SYNFLORIX

SCHEDULING STATUS:

S2

PROPRIETARY NAME AND DOSAGE FORM:

SYNFLORIX

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

Suspension for injection.

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 *Haemo influenzae*) carrier protein	13 micrograms
[3] conjugated to tetanus toxoid carrier protein	8 micrograms
[4] conjugated to diphtheria toxoid carrier protein	5 micrograms

Excipients:

Sodium chloride, water for injections.

PHARMACOLOGICAL CLASSIFICATION:

A 30.2 Antigens

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

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 etiologies. 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-randomized, 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 % CI, 85,6-100,0 %; 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 immunization:

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 etiology	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.

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 immunization programme (2 primary doses to infants less than 6 months of age and a booster dose at 12 months) following 4,5 years of use of 7-valent 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

2-dose primary schedule:

In addition to the 3-dose primary schedule, the immunogenicity of SYNFLORIX following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in a clinical study.

Although there was no significant difference between the two groups in the percentages of subjects with antibody concentration ≥ 0,2 µg/ml (ELISA), a lower percentage of subjects with OPA titers ≥ 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, a lower percentage of subjects with OPA titers ≥ 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.

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.

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 (serotypes 1, 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 three dose primary vaccination course at 2, 4, 6 months of age. Immunogenicity was evaluated in 44 very preterm, 69 preterm and 127 full term infants following a booster dose at 15 to 18 months of age.

Regardless of maturity, one month after primary vaccination, 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.

Pharmacokinetic Properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

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.

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.*

CONTRA-INDICATIONS:

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

WARNINGS AND SPECIAL PRECAUTIONS:

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

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

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

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

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

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

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

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

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

- the appropriate-for-age SYNFLORIX vaccination series should be given below 2 years of age (see DOSAGE AND DIRECTIONS FOR USE)
- a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a

previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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, immunization with SYNFLORIX does not substitute routine immunization 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.

INTERACTIONS:

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.

Incompatibilities:

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

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.

DOSAGE AND DIRECTIONS FOR USE:

Infants from 6 weeks to 6 months of age:

Three-dose primary series:

The recommended immunisation series to ensure optimal protection consists of four doses, each of 0,5 ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A booster dose is recommended at least 6 months after the last primary dose (see Pharmacodynamic Properties).

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 administered from the age of 2 months, with a second dose 2 months later. A booster dose is recommended at least 6 months after the last primary dose (see 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 Pharmacodynamic Properties).

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.

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

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

Method of administration:

The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in 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.

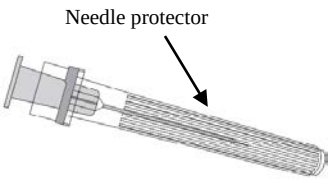
The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

In the event of either being observed, discard the vaccine.

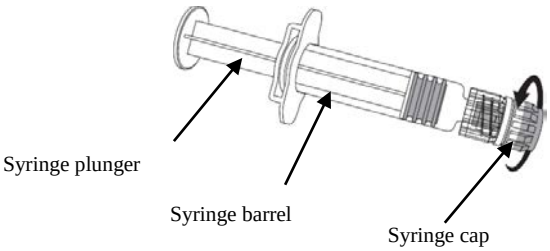
The vaccine should be well shaken before use.

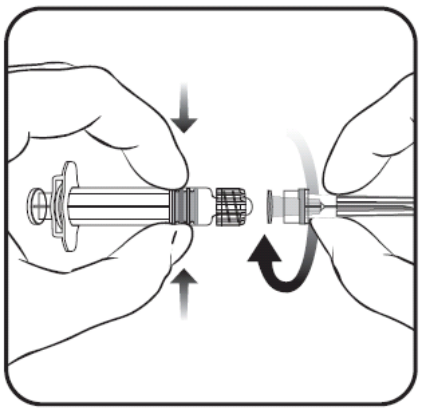
Instructions for administration of the vaccine presented in pre-filled syringe:

Needle



Syringe





1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

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

SIDE EFFECTS:

Clinical Trial Data:

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.

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 WARNINGS AND SPECIAL PRECAUTIONS for apnoea in very premature infants (≤ 28 weeks of gestation))

Gastro-intestinal disorders:

Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:

Uncommon: rash

Rare: uticaria

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

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

Nervous system disorders:

Uncommon: headache (age 2 to 5 years)

Gastrointestinal disorders:

Uncommon: nausea (age 2 to 5 years)

General disorders and administration site conditions:

Common: fever ≥ 38 °C rectally (age 2 to 5 years)

Uncommon: 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.

Post-marketing Data:

Immune system disorders: anaphylaxis

Nervous system disorders: hypotonic-hyporesponsive episode.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Insufficient data are available.

IDENTIFICATION:

Suspension for injection. Turbid liquid after shaking. Colourless supernatant and white deposit after sedimentation.

PRESENTATION:

SYNFLORIX is presented:

- in pre-filled syringes for 1 dose (0,5 ml) with a plunger stopper (butyl rubber) with or without needles. Pack sizes of 1 or 10, 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.

STORAGE INSTRUCTIONS:

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 multidose 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.

Keep out of the reach of children.

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 b**

passed, USE the vaccine.

At a later time, inner square still lighter than outer circle. **If the exp**

date has not been passed, USE the vaccine.

Discard point: Inner square matches colour of outer circle. **DO N**

use the vaccine.

Beyond the discard point: Inner square darker than outer ring. **D**

NOT use the vaccine.

REGISTRATION NUMBER:

43/30.2/0401

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 04 June 2010

Date of last revision: 01 December 2017

GDS-13

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS:

S2

PROPRIETARY NAME AND DOSAGE FORM:

SYNFLORIX

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

Suspension for injection.

Read all of this leaflet carefully before SYNFLORIX is given to your child.

- SYNFLORIX is not for self-medication and must be administered by a healthcare professional
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist
- SYNFLORIX has been prescribed for your child only and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT SYNFLORIX CONTAINS:

One dose (0,5 ml) contains 1 microgram of polysaccharide of 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 *Haemo influenzae*) carrier protein	13 micrograms
[3] conjugated to tetanus toxoid carrier protein	8 micrograms
[4] conjugated to diphtheria toxoid carrier protein	5 micrograms

The other ingredients are sodium chloride and water for injections.

WHAT SYNFLORIX IS USED FOR:

SYNFLORIX is a vaccine given to children from 6 weeks of age up to 5 years of age to protect against diseases caused by some types of a bacteria called *Streptococcus pneumoniae*. This bacteria can cause serious illnesses including meningitis, blood infection, pneumonia and ear infection. This vaccine also helps protect your child against ear infection caused by another bacteria called non-typeable *Haemophilus influenzae*.

The vaccine works by helping the body to make its own antibodies, which protect your child against diseases.

As will all vaccines, SYNFLORIX may not fully protect all children who are vaccinated.

BEFORE YOUR CHILD IS GIVEN SYNFLORIX:

SYNFLORIX should not be given:

- if your child has previously had any allergic reaction to SYNFLORIX or any component contained in this vaccine. The active substances and other ingredients in SYNFLORIX are listed at the beginning of this leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Take special care with SYNFLORIX if your child:

- has a severe infection with a high temperature (over 38 °C). A minor infection such as a cold should not be a problem, but talk to your doctor first
- has a bleeding problem or bruises easily
- has any illness that weakens the immune system
- takes any medicine that can weaken the immune system
- has breathing difficulties, please contact your doctor. This may be more common in the first three days following vaccination if your child is born prematurely (before or at 28 weeks of pregnancy).

Pregnancy and breastfeeding:

SYNFLORIX is not intended for use in adults.

Taking other medicines with SYNFLORIX:

Always tell your healthcare professional if your child is taking any other medicine. (This includes complementary or traditional medicines.)

Please tell your doctor if your child is taking or has recently taken paracetamol.

SYNFLORIX may be given at the same time your child receives other normally recommended vaccinations, such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated polio, hepatitis B, measles, mumps and rubella, varicella (chickenpox), oral polio and rotavirus vaccines.

SYNFLORIX can be given at the same time as other childhood vaccines. A different injection site will be used for each type of vaccine.

HOW TO RECEIVE SYNFLORIX:

The doctor or nurse will inject the recommended dose of vaccine.

Your doctor may wipe the skin with alcohol or other disinfecting agents and will let the skin dry before the injection.

SYNFLORIX will be injected into a muscle, usually in the thigh or upper arm.

Infants from 6 weeks of age to 6 months of age:

Usually, your child will receive three injections with an interval of at least one month between each one. The first injection can be given from the age of 6 weeks onwards. At least six months after the last injection, your child will receive an additional injection (booster).

Alternatively, your child may receive 2 injections with an interval of two months between injections. The first injection can be given from the age of 2 months. At least six months after the last injection, your child will receive an additional injection (booster).

Preterm infants: Your child will receive three injections with an interval of at least one month between each dose. At least six months after the last injection, your child will receive an additional injection (booster).

Previously unvaccinated older infants and children:

- ***infants aged 7-11 months:*** your child will receive 2 injections with an interval of at least one month between injections. At least 2 months after the last injection and during his/her second year of life, your child will receive a third injection (booster).
- ***children aged 12 months to 5 years:*** your child will receive a total of 2 injections with an interval of at least two months between injections.

If you miss a dose of SYNFLORIX:

You will be informed when your child should come back for their next injection. If your child misses a scheduled injection, it is important that you make another appointment. Make sure your child finishes the complete vaccination course.

POSSIBLE SIDE EFFECTS:

SYNFLORIX can cause side effects.

Not all side effects reported for SYNFLORIX are included in this leaflet. Should your child's general health worsen or if your child experiences any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

Severe allergic reactions which can be recognised by:

- raised and itchy rash
- swelling of the face or mouth (angioedema), causing difficulty in breathing
- a sudden drop in blood pressure and loss of consciousness.

These reactions will usually occur before leaving the doctor's surgery. However, if any of the above happens, tell your doctor immediately or go to the nearest nearest casualty department at your nearest hospital.

- These are all very serious side effects. If your child has them, your child may have had a very serious allergic reaction to SYNFLORIX.

Tell your doctor immediatey or go the casualty department at your nearest hospital if you notice the following:

- Kawasaki disease (major signs of the illness are for instance: fever which lasts for more than five days, associated with a rash on the trunk sometimes followed by a

peeling of the skin on the hands and fingers, swollen glands in the neck, red eyes, lips, throat and tongue).

➔ These are all serious side effects. Your child may need urgent medical attention.

Frequent side effects include:

- drowsiness
- loss of appetite
- pain, redness, swelling at the injection site
- fever (38 °C or higher)
- irritability
- hardness at the injection site.

Less frequent side effects include:

- nausea (feeling sick), diarrhoea, vomiting (being sick)
- itching, blood clot, bleeding and small lump at the injection site
- unusual crying
- temporarily stopping breathing (apnoea)
- headache
- skin rash
- swelling larger than 5 cm where the injection was given
- hives.

If your child is more than 12 months of age when he/she receives his/her booster injection, he/she is more likely to experience reactions at the site of injection.

Other side effects include:

- fits without fever or due to fever
- allergic reactions such as skin allergies
- collapse (sudden onset of muscle floppiness), periods of unconsciousness or lack of awareness and paleness or bluish skin discolouration.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

STORING AND DISPOSING OF SYNFLORIX:

DO NOT FREEZE.

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

Discard if freezing has occurred.

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

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

Store all medicines out of reach of children.

Do not use SYNFLORIX after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF SYNFLORIX:

SYNFLORIX is presented:

- in pre-filled syringes for 1 dose (0,5 ml) with a plunger stopper (butyl rubber) with or without needles. Pack sizes of 1 or 10, 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 and vials are made of neutral glass type 1.

IDENTIFICATION OF SYNFLORIX:

Cloudy liquid after shaking. A fine white deposit with a clear, colourless liquid may form upon storage.

REGISTRATION NUMBER:

43/30.2/0401

NAME AND ADDRESS OF THE REGISTRATION HOLDER:

GlaxoSmithKline South Africa (Pty) Ltd

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