

DATA SHEET

SYNFLORIX® PRODUCT INFORMATION

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 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.

Mechanism of action

Pharmacodynamic Effects

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.

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 STUDIES

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 subjects 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 22 F 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 subjects with an OPA titre ≥ 8 is used for comparison between

vaccines.

Vaccine Efficacy

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.

3-dose primary schedule

In clinical trials conducted in various European countries, in Chile and in the Philippines, approximately 3,500 subjects 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 studies approximately 1,900 subjects 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 subjects with antibody concentrations of $\geq 0.2 \mu\text{g/ml}$ and percentage of subjects with OPA titres ≥ 8 for each of the vaccine serotypes in a 2-4-6 schedule are presented in Table 1 below:

TABLE 1. Percentage of subjects with antibody concentrations $\geq 0.2 \mu\text{g/ml}$ by ELISA and percentage of subjects 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 subjects 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 2.

TABLE 2. Percentage of subjects with antibody concentrations $\geq 0.2 \mu\text{g/ml}$ by ELISA and percentage of subjects 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 subjects 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.

Regardless of maturity, one month after primary vaccination, at least 92.7% of subjects 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 subjects 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 subjects 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 subjects 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 subjects 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 subjects with antibody concentration $\geq 0.2 \mu\text{g/ml}$ (ELISA), a lower percentage of subjects with OPA titres ≥ 8 in 2-dose primed subjects compared to 3-dose primed subjects 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 subjects 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 subjects with at least 83.7% of subjects remaining seropositive for vaccine serotypes (i.e. detectable antibody $\geq 0.05 \mu\text{g/ml}$) of which at least 96% of subjects were seropositive for serotypes 5, 7F, 9V, 14, 18C, and 19F had at least 96.0% of subjects 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 subjects (ranging from 4.00 to 20.28 $\mu\text{g/ml}$) and 3-dose primed subjects (ranging from 4.72 to 30.55 $\mu\text{g/ml}$) compared with unprimed subjects

(ranging from 0.10 to 2.37 µg/ml). This was indicative of an anamnestic immune response in primed subjects for all vaccine serotypes. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, in 2-dose primed subjects was similar to that observed in 3-dose primed subjects.

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 subjects and for OPA GMTs, a 25 fold and a 15 fold-increase were observed in the 2 dose and the 3 dose primed subjects respectively. In unprimed subjects, 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 subjects respectively while for OPA GMTs, a 99 fold and a 217 fold increase were observed in 2-dose and 3-dose primed subjects respectively. In unprimed subjects, 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 studies.

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 3.

TABLE 3. 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 subjects 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 subjects 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 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.

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 48-72h should be considered when administering the primary immunization 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

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), oral polio vaccine (OPV) and rotavirus vaccine. Different injectable vaccines should always be given at different injections 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, for which inconsistent results were observed across studies. No interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM₁₉₇ and TT conjugates). Enhancement of antibody response to diphtheria toxoid and tetanus toxoid was observed.

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 REACTIONS

Clinical trials involved the administration of over 12,800 doses of Synflorix to more than 4,500 healthy infants as primary vaccination and 137 preterm infants. More than 3,800 infants and 116 preterm infants received a booster dose of Synflorix in the second year of life. Safety was also assessed in approximately 200 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.

An increase in injection site reactions was reported in children >12 months of age compared to the rates observed in infants during the primary series with Synflorix.

The most common adverse reactions observed after primary vaccination were redness at the injection site and irritability which occurred after 38.3% and 52.3% of all doses respectively. Following booster vaccination, these adverse reactions occurred at 52.6% and 55.4% of subjects 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 4 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 subjects with at least one documented dose, % = percentage of subjects 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 5 Pooled safety analysis: Comparison of percentage of subjects 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 subjects with at least one documented dose, % = percentage of subjects 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 $< 1/1,000$)

Immune system disorders:

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

Metabolism and nutrition disorders:

Very common: appetite lost

Psychiatric disorders:

Very common: irritability

Uncommon: crying abnormal

Nervous system disorders:

Very common: drowsiness

Uncommon: febrile and non-febrile convulsions

Respiratory, thoracic and mediastinal disorders:

Uncommon: apnoea (see *Precautions*)

Gastro-intestinal disorders:

Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:

Rare: rash, 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 induration, fever $> 39^{\circ}\text{C}$ rectally (age < 2 years), fever $\geq 38^{\circ}\text{C}$ rectally (age 2 to 5 years)

Uncommon: injection site haematoma, haemorrhage and nodule, fever $> 40^{\circ}\text{C}$ rectally* (age < 2 years), fever $> 39^{\circ}\text{C}$ rectally (age 2 to 5 years)

*reported following booster vaccination of primary series

Post –marketing data

Nervous system disorders:

Rare: hypotonic-hyporesponsive episode

DOSAGE AND ADMINISTRATION

Dosage

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

Three-dose primary series

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 Studies*).

Two-dose primary series

Alternatively, when Synflorix is given as part of a routine infant immunisation programme, a series consisting of a total of three doses, each of 0.5 ml may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. A booster dose is recommended at least 6 months after the last primary dose (see section

Clinical Studies).

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 at 2 months of age and with an interval of at least 1 month between doses. A booster dose is recommended at least 6 months after the last primary dose (see section *Clinical Studies*).

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.

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.

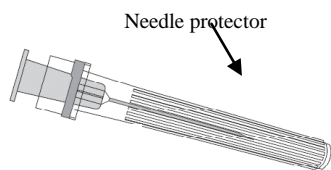
Method of administration:

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.

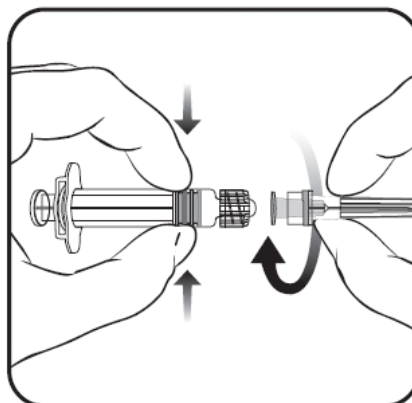
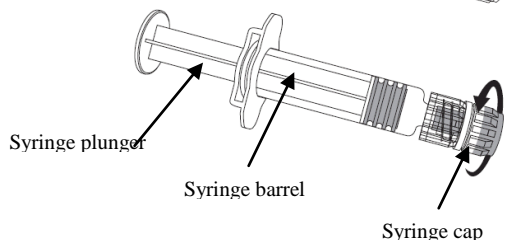
Synflorix syringe or vials are for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

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 National Poisons Centre on 0800 764 766 (0800 POISON).

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.

PRESENTATIONS

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.

SHELF LIFE

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

MANUFACTURER:

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut, 89
1330 Rixensart
Belgium

DISTRIBUTED IN NEW ZEALAND BY:

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown
Auckland 1143
New Zealand
Phone: (09) 367 2900
Facsimile (09) 367 2910

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