NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SYNFLORIX pneumococcal polysaccharide conjugate vaccine, 10 valent adsorbed.

Suspension for injection.

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 18C[1,3]	3 micrograms
Pneumococcal polysaccharide serotype 19F[1,4]	3 micrograms
Pneumococcal polysaccharide serotype 23F[1,2]	1 microgram

[1] adsorbed on aluminium phosphate 0.5 milligram Al^{3+}
[2] conjugated to protein D (derived from Non-Typeable *Haemophilus influenza (NTHi)*) 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 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for injection.

SYNFLORIX is a turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dose

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.

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 5.1 Pharmacodynamic properties).

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 given as early as six weeks of age with a second dose administered 2 months later. A booster dose is recommended at least 6 months after the last primary dose and may be given from the age of 9 months onwards (see section 5.1 Pharmacodynamic properties).

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 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 5.1 Pharmacodynamic properties).

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 months – 5 years

The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

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 section 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties)

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.

4.3 Contraindications

SYNFLORIX should not be administered to subjects with known hypersensitivity to any component of the vaccine (see section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION and 6.1 List of excipients).

4.4 Special warnings and precautions for use

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 are available for HIV infected infants, children with sickle cell disease and children with splenic dysfunction (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). 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.

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 those who have other immunocompromising conditions),the appropriate-for-age SYNFLORIX vaccination series should be given (see section 4.2 Dose and method of administration). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines which should be given according to local recommendations in those children.

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 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.

Carcinogenicity

No animal carcinogenicity studies have been conducted with SYNFLORIX.

Genotoxicity

SYNFLORIX has not been evaluated for genotoxicity.

4.5 Interaction with other medicines 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-varicella vaccine (MMRV), varicella vaccine, 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 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 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 toxoids 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.

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable 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 preterm infants 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 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% 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 9: 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 10: 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: ≥ 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

System organ class	**Frequency**	**Adverse reactions**
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
	Rare	convulsions (including febrile convulsions)
Vascular disorders	Very rare	Kawasaki disease
Respiratory, thoracic and mediastinal disorders	Uncommon	apnoea [see section 4.4 Special warnings and precautions for use, for apnoea in very premature infants (≤ 28 weeks of gestation)]

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 ≥38°C rectally (age < 2 years)
	Common	injection site reactions like injection site induration, fever >39°C rectally (age < 2 years)
	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)
Gastro-intestinal 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	injection site reactions like pruritus, fever >40°C rectally (age < 2 years), fever >39°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.

Special Populations

Safety of SYNFLORIX was assessed in 83 HIV positive (HIV+/+) infants, 101 HIV negative infants born from an HIV positive mother (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.

Post–marketing data

System organ class	Frequency	Adverse reactions
Immune system disorders	Very rare	anaphylaxis
Nervous system disorders	Rare	hypotonic-hyporesponsive episode

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Insufficient data are available. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines, ATC code: J07AL52

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

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

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 bacterial pneumonia cases.

Acute Otitis Media (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.

1. 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 dose received 2 doses of either SYNFLORIX or hepatitis B control vaccine followed by a booster and children between 12-18 months of age at first 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, hospital-diagnosed pneumonia and outpatient

antimicrobial prescriptions. In a nested study, infants were followed up till approximately 21 months of age to assess impact on nasopharyngeal carriage.

In a large-scale phase III, randomised, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS), 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.

1.1 IPD

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)

	FinIP					**COMPAS**		
Type of IPD	**No. of IPD cases**			**VE (95% CI)**		**No. of IPD cases**		**VE (95% CI)**
	SYNFLORIX 3+1 schedule	**SYNFLORIX 2+1 schedule**	**Control**	**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% (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

In FinIP, 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. 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 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).

1.2 Pneumonia

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 COMPAS study during a follow up of 38 months from study start.

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 95% CI**
n	**% (n/N)**	**n**	**% (n/N)**	
240	2.3%	304	3.0%	22.0% (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 (during an observation period of 38 months from study start), 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).

During a longer observation period of 48 months from study start, the vaccine efficacy against likely bacterial CAP was 18.2% (95% CI: 4.1; 30.3), against CAP with alveolar consolidation or pleural effusion 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).

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.

1.3 AOM:

Efficacy against 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 regardless of aetiology	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)
Vaccine-related pneumococcal serotypes	25.7% (-232.2; 83.4)
Non-vaccine/non-vaccine related pneumococcal serotypes	25.7% (-231.9; 83.4)
Hi (including NTHi)	15.0% (-83.8; 60.7)
NTHi only	15.0% (-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 clinical AOM episodes was 19% (95% CI: 4.4; 31.4)

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 the control vaccine, according to a 3, 4, 5 and 12-15 months vaccination schedule (Table 4).

Table 4: Vaccine efficacy observed against AOM[1] in POET

Type or cause of AOM	11Pn-PD vaccine Vaccine efficacy (95% CI)
	(ATP)[2]
Clinical AOM regardless of aetiology	33.6 % (20.8; 44.3)
Any pneumococcal serotype	51.5% (36.8;62.9)
Pneumococcal serotypes covered by the 11Pn-PD vaccine	57.6% (41.4;69.3)
10 common pneumococcal serotypes	67.9% (53.0;78.1)
Vaccine-related pneumococcal serotypes	65.5% (22.4;84.7)
Non-vaccine/non-vaccine related pneumococcal serotypes	8.5% (-64.2;49.0)

Hi (including NTHi)	35.6% (3.8; 57.0)
NTHi only	35.3% (1.8;57.4)

CI Confidence Interval
(1) All episodes
(2) Follow up period for a maximum of 24 months from 2 weeks after third primary dose

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

Impact on antimicrobial prescriptions

In the FinIP infant total vaccinated cohort, vaccination with SYNFLORIX reduced outpatient prescriptions for amoxicillin, the most frequently prescribed antibiotic for AOM, by 7.9% (95% CI: 2.0; 13.4) in the 3+1 schedule and 7.5% (95% CI: 0.9; 13.6) in the 2+1 schedule. In the SYNFLORIX groups, there was a trend for a reduction in any outpatient antimicrobial prescriptions and in antimicrobial prescriptions usually recommended for otitis media and respiratory infections.

1.4 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 (5,092 subjects) and in COMPAS (1,921 subjects).

In both studies, SYNFLORIX significantly reduced vaccine type carriage (combined and 6B, 19F and 23F individually) with a trend for increase after booster vaccination in non-vaccine/non-vaccine related type NPC resulting in net decrease in overall pneumococcal carriage. In the nested study, a significant reduction was also observed for vaccine serotype 14 and for the cross-reactive serotype 19A.

In a clinical study assessing NPC in HIV positive infants (N = 83) and HIV negative infants born from an HIV positive mother (N = 101), the HIV exposure or infection did not appear to alter the effect of SYNFLORIX on pneumococcal carriage when compared to the effect in HIV negative infants born from an HIV negative mother (N = 100).

2. Effectiveness in post-marketing surveillance

In Brazil, SYNFLORIX was introduced into the national immunisation programme (NIP) in March 2010, 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 5: 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 Finland, SYNFLORIX was introduced into NIP in September 2010, 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 6: Rates of IPD and the corresponding rate reductions in Finland(1)

IPD	**Incidence per 100,000 person years**		**Relative rate reduction(2) % (95% CI)**
	Before NIP	**After NIP**	
Any culture confirmed	62.9	12.9	80% (72;85)
Any vaccine serotype(3)	49.1	4.2	92% (86;95)
Serotype 19A	5.5	2.1	62% (20;85)

(1) Children of ≤5 years of age during the first three years after NIP introduction
(2) The relative rate reduction indicates how much the incidence of IPD was reduced in the SYNFLORIX cohort versus non-vaccinated cohorts
(3) 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 Pneumococcal Conjugate Vaccine (PCV). 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.

3. Immunogenicity data

3.1 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.

3.2 Immunogenicity in infants from 6 weeks to 6 months of age

3-dose primary schedule

In clinical trials the immunogenicity of SYNFLORIX was evaluated after a 3-dose primary vaccination course according to different schedules (including 6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age).

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.

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 ≥ 0.2 µg/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 7 below:

Table 7: Percentage of subjects with antibody concentrations ≥ 0.2 µg/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	2nd year of life
1	ELISA (≥0.2 µg/ml)	93.1-100%	96.7-100%
	OPA (≥8)	50.3-75.5%	77.8-91.0%
4	ELISA (≥0.2 µg/ml)	98.3-100%	99.7-100%
	OPA (≥8)	97.5-100%	99.0-100%
5	ELISA (≥0.2 µg/ml)	98.8-100%	99.1-100%
	OPA (≥8)	86.5-95.9%	96.3-97.5%
6B	ELISA (≥0.2 µg/ml)	87.3-94.1%	93.4-96.6%
	OPA (≥8)	81.8-95.9%	90.3-96.6%
7F	ELISA (≥0.2 µg/ml)	98.8-100%	100%
	OPA (≥8)	96.8-100%	99.7-100%
9V	ELISA (≥0.2 µg/ml)	97.7-99.1%	99.1-100%
	OPA (≥8)	98.7-100%	100%
14	ELISA (≥0.2 µg/ml)	100%	98.6-100%
	OPA (≥8)	95.9-98.1%	100%
18C	ELISA (≥0.2 µg/ml)	98.8-99.4%	98.9-100%
	OPA (≥8)	91.7-98.2%	98.5-99.7%
19F	ELISA (≥0.2 µg/ml)	98.2-100%	97.1-100%
	OPA (≥8)	93.9-98.1%	94.9-96.1%

23F	ELISA (≥0.2 µg/ml) OPA (≥8)	92.5-96.0% 90.4-95.9%	94.3-98.9% 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.

In addition to eliciting significant responses against vaccine serotypes, administration of SYNFLORIX also elicited antibody responses and evidence of OPA activity against cross-reactive serotypes 6A and 19A. These responses are presented below in Table 8.

Table 8: Percentage of subjects with antibody concentrations ≥ 0.2 µg/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	2nd year of life
6A	ELISA (≥0.2 µg/ml) OPA (≥8)	44.2-52.7 % 70.7-85.6%	72.8-84.4% 68.6-85.0%
19A	ELISA (≥0.2 µg/ml) OPA (≥8)	45.0-86.8% 19.8-32.4%	83.0-83.8% 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))

2-dose primary schedule

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

In a clinical study which evaluated the immunogenicity of SYNFLORIX in 2-dose or 3-dose primed subjects in four European countries, there was no significant difference between the two groups in the percentage of subjects with antibody concentration ≥0.20 µg/ml (ELISA). A lower percentage of subjects with OPA titres ≥8 was observed for vaccine serotypes 6B, 18C and 23F as well as the cross-reactive serotype 19A in 2-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed for each vaccine serotype and serotype 19A. Following the booster (at 11 months of age for both schedules), a lower percentage of subjects with OPA titres ≥8 was observed with the 2+1 schedule for vaccine serotype 5

and serotype 19A. While the clinical relevance of these observations remains unknown, the persistence of the immune response was evaluated in a follow-up of this study (see Immune memory).

A 3-dose primary schedule showed a higher antibody response against protein D compared to a 2-dose primary schedule. However, the clinical relevance of this observation remains unknown.

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

A study conducted in South Africa assessed the immunogenicity of SYNFLORIX given as a booster dose at 9 to 10 months of age after a 3-dose (at 6, 10 and 14 weeks of age) or 2-dose (at 6 and 14 weeks of age) priming. The booster dose 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.

Immune memory.

A plain polysaccharide challenge at 12 months of age elicited an anamnestic antibody response for the vaccine serotypes and the cross-reactive serotype 19A which is considered indicative for the induction of immune memory following the primary series with SYNFLORIX.

In the follow-up of the study, evaluating the 2-dose and 3-dose primary vaccination schedules, 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 ≥ 0.05 µg/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. After 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 µg/ml) and 3-dose primed subjects (ranging from 4.72 to 30.55 µg/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 and 3-dose primed subjects was similar and indicative of an anamnestic immune response for all vaccine serotypes and cross reactive serotypes 6A and 19A. Anamnestic immune responses to protein D were also shown with both schedules.

3.3 Immunogenicity in unvaccinated infants and children ≥ 7 months of age (catch-up)

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 2 doses were comparable to the responses elicited after 3 doses in infants, 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 for 6 vaccine serotypes as well as serotype 19A were similar to those achieved following a 3 dose vaccination schedule in infants while they were lower for 4 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.

In the second clinical study, a single dose administered during the second year of life after 2 catch-up doses at 12-20 months of age elicited a marked increase of antibody GMCs and OPA GMTs, indicative of an immunological memory.

In the third clinical study, 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. A similar immune response was observed for protein D.

3.4 Immunogenicity in 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 3-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, for each vaccine serotype at least 92.7% of subjects achieved ELISA antibody concentrations ≥ 0.2 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 and 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.

Increases of ELISA antibody GMCs and OPA GMTs were seen for each vaccine serotype and the cross-reactive serotype 19A 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 ≥ 0.2µg/ml and at least 91.9% achieved OPA titres ≥ 8.

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

3.5 *Immunogenicity in special populations*

HIV positive (HIV+/+) infants and HIV negative infants born from an HIV positive mother (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 (asymptomatic or mild disease), 91 HIV negative infants born from an HIV positive mother (HIV+/-) and 93 HIV negative infants born from an HIV negative mother (HIV-/-).

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.

Children with sickle cell disease

A clinical study conducted in Burkina Faso assessed the immunogenicity of SYNFLORIX administered to 146 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) compared to 143 age-matched children without SCD. The immune response to SYNFLORIX for each of the vaccine serotype 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 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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

1. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (NaCl)
Water for injection

SYNFLORIX does not contain a preservative.

6.2 Incompatibilities

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

6.3 Shelf life

4 years

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

6.4 Special precautions for 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.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

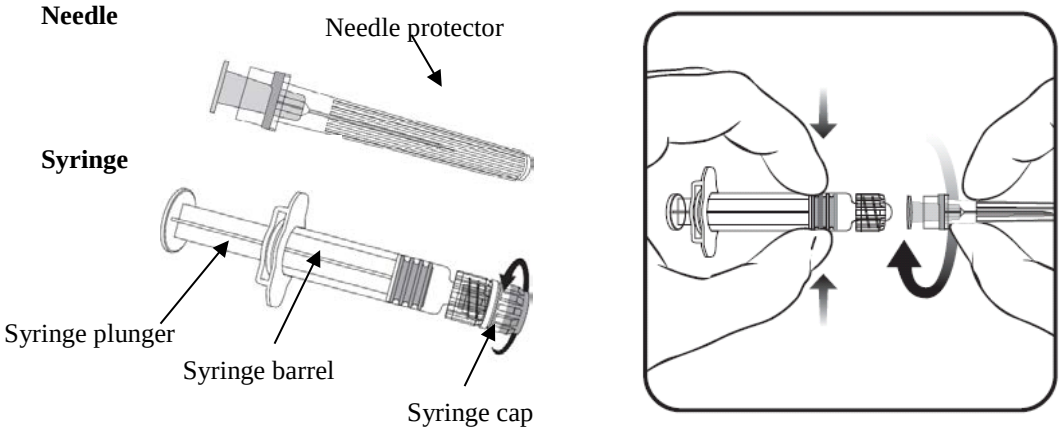
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

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.

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

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 21 May 2009

10. DATE OF REVISION OF THE TEXT

21 November 2018

Summary table of changes:

Section changed	Summary of new information
4.2	Special populations - change to presentation of information
4.4	Removal of upper age bracket for children with immunocompromising conditions and update to statement on 23-valent pneumococcal vaccines
8	Removal of manufacturer

Version 14.0