Haemophilus influenzae* (NTHi). Each 0.5ml dose of Synflorix contains 1 microgram of Pneumococcal polysaccharide serotypes 1*, 5*, 6B*, 7F*, 9V*, 14* and 23F* and 3 micrograms of Pneumococcal polysaccharide serotypes 4*, 18C[†] and 19F[#] adsorbed onto Aluminium phosphate (0.5 mg Al³⁺). Synflorix also contains approximately 9 to 16 micrograms of Protein D carrier protein, 5 to 10 micrograms of tetanus toxoid carrier protein and 3 to 6 micrograms of diphtheria toxoid carrier protein. Synflorix also contains 4.3 milligrams of sodium chloride (NaCl) and water for injection as excipients. Synflorix does not contain a preservative.

* conjugated to Protein D

conjugated to diphtheria toxoid carrier protein

† conjugated to tetanus toxoid carrier protein.

PHARMACOLOGY

Synflorix is a pneumococcal polysaccharide conjugate vaccine using Protein D as the main carrier protein. Protein D is a highly conserved surface protein from Non-Typeable *Haemophilus influenzae* (NTHi). The vaccine contains 10 *Streptococcus pneumoniae* serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F).

Protection against the *Streptococcus pneumoniae* bacterium is triggered by antibodies, directed against its polysaccharide capsule, which can mediate bacterial killing.

Epidemiological data

Invasive pneumococcal disease (IPD)

The 10 serotypes included in this vaccine represent the major disease-causing serotypes worldwide covering approximately 50% to 96% of IPD in children <5 years of age.

Pneumonia

Pneumonia of different aetiologies is a leading cause of childhood morbidity and mortality globally. In studies in developing and developed countries, *Streptococcus pneumoniae* was estimated to be responsible for up to 50% of bacterial pneumonia cases in young children

Acute otitis media (AOM)

AOM is a common childhood disease with different aetiologies. Bacteria are believed to be responsible for at least 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and NTHi are the most common causes of bacterial AOM worldwide.

CLINICAL TRIALS

World Health Organisation Criteria

The WHO recommendations state that approval of any new pneumococcal conjugate vaccines against IPD can be based on the demonstration of immunological non-inferiority to the 7 valent pneumococcal conjugate vaccine (PCV7) by measuring the total amount of anticapsular IgG with an enzyme-linked immunosorbent assay (ELISA). The WHO recognises that measuring total IgG does not provide evidence that these antibodies are functional, i.e. involved in the immune response resulting in bacterial (*Streptococcus pneumoniae*) death. The WHO therefore also requires evidence that the antibodies elicited by the vaccine are functional.

According to these recommendations, demonstration of immunological non-inferiority is the percentage of participants reaching a predetermined antibody threshold (total IgG) one month after three primary doses of pneumococcal conjugate vaccine. Immunological non-inferiority (total IgG) to each of the serotypes in PCV7 is desirable, but not an absolute requirement with registration of products in which one or more serotypes do not meet non-inferiority criteria on an individual basis.

As serotype specific thresholds were not identified, the WHO recommended the use of a single antibody threshold for all serotypes. This threshold was derived from a pooled analysis of three efficacy trials conducted with pneumococcal conjugated vaccines and was found to be 0.35 µg/mL with the second generation ELISA available at that time. This threshold does not represent an individual antibody protection level.

To increase specificity, third generation ELISAs including a 22F adsorption step have been developed. GSK, in its clinical trials has used a third generation ELISA that includes the use of highly purified polysaccharides and a 22F pre-adsorption step, both designed to increase the specificity of the assay. The WHO recommendations state that third generation ELISAs must be bridged to the second generation ELISA. An antibody concentration of 0.2 µg/mL in the GSK third generation ELISA was shown in bridging experiments to be equivalent to the 0.35 µg/mL WHO reference threshold. The 0.2 µg/mL threshold was therefore used for the demonstration of immunological non-inferiority compared to PCV7 in a head-to-head comparative study.

The WHO, as noted above, also required demonstration of functionality of the elicited antibodies. Opsonophagocytosis (antibody mediated killing of bacteria) is recognised as the main mechanism of protection against pneumococcal disease. Measurement of the ability of the vaccine-elicited antibodies to opsonise and promote killing of the pneumococcus can be performed *in vitro* through an opsonophagocytosis activity assay (OPA). The percentage of participants with an OPA titre ≥ 8 is used for comparison between vaccines.

Efficacy and effectiveness against invasive pneumococcal disease:

It has been demonstrated that Synflorix induces an appropriate immune response to protect against IPD caused by serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

Protective effectiveness against IPD in a clinical trial

In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), 30,528 infants less than 7 months of age at enrolment and 15,449 children aged 7 months to 18 months at enrolment were followed for invasive disease for an average of 25 and 28 months respectively and included in the analysis of effectiveness. Children were enrolled into 78 study clusters. Clusters were randomised into 4 groups according to the two infant vaccination schedules (2-dose or 3-dose primary schedule followed by a booster dose: 2+1 or 3+1 schedule) to receive either Synflorix (52 clusters) or hepatitis vaccines as control (26 clusters).

Effectiveness in infant cohort below 7 months of age at enrolment

Vaccine effectiveness (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 (see Table 1).

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

Type of IPD	No. of IPD cases			VE (95% CI)	
	Synflorix 3+1 schedule (N=10,273)	Synflorix 2+1 schedule (N=10,054)	Control (HBV) ⁽²⁾ (N=10,201)	3+1 schedule	2+1 schedule
Vaccine serotype IPD ⁽¹⁾	0	1	12	100% ⁽³⁾ (82.8; 100)	91.8% ⁽⁴⁾ (58.3; 99.6)
Serotype 6B IPD	0	0	5	100% (54.9; 100)	100% (54.5; 100)
Serotype 14 IPD	0	0	4	100% (39.6; 100)	100% (43.3; 100)

IPD Invasive Pneumococcal Disease

VE Vaccine Effectiveness

N number of subjects per group

CI Confidence Interval

(1) 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).

(2) the 2 groups of control clusters of infants were pooled

(3) p-value<0.0001

(4) p-value=0.0009

The observed VE against culture-confirmed IPD due to any serotype 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.

Effectiveness following catch-up immunization

In the catch-up cohorts, children between 7-11 months of age at first vaccine dose received Synflorix or hepatitis B 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.

Among the 15,449 children in the catch-up vaccinated cohorts, there were no culture-confirmed IPD cases in the Synflorix groups while 7 IPD cases were observed in the control groups (serotypes 7F and 14 in the 7-11 month cohort and serotypes 3, 4, 6B, 15C and 19F in the 12-18 month cohort).

Protective effectiveness against IPD in post-marketing surveillance

In Quebec, Canada, Synflorix was introduced into the infant immunization 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 PCV vaccine. 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, leading to an overall decrease in IPD incidence in the target age group compared to the incidence reported during the preceding period.

Efficacy against Pneumonia

Efficacy against pneumonia was assessed in a large-scale randomised, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS). 23,738 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.

Efficacy of Synflorix against likely bacterial Community Acquired Pneumonia (CAP) was demonstrated in the according-to-protocol (ATP) cohort (immunized with at least the three-dose primary series) (P value ≤ 0.002) as the primary objective of the study.

Likely bacterial 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 likely bacterial CAP observed in this study, is presented below (table 2).

Table 2: Numbers and percentages of subjects with likely bacterial CAP(*) after 3 doses of Synflorix or a control vaccine and vaccine efficacy (ATP cohort for efficacy)

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 of subjects reporting a first episode of likely bacterial CAP anytime from 2 weeks after the administration of the 3rd dose

% percentage of subjects reporting a first episode of likely bacterial CAP anytime from 2 weeks after the administration of the 3rd dose

CI Confidence Interval

* Final analysis of primary objective – observation period of 38 months

In an interim analysis (observation period of 38 months), the vaccine efficacy against CAP with alveolar consolidation or pleural effusion was 25.7% (95% CI: 8.4; 39.6) and against clinically suspected CAP referred for X-ray was 6.7% (95% CI: 0.7; 12.3).

3-dose primary schedule

In clinical trials conducted in various European countries, in Chile and in the Philippines, approximately 3,500 infants received Synflorix as a primary vaccination course according to different vaccination schedules, at either 6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age.

In six clinical trials approximately 1,900 infants received a fourth (booster) dose of Synflorix in the second year of life.

One month after completion of primary vaccination using any of the dose schedules referred to above, Synflorix induces a significant antibody response (ELISA) as well as functional antibodies (as measured by an opsonophagocytic assay (OPA)) to all vaccine serotypes. Opsonophagocytosis is the main mechanism of protection against pneumococcal infections.

Following booster vaccination, a significant increase of the immune response was observed for all serotypes both in terms of ELISA antibody concentrations and OPA titres.

The percentage of infants with antibody concentrations of ≥ 0.2 $\mu\text{g/ml}$ and percentage of infants with OPA titres ≥ 8 for each of the vaccine serotypes in a 2-4-6 schedule are presented in Table 3 below:

TABLE 3. Percentage of infants with antibody concentrations $\geq 0.2 \mu\text{g/ml}$ by ELISA and percentage of infants with opsonophagocytic assay (OPA) titres ≥ 8 following SYNFLORIX administration in a 2-4-6 schedule.

Vaccine Serotypes		Primary vaccination schedule [†]	Booster vaccination*
		2-4-6 months of age	2 nd year of life
1	ELISA ($\geq 0.2\mu\text{g/ml}$)	93.1-100%	96.7-100%
	OPA (≥ 8)	50.3-75.5%	77.8-91.0%
4	ELISA ($\geq 0.2\mu\text{g/ml}$)	98.3-100%	99.7-100%
	OPA (≥ 8)	97.5-100%	99.0-100%
5	ELISA ($\geq 0.2\mu\text{g/ml}$)	98.8-100%	99.1-100%
	OPA (≥ 8)	86.5-95.9%	96.3-97.5%
6B	ELISA ($\geq 0.2\mu\text{g/ml}$)	87.3-94.1%	93.4-96.6%
	OPA (≥ 8)	81.8-95.9%	90.3-96.6%
7F	ELISA ($\geq 0.2\mu\text{g/ml}$)	98.8-100%	100%
	OPA (≥ 8)	96.8-100%	99.7-100%
9V	ELISA ($\geq 0.2\mu\text{g/ml}$)	97.7-99.1%	99.1-100%
	OPA (≥ 8)	98.7-100%	100%
14	ELISA ($\geq 0.2\mu\text{g/ml}$)	100%	98.6-100%
	OPA (≥ 8)	95.9-98.1%	100%
18C	ELISA ($\geq 0.2\mu\text{g/ml}$)	98.8-99.4%	98.9-100%
	OPA (≥ 8)	91.7-98.2%	98.5-99.7%
19F	ELISA ($\geq 0.2\mu\text{g/ml}$)	98.2-100%	97.1-100%
	OPA (≥ 8)	93.9-98.1%	94.9-96.1%
23F	ELISA ($\geq 0.2\mu\text{g/ml}$)	92.5-96.0%	94.3-98.9%
	OPA (≥ 8)	90.4-95.9%	98.3-99.7%

[†] Primary immunisation results is the range obtained from 2 separate studies using a 2-4-6 schedule (Total N ~ 600 (ELISA and OPA), although number of infants may vary for each serotype)

* Results expressed reflect immunological responses seen following booster vaccination across all primary immunisation schedules (Total N = ~800 (ELISA) and N = ~ 500 (OPA))

Similar immunological responses were also observed for ELISA and OPA when Synflorix was administered using other vaccination schedules (e.g. at 2-3-4 and 3-4-5 months).

The protective efficacy of Synflorix is based on a non-inferiority head-to-head comparative study against PCV7 for which efficacy studies have been conducted. No efficacy data for Serotypes 1, 5 and 7F are available but, efficacy is inferred from the robust antibody response to vaccination.

In addition to eliciting significant responses against vaccine serotypes, administration of

Synflorix also elicited antibody responses and evidence of OPA activity against vaccine-related serotypes 6A and 19A. These responses are presented below in Table 4.

TABLE 4. Percentage of infants with antibody concentrations $\geq 0.2 \mu\text{g/ml}$ by ELISA and percentage of infants with opsonophagocytic assay (OPA) titres ≥ 8 following SYNFLORIX administration in vaccine related serotypes in a 2-4-6 schedule.

Vaccine-related Serotypes		Primary vaccination schedule [†]	Booster vaccination*
		2-4-6 months of age	2 nd year of life
6A	ELISA ($\geq 0.2\mu\text{g/ml}$)	44.2-52.7 %	72.8-84.4%
	OPA (≥ 8)	70.7-85.6%	68.6-85.0%
19A	ELISA ($\geq 0.2\mu\text{g/ml}$)	45.0-86.8%	83.0-83.8%
	OPA (≥ 8)	19.8-32.4%	46.6-48.8%

† Primary immunisation results is the range obtained from 2 separate studies using a 2-4-6 schedule (Total N ~600, although number of infants vary for each serotype)

* Results expressed reflect immunological responses seen following booster vaccination across all primary immunisation schedules (Total N = ~500 (ELISA and OPA))

A plain polysaccharide challenge at 12 months of age elicited an anamnestic antibody response for the 10 pneumococcal serotypes included in the vaccine, which is considered indicative for the induction of immune memory following the primary series with Synflorix.

Preterm infants

Immunogenicity of Synflorix in very preterm (born after a gestation period of 27-30 weeks) (N=42), preterm (born after a gestation period of 31-36 weeks) (N=82) and full term (born after a gestation period of more than 36 weeks) (N=132) infants was evaluated following a three dose primary vaccination course at 2, 4, 6 months of age. Immunogenicity was evaluated in 44 very preterm, 69 preterm and 127 full term infants following a booster dose at 15 to 18 months of age. All enrolled infants were classified as healthy or medically stable i.e premature infants who did not require significant medical support or ongoing management for debilitating disease and who had demonstrated a clinical course of sustained recovery.

In the primary vaccination study, age at first vaccination ranged between 8 and 16 weeks with a mean age of 9.5 weeks (standard deviation of 1.73). Overall, 41.8% of the infants were female, and 88.7% of infants were white/Caucasian. The mean weight at first vaccination was 3.1 kg in the very preterm group, 4.2 kg in the preterm group and 5.2 kg in the full term group. The mean weight at birth was 1.2 kg in the very preterm group, 2.0 kg

in the preterm group and 3.2 kg in the full term group. The mean gestational age was 28.6 weeks in the very preterm group and 33.5 weeks in the preterm group.

Regardless of maturity, one month after primary vaccination, at least 92.7% of infants achieved ELISA antibody concentrations $\geq 0.2 \mu\text{g/ml}$ and at least 81.7% achieved OPA titres ≥ 8 for all vaccine serotypes, 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 and 9V in very preterms and serotype 9V in preterms and lower OPA GMT for serotype 5 in very preterms.

Increases of ELISA antibody GMCs and OPA GMTs were seen for all serotypes one month after the booster dose, 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, at least 97.6% of infants achieved ELISA antibody concentrations $\geq 0.2 \mu\text{g/ml}$ and at least 91.9% achieved OPA titres ≥ 8 for all vaccine serotypes.

Protein D immune responses post-primary and booster vaccination were similar for very preterm, preterm and full term infants.

2-dose primary schedule

In addition to the 3-dose primary schedule, the immunogenicity of Synflorix following a 2-dose primary vaccination schedule in 670 infants less than 6 months of age was evaluated in two clinical studies.

In the first study, the immunogenicity two months after the second dose of Synflorix was compared with a PCV7 vaccine and the percentage of infants with ELISA antibody concentration $\geq 0.2 \mu\text{g/ml}$ was within the same range for each of the serotypes common to both vaccines with the exception of serotypes 6B (64.1% for Synflorix and 30.7% for the PCV7 vaccine), and 18C (87.1% for Synflorix and 97.6% for the PCV7 vaccine). Antibody GMCs were similar in both groups, with the exception of serotypes 6B (0.34 $\mu\text{g/ml}$, for Synflorix and 0.16 $\mu\text{g/ml}$ for the PCV7 vaccine) and 4, 9V and 18C (1.23 $\mu\text{g/ml}$, 0.92 $\mu\text{g/ml}$, 1.21 $\mu\text{g/ml}$ respectively for Synflorix and 2.02 $\mu\text{g/ml}$, 2.24 $\mu\text{g/ml}$, 1.79 $\mu\text{g/ml}$ respectively for the PCV7 vaccine). Similarly, the percentage of infants reaching OPA titres ≥ 8 and the OPA GMTs two months post dose 2 was within the same range for each of the serotypes common to both vaccines, with the exception of serotypes 6B and 19F for which responses were higher in the Synflorix vaccinees group (94.2 for Synflorix versus 22.8 for PCV7 vaccine for serotype 6B; 65.8 for Synflorix versus 19.3 for PCV7 vaccine for

serotype 19F).

In the second study, the immunogenicity after two doses of Synflorix was compared to three doses of Synflorix. Although there was no significant difference between the two groups in the percentage of infants with antibody concentration $\geq 0.2\mu\text{g/ml}$ (ELISA), a lower percentage of infants with OPA titres ≥ 8 in 2-dose primed infants compared to 3-dose primed infants was observed 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). In both schedules, a booster response indicative of immunological priming was observed for each serotype. Following the booster, a lower percentage of infants with OPA titres ≥ 8 was observed with the 2+1 schedule for serotype 5 (87.2% for the 2+1 schedule and 97.5% for the 3+1 schedule). While the clinical relevance of these observations remains unknown, the persistence of the immune response was evaluated in a follow-up of this second study.

In the follow-up of the second study, the persistence of antibodies at 36-46 months of age was demonstrated in 2-dose primed infants with at least 83.7% of infants remaining seropositive for vaccine serotypes (i.e. detectable antibody $\geq 0.05\ \mu\text{g/ml}$) of which at least 96% of infants were seropositive for serotypes 5, 7F, 9V, 14, 18C and 19F had at least 96.0% of infants seropositive. A single dose of Synflorix administered during the 4th year of life, as a challenge dose, elicited higher ELISA antibody GMCs 7-10 days following vaccination in 2-dose primed infants (ranging from 4.00 to 20.28 $\mu\text{g/ml}$) and 3-dose primed infants (ranging from 4.72 to 30.55 $\mu\text{g/ml}$) compared with unprimed subjects (ranging from 0.10 to 2.37 $\mu\text{g/ml}$). This was indicative of an anamnestic immune response in primed infants for all vaccine serotypes. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, in 2-dose primed infants was similar to that observed in 3-dose primed infants.

For the vaccine-related serotypes 6A and 19A, induction of immune memory was demonstrated. For serotype 6A, a 4 fold-increase in ELISA GMCs was observed for both 2-dose and 3-dose primed infants and for OPA GMTs, a 25 fold and a 15 fold-increase were observed in the 2 dose and the 3 dose primed infants respectively. In unprimed infants, there was a 1.4 fold increase in antibody GMCs and an 11 fold increase in OPA GMTs. For serotype 19A, an 11 fold and a 14 fold increase in ELISA GMCs were observed in the 2 dose and the 3 dose primed infants respectively while for OPA GMTs, a 99 fold and a 217 fold increase were observed in 2-dose and 3-dose primed infants respectively. In unprimed infants, there was a 2.5 fold increase in antibody GMCs and a 39 fold increase in OPA GMTs.

A 3-dose primary schedule showed a higher antibody response against protein D

compared to a 2-dose primary schedule. Anamnestic immune responses to protein D were shown with both schedules. However, the clinical relevance of these observations remains unknown.

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

Catch-up

The immune responses in previously unvaccinated older children were evaluated in two clinical trials.

The first study evaluated vaccination in children aged 7-11 months, 12-23 months and 2 to 5 years.

In the 7-11 months group, children received 2 primary doses followed by a booster dose in the second year of life. The immune responses after the booster dose of Synflorix 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.

The immune response elicited after two doses of Synflorix in children 12-23 months of age was comparable to the response elicited after three doses in infants, except for serotypes 18C and 19F for which responses were higher in the 12-23 months children. The need for a booster dose after two doses in children aged 12-23 months has not been established.

In the 2 to 5 years group, where children received 1 dose of Synflorix, the ELISA antibody GMCs for 6 out of the 10 vaccine serotypes were similar to those achieved following a 3 dose vaccination schedule in infants while they were lower for 4 out of the 10 vaccine serotypes (serotypes 1, 5, 14 and 23F) and for anti-protein D. The OPA GMTs were similar or higher following a single dose at 2 to 5 years of age than a 3 dose primary course in infants, except for serotype 5.

The second 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 cross reactive serotypes 6A and 19A and a similar immune response for protein D.

Efficacy against Acute Otitis Media:

In a large randomised double-blind Pneumococcal Otitis Media Efficacy Trial (POET) conducted in the Czech Republic and in Slovakia, 2,489 infants received an 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of Synflorix along with

serotype 3 for which efficacy was not demonstrated according to a 3, 4, 5 and 12-15 months vaccination schedule.

The vaccine efficacy against AOM episodes observed during this study is presented below in Table 5.

TABLE 5. Vaccine efficacy observed against AOM observed during POET (ATP cohort)

Type or cause of AOM	Vaccine efficacy
Clinical AOM episodes regardless of etiology	33.6 % (95% CI: 20.8; 44.3)
AOM episodes due to any pneumococcal serotype	51.5% (95% CI: 36.8;62.9)
AOM episodes due to pneumococcal serotypes covered by the 11Pn-PD vaccine	57.6% (95% CI: 41.4;69.3)
AOM episodes due to pneumococcal serotypes covered by Synflorix	67.9% (95% CI: 53.0;78.1)
AOM episodes due to vaccine related pneumococcal serotypes	65.5% (95 % CI: 22.4;84.7)
AOM episodes caused by Hi (including NTHi)	35.6% (95% CI: 3.8; 57.0)
AOM episodes caused by NTHi only	35.3% (95% CI: 1.8;57.4)

No increase in the incidence of AOM due to other bacterial pathogens was observed. The incidence of recurrent AOM (≥ 3 episodes in 6 months or ≥ 4 in 12 months) was reduced by 56% (95% CI:-1.9; 80.7) and ventilation tube placement by 60.3% (95% CI:-6.7; 87.5).

Based on immunological bridging of the functional vaccine response of Synflorix with the formulation used within POET, it is expected that Synflorix provides similar protective efficacy against pneumococcal AOM. In all studies, between 98.3% and 100% of infants receiving Synflorix vaccine were seropositive (≥ 100 EL.U/ml) for antibodies against Protein D. Furthermore, anti-protein D immune responses elicited by Synflorix were slightly lower to those elicited in POET; however the differences were not statistically significant. The relevance of the levels of such antibodies is uncertain as they do not correlate with protection from NTHi AOM. Accordingly, it is unknown whether Synflorix will elicit a level of protection from NTHi AOM as seen in the POET study.

INDICATIONS

Active immunisation of infants and children from the age of 6 weeks up to 5 years against disease caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia and acute otitis media).

CONTRAINDICATIONS

Synflorix should not be administered to infants with known hypersensitivity to any component of the vaccine (*See Description*).

PRECAUTIONS

It is good clinical practice to precede vaccination 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 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 with other vaccines, the administration of Synflorix should be postponed in infants 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.

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

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.

Synflorix will not protect against pneumococcal serogroups other than those included in the vaccine. Although antibody response to diphtheria toxoid, tetanus toxoid and Protein D (Protein D is highly conserved in all *Haemophilus influenzae* strains including NTHi) occurs, immunisation with Synflorix does not substitute routine immunisation with diphtheria, tetanus or *Haemophilus influenzae* type b vaccines. Official recommendations for the immunisations against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Safety and immunogenicity data in children with increased risk for pneumococcal infections (sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

For children at high-risk for pneumococcal disease (such as children with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised),

- the appropriate-for-age Synflorix vaccination series should be given below 2 years of age (see *Dosage and Administration*)
- a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age.

Prophylactic administration of antipyretics before or immediately after vaccines administration can reduce the incidence and intensity of post-vaccination febrile reactions. Data however, suggest that the use of prophylactic paracetamol might reduce the immune response to pneumococcal vaccines. The clinical relevance of this observation remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48 to 72 hours 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.

Use in Pregnancy (Category B2)

As Synflorix is not intended for use in adults or adolescents, adequate human data on use during pregnancy and adequate animal reproduction studies are not available.

Use in Lactation

As Synflorix is not intended for use in adults or adolescents, adequate human data on use during lactation and adequate animal reproduction studies are not available.

Fertility

There are no data on the potential of Synflorix to impair fertility.

Carcinogenicity

No animal carcinogenicity studies have been conducted with Synflorix.

Genotoxicity

Synflorix has not been evaluated for genotoxicity.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

INTERACTIONS WITH OTHER MEDICINES

Incompatibilities

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

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-varicella vaccine (MMRV), varicella vaccine, meningococcal serogroup C conjugate vaccine (CRM₁₉₇ and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral polio vaccine (OPV) and rotavirus vaccine. Different injectable vaccines should always be given at different injections sites.

Clinical trials 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 seroprotection levels, for which inconsistent results were observed across studies. 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 has also been observed. The clinical relevance of the above observations is unknown.

Use with systemic immunosuppressive medications

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

ADVERSE EFFECTS

Safety assessment of Synflorix was based on clinical trials involving the administration of approximately 64,000 doses of Synflorix to approximately 22,500 healthy children and 137 healthy or medically stable preterm infants (at least 27 weeks gestation at birth) as primary vaccination. Furthermore, approximately 19,500 healthy children and 116 preterm infants received a booster dose of Synflorix in the second year of life. Safety was also assessed in approximately 400 children from 2 to 5 years old. In all trials, Synflorix was administered concurrently with the recommended childhood vaccines.

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

The most common adverse reactions observed after primary vaccination were redness at 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.

The following table summarises data from 3 pivotal studies comparing Synflorix with a 7 valent pneumococcal conjugate vaccine (PCV7) for solicited local and general symptoms reported during a 4 day follow-up period after vaccination.

Table 6 Pooled safety analysis: Incidence of solicited local and general symptoms reporting during the 4-day (Days 0-3) post-vaccination period following all doses (Total vaccinated cohort)

		SYNFLORIX		PCV7	
Symptom	Type	N	%	N	%
Pain	All	2442	54.9	865	48.4
	Grade 3	2442	6.3	865	4.5
Redness (mm)	All	2442	64.8	865	65.4
	> 20	2442	10.6	865	9.1
	> 30	2442	4.1	865	3.7
Swelling (mm)	All	2442	53.8	865	49.5
	> 20	2442	15.2	865	11.8
	> 30	2442	6.8	865	5.7
Drowsiness	All	2442	71.7	865	68.2
	Grade 3	2442	2.9	865	3.2
Irritability	All	2442	80.5	865	78.0
	Grade 3	2442	10.1	865	8.6
Loss of appetite	All	2442	50.0	865	47.2
	Grade 3	2442	1.0	865	0.9
Fever (Rectal) (°C)	> 38	2442	60.1	865	59.5
	> 39	2442	7.2	865	6.2
	> 40	2442	0.2	865	0.2

Both groups pooled from Studies 001, 003 and 011; N = Number of infants with at least one documented dose, % = percentage of infants reporting at least one specified symptom whatever the number of injections

The following table summarises data from 1 pivotal study comparing Synflorix with a 7 valent pneumococcal conjugate vaccine (PCV7) for solicited local and general symptoms reported during a 4 day follow-up period after controlled booster vaccination.

Table 7 Pooled safety analysis: Comparison of percentage of infants reporting solicited local and general symptoms during the 4-day (Days 0-3) post-booster vaccination period in a controlled booster vaccination study (Total vaccinated cohort)

		SYNFLORIX		PCV7	
Symptom	Type	N	%	N	%
Pain	All	1017	59.2	91	52.7
	Grade 3	1017	6.4	91	3.3
Redness (mm)	All	1017	59.4	91	64.8
	> 20	1017	17.8	91	16.5
	> 30	1017	11.3	91	7.7
Swelling (mm)	All	1017	44.2	91	46.2
	> 20	1017	15.1	91	11.0
	> 30	1017	8.6	91	7.7

Drowsiness	All	1017	42.6	91	52.7
	Grade 3	1017	1.0	91	0.0
Irritability	All	1017	60.4	91	60.4
	Grade 3	1017	2.7	91	2.2
Loss of appetite	All	1017	31.7	91	34.1
	Grade 3	1017	0.7	91	0.0
Fever (Rectal) (°C)	> 38	1017	35.1	91	36.3
	> 39	1017	3.3	91	7.7
	> 40	1017	0.4	91	2.2

Both groups pooled from Study 007; N = Number of infants with at least one documented dose, % = percentage of infants reporting at least one specified symptom whatever the number of injections

Other events

Other adverse reactions reported (for all age groups) are listed according to the following frequency:

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

Immune system disorders:

Rare: allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema)

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

Uncommon: convulsions (including febrile convulsions)

Vascular disorders

Very rare: Kawasaki disease

Respiratory, thoracic and mediastinal disorders:

Uncommon: apnoea (see *Precautions*)

Gastro-intestinal disorders:

Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:

Uncommon: rash

Rare: urticaria

General disorders and administration site conditions:

Very common: pain, redness, swelling at the injection site, fever $\geq 38^{\circ}\text{C}$ rectally (age < 2 years)

Common: injection site reactions like injection site induration, fever $> 39^{\circ}\text{C}$ rectally (age < 2 years),

Uncommon: injection site reactions like injection site haematoma, haemorrhage and nodule,

The following adverse reactions have additionally been reported after booster vaccination of primary series and/or catch-up vaccination:

Nervous system disorders:

Uncommon: headache (age 2 to 5 years)

Gastro-intestinal disorders:

Uncommon: nausea (age 2 to 5 years)

General disorders and administration site conditions:

Common: fever $\geq 38^{\circ}\text{C}$ rectally (age 2 to 5 years)

Uncommon: injection site reactions like pruritus, fever $> 40^{\circ}\text{C}$ rectally (age < 2 years), fever $> 39^{\circ}\text{C}$ rectally (age 2 to 5 years), diffuse swelling of the injected limb, sometimes involving the adjacent joint

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.

Post-marketing data

Immune system disorders

Very rare: anaphylaxis

Nervous system disorders:

Rare: hypotonic-hyporesponsive episode

DOSAGE AND ADMINISTRATION

Immunisation schedules:

Official recommendations should be taken into account when immunising with Synflorix.

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

Dosage

Vaccination of infants from 6 weeks to 6 months of age:

Three-dose primary series with booster

The recommended immunisation series to ensure optimal protection consists of a total of four doses, each of 0.5 ml. The primary infant series consists of three doses of 0.5 ml 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 six weeks of age. A booster dose is recommended at least 6 months after the last primary dose (see section *Clinical Trials*).

Two-dose primary series with booster

Alternatively, Synflorix may be given as a total of 3 doses, consisting of two primary doses and a booster, each of 0.5 mL. The first dose may be administered from the age of 2 months, with a second dose 2 months later and a booster dose at least 6 months after the second primary dose (see section *Clinical Trials*).

Preterm infants born after at least 27 weeks of gestational age

The recommended immunisation series consists of four doses, each of 0.5ml. The primary infant series consists of three doses with the first dose usually given from 2 months of age. A booster dose is recommended at least 6 months after the last primary dose (see section *Clinical Trials*).

Previously unvaccinated older infants (>7 months of age) and children (up to 5 years of age):

- **infants aged 7-11 months:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 1 month between doses. A third dose is recommended in the second year of life with an interval of at least 2 months.
- **children aged 12-23 months:** The vaccination schedule consists of two doses of 0.5 ml

with an interval of at least 2 months between doses. The need for a booster dose after this immunisation schedule has not been established.

- **children aged 24 months – 5 years:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

Method of administration:

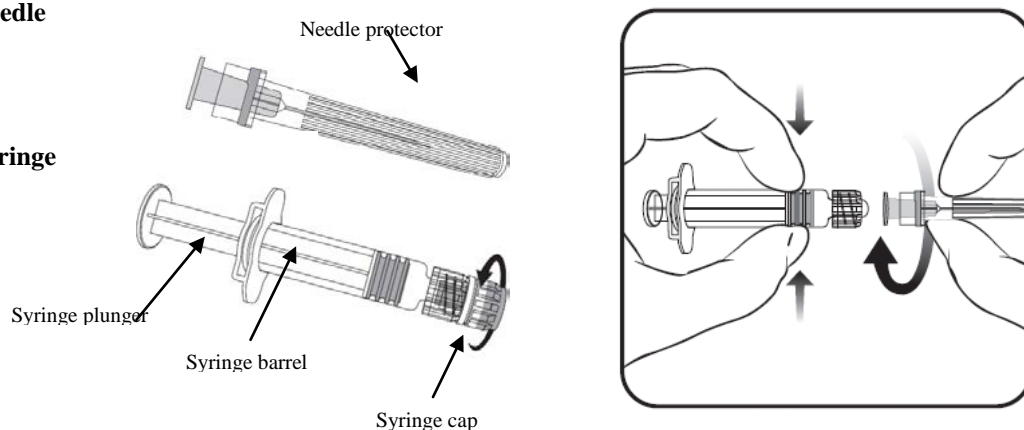
The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in children under 12 months of age or the deltoid muscle of the upper arm in children over 12 months of age.

Synflorix syringe or vials are for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling of the vaccine presented in pre-filled syringe

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. Administer the vaccine.

OVERDOSAGE:

Insufficient data are available. In the event of overdosage, please contact the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Synflorix is presented as a turbid white suspension. A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

The content of the syringe/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 well shaken before use.

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

Synflorix is presented as:

- 0.5 ml of suspension in a pre-filled syringe (type I glass) for 1 dose with a plunger stopper (rubber butyl) – pack sizes of 1 or 10
- 0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (rubber butyl) pack sizes of 1 or 10

Not all presentations and pack sizes may be marketed.

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

Storage

Store at 2°C – 8°C. (Refrigerate, Do not freeze.)

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

Synflorix should be administered as soon as possible after being removed from the refrigerator.

MANUFACTURER:

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1330 Rixensart

Belgium

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

19 March 2009

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