SCHEDULING STATUS: S2

1. NAME OF MEDICINE:

SYNFLORIX

Pneumococcal polysaccharide and Non-Typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine, adsorbed.

Suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

One dose (0,5 mL) contains 1 microgram of polysaccharide for serotypes $1^{1,2}$, $5^{1,2}$, $6B^{1,2}$, $7F^{1,2}$, $9V^{1,2}$, $14^{1,2}$ and $23F^{1,2}$, and 3 micrograms of serotypes $4^{1,2}$, $18C^{1,3}$ and $19F^{1,4}$.

[1] adsorbed on aluminium phosphate	0,5 milligram Al^{3+}
[2] conjugated to protein D (derived from Non-Typeable *Haemophilus influenzae*) carrier protein	13 micrograms
[3] conjugated to tetanus toxoid carrier protein	8 micrograms
[4] conjugated to diphtheria toxoid carrier protein	5 micrograms

Sugar-free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Suspension for Injection.

Turbid liquid after shaking. Colourless supernatant and white deposit after sedimentation.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

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

Posology:

Infants from 6 weeks to 6 months of age:

Three-dose primary series:

The recommended immunisation series to ensure optimal protection consists of four doses, each of 0,5 mL. The primary infant series consists of three doses with 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 and may be given from the age of 9 months onwards (see section 5.1).

Two-dose primary series:

Alternatively, when SYNFLORIX is given as part of a routine infant immunisation programme, a series consisting of three doses, each of 0,5 mL may be given. The first dose may be given as early as 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).

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).

Previously unvaccinated older infants and children:

- **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 to 5 years**: The vaccination schedule consists of two doses of 0,5 mL with an interval of at least 2 months between doses.

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

Special populations:

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

Method of administration:

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

Use and handling:

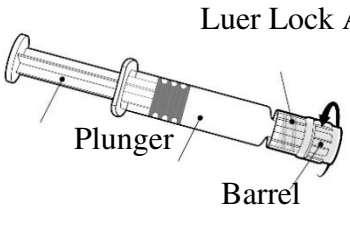
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

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.

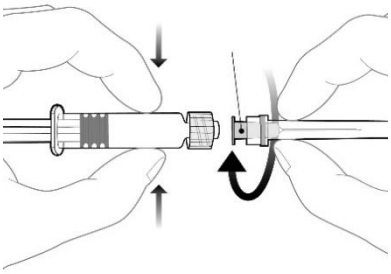
The vaccine should be well shaken before use.

Instructions for the pre-filled syringe:



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

4.3 Contraindications:

SYNFLORIX should not be administered to subjects with known hypersensitivity to any component of the vaccine.

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.

Safety and immunogenicity data are available for HIV infected infants, children with sickle cell disease and children with splenic dysfunction (see sections 4.8 and 5.1). Safety and immunogenicity data for SYNFLORIX are not available for individuals in other specific immunocompromised groups and vaccination should be considered on an individual basis.

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)
- 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.

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

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.

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.

Sodium content:

This medicine contains less than 1 mmol sodium (23 mg) per dose, essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction:

SYNFLORIX can be given concomitantly with any of the following monovalent or combination vaccines (including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib): diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine, 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

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

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:

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

4.7 Effects on ability to drive and use machines:

Not applicable.

4.8 Undesirable effects:

Summary of the safety profile:

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 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 of age.

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.

Reactogenicity was higher in children receiving whole cell pertussis vaccines concomitantly.

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

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 loss
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

System organ class	Frequency	Adverse reactions
Respiratory, thoracic and mediastinal disorders	Uncommon	apnoea (see section 4.4 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:

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 a medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the'**6.04 Adverse Drug Reactions Reporting form,'** found under SAHPRA publications: https:/www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Insufficient data are available.

5. PHARMACOLOGICAL PROPERTIES :

5.1 Pharmacodynamic properties :

A 30.2 Antigens

ATC code :

Pharmaco-therapeutic 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).

1. 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.

2. *Efficacy and effectiveness in clinical trials:*

In a large-scale phase III/IV, double-blind, cluster-randomised, controlled, clinical trial in Finland (FinIP), children were enrolled into 78 study clusters. Clusters 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.

2.1 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)

Type of IPD	FinIP					COMPAS		
	No. of IPD cases			VE (95 % CI)		No. of IPD cases	VE (95 % CI)	
	SYNFLORIX 3+1 schedule	SYNFLORIX 2+1 schedule	Control[2]	3+1 schedule	2+1 schedule	SYNFLORIX 3+1 schedule	Control	3+1 schedule
	N 10 273	N 10 054	N 10 200			N 11 798	N 11 799	
Vaccine serotype IPD[1]	0	1	12	100 %[3] (82,8; 100)	91,8 %[4] (58,3; 99,6)	*0*	*18*	*100 % (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 < 0,0001
(4) p = 0,0009

In FinIP, the observed VE against culture-confirmed IPD due to any serotype was 100 % (95 % C: 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).

2.2 Pneumonia:

Efficacy of SYNFLORIX against likely bacterial Community Acquired Pneumonia (CAP) was demonstrated in the according-to-protocol (ATP) cohort (immunised 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 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.

2.3 Acute Otitis Media (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), 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 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).

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.

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.

2.4 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).

3. 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.

4. Immunogenicity data

4.1 Immunologic non-inferiority to 7-valent PCV vaccine:

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

In a head-to-head comparative trial with the 7-valent PCV vaccine, non-inferiority of the immune response to SYNFLORIX measured by ELISA was demonstrated for all serotypes, except for 6B and 23F (upper limit of the 96,5 % CI around the difference between groups > 10 %). For serotypes 6B and 23F, respectively, 65,9 % and 81,4 % of infants vaccinated at 2, 3 and 4 months reached the antibody threshold (i.e. 0,20 µg/mL) one month after the third dose of SYNFLORIX versus 79,0 % and 94,1 % respectively, after three doses of the 7-valent PCV vaccine. The clinical relevance of these differences

is unclear, as SYNFLORIX was observed to be effective against IPD caused by serotype 6B in a double-blind randomised clinical study (see Table 1).

The percentage of vaccinees reaching the threshold for the three additional serotypes in SYNFLORIX (1, 5 and 7F) was respectively 97,3 %, 99,0 % and 99,5 % and was at least as good as the aggregate 7-valent PCV vaccine response against the 7 common serotypes (95,8 %).

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

In the same study, SYNFLORIX was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87,7 % to 100 % of SYNFLORIX vaccinees and 92,1 % to 100 % of 7-valent PCV vaccinees reached an OPA titre ≥ 8 one month after the third dose. The difference between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was < 5 % for all serotypes in common, including 6B and 23F. Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by SYNFLORIX were lower than those elicited by the 7-valent PCV vaccine for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of SYNFLORIX vaccinees reaching an OPA titre ≥ 8 were respectively 65,7 %, 90,9 % and 99,6 % after the primary vaccination course and 91,0 %, 96,3 % and 100 % after the booster dose. The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

The administration of a fourth dose (booster dose) in the second year of life elicited an anamnestic antibody response as measured by ELISA and OPA for the 10 serotypes

included in the vaccine demonstrating the induction of immune memory after the 3-dose primary course.

It has also been demonstrated that SYNFLORIX induces an immune response to the cross-reactive serotypes 6A and 19A with increases in GMCs (5,5- and 6,1-fold increases respectively) and OPA GMT (6,7- and 6,1-fold increases respectively) observed one month after a booster dose compared to pre-booster concentrations.

In a clinical study where infants were vaccinated at 6, 10, 14 weeks, the percentage of SYNFLORIX vaccinees with antibody concentrations ≥ 0,20 µg/mL and with OPA titre ≥ 8 was in the same range as the percentage of 7-valent PCV vaccinees for the 7 serotypes in common. The observed differences in the percentage of subjects with OPA titres ≥ 8 were below 5 % for all serotypes except 19F (higher percentage in SYNFLORIX group).

4.2 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) and after a fourth (booster) dose given at least 6 months after the last primary dose and from the age of 9 months onwards.

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 4 European countries, there was no significant difference between the two groups in the percentages 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 subsection 'Immune memory).

A 3-dose primary schedule has shown 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 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. After a single challenge dose of SYNFLORIX administered during the 4th year of life, 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 the cross-reactive serotypes 6A and 19A. Anamnestic immune responses to protein D were also shown with both schedules.

4.3 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 response 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 12-23 months children.
- In children 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 (serotypes1, 5, 14 and 23F) and for anti-protein D. The OPA GMTs were similar or higher following a single dose 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 the cross-reactive serotype 19A. A similar immune response was observed for protein D.

4.4 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, 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, for each vaccine serotype at least 97,6 % of subjects achieved ELISA antibody concentrations ≥ 0,2 µg/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.

4.5 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 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.

5.3 Preclinical safety data:

A repeated dose toxicity study of pneumococcal conjugate vaccine in rabbit revealed no evidence of any significant local or systemic toxic effects.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium chloride, water for injection.

6.2 Incompatibilities:

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

6.3 Shelf life:

48 months for vaccine presented in a vial (1-dose and 2-doses)

48 months for vaccine presented in a prefilled syringe.

6.4 Special precautions for storage:

DO NOT FREEZE.

Store at +2 °C to +8 °C (in a refrigerator).

The shake test as recommended by WHO can detect if a SYNFLORIX vial has been frozen during storage. Discard if freezing has occurred.

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

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

For state packs only: The Vaccine Vial Monitor (VVM) is either part of the label or the vial cap used for all SYNFLORIX batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial for 1 dose (0,5 mL) of vaccine is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the glass container should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event SYNFLORIX has not been stored in compliance with the storage instructions. Furthermore, GlaxoSmithKline Biologicals assumes no responsibility in case a VVM is defective for any reason.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

Discard point: Inner square matches colour of outer circle. **DO NOT use the vaccine.**

Beyond the discard point: Inner square darker than outer ring. **DO NOT use the vaccine.**

6.5 Nature and contents of container:

SYNFLORIX is presented:

- in pre-filled syringes for 1 dose (0,5 mL) with a plunger stopper (butyl rubber) and with a rubber tip cap. Pack sizes of 1 or 10 with or without needles, or
- in vials for 1 dose (0,5 mL) with a grey stopper (butyl rubber) secured with an aluminium seal. Pack sizes of 1, 10 or 100, or
- in vials for 2 doses (1 mL) with a grey stopper (butyl rubber) secured with an aluminium seal. Pack size of 100.

The pre-filled syringes are made of neutral glass type 1.

The vials are made of uncoloured neutral glass type 1.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

6.6 Special precautions for disposal and other handling:

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

43/30.2/0401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

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10. DATE OF REVISION OF TEXT:

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GDS 14-16 &17&18

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