Synflorix™

Pneumococcal polysaccharide conjugate vaccine, adsorbed

481330

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 for 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 NTHi) carrier protein	~13 micrograms
[3] conjugated to tetanus toxoid carrier protein	~8 micrograms
[4] conjugated to diphtheria toxoid carrier protein	~5 micrograms

Synflorix™ is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

Indications

Active immunisation against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age.

The use of ***Synflorix™*** should be determined on the basis of official recommendations taking into consideration the impact on pneumococcal diseases in different age groups as well as the variability of the epidemiology in different geographical areas.

Dosage and Administration

<u>Infants from 6 weeks to 6 months of age:</u>

3-dose primary series
The recommended immunization series to ensure optimal protection consists of 4 doses, each of 0.5 ml. The primary infant series consists of 3 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 6 weeks of age. A booster dose is recommended at least 6 months after the last primary dose and preferably between 12 and 15 months of age (see Pharmacodynamics).

2-dose primary series
Alternatively, when ***Synflorix™*** is given as part of a routine infant immunization programme, a series consisting of 3 doses, each of 0.5 ml may be given. The first dose may be given 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 Pharmacodynamics).

Preterm infants born after at least 27 weeks of gestational age
The recommended immunization series consists of 4 doses, each of 0.5 ml. The primary infant series consists of 3 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 Pharmacodynamics).

<u>Previously unvaccinated older infants and children:</u>

- <u>**7-11 months of age**</u>: 2 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.
- <u>**12 months - 5 years of age**</u>: 2 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™***.

<u>Paediatric population</u>

The safety and efficacy of ***Synflorix™*** in children over 5 years of age have not been established.

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.

Contraindications

Synflorix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see Qualitative and quantitative composition and List of excipients).

Warnings and Precautions

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

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

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

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

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

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

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

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

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

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

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

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

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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 injection 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 serotype 18C only. Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed. The clinical relevance of the above observations is unknown.

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

Adverse Reactions

Clinical trials involved the administration of approximately 64,000 doses of ***Synflorix™*** to approximately 22,500 healthy children and 137 preterm infants as primary vaccination. Approximately 19,500 healthy children and 116 preterm infants received a booster dose of ***Synflorix™*** in the second year of life. Safety was also assessed in approximately 400 children from 2 to 5 years old. In all trials, ***Synflorix™*** was administered concurrently with the recommended childhood vaccines.

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

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

The most common adverse reactions observed were redness at the injection site (after primary vaccination), irritability (after primary and booster vaccination) and pain at the injection site (after booster vaccination). 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

Frequency	Adverse reactions
Clinical trials	
Very common	Appetite lost, irritability, drowsiness, 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	Crying abnormal, apnoea in very premature infants (≤28 weeks of gestation) (see Warnings and Precautions), diarrhoea, vomiting, rash, injection site reactions like injection site haematoma, haemorrhage and nodule
Rare	Allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema), convulsions (including febrile convulsions), urticaria(1)
Very rare	Angioedema, Kawasaki disease
Adverse reactions additionally reported after booster vaccination of primary series and/or catch-up vaccination:	
Common	Fever ≥38°C rectally (age 2 to 5 years)
Uncommon	Injection site reactions(2) like pruritus, diffuse swelling of the injected limb, sometimes involving the adjacent joint; age < 2 years: fever > 40°C rectally; age 2 to 5 years: headache, nausea and fever >39°C rectally
Post-marketing experience	
Rare	Hypotonic-hyporesponsive episode
Very rare	Anaphylaxis

(1) Uncommon following catch-up vaccination in children 12 to 23 months of age.
(2) Following booster vaccination, children > 12 months of age are more likely to experience injection site reactions when compared to infants during the primary series.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmaco-therapeutic group: pneumococcal vaccines, ATC code: J07AL52

<u>1. Efficacy and effectiveness in clinical trials</u>

In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), children were randomised into 4 groups according to the 2 infant schedules [2+ 1 (3, 5 months of age, booster at 11 months) or 3+ 1 (3, 4, 5 months of age, booster at 11 months)] 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 vaccine dose received ***Synflorix™*** or hepatitis B control vaccine according to a 2-dose primary schedule followed by a booster dose and children between 12-18 months of age at first vaccine dose received 2 doses of either ***Synflorix™*** or hepatitis A 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 to 21 months of age to assess impact on nasopharyngeal carriage.
In a large-scale phase III, randomized, 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.

<u>1.1 Invasive Pneumococcal Disease (IPD)</u>

<u>Infant cohort below 7 months of age at enrolment</u>
Vaccine effectiveness (in FinIP) or efficacy (in COMPAS) was demonstrated in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes (Table 1).

Table 1: Prevention of IPD in infants receiving at least one dose of *Synflorix™* (Infant total vaccinated cohort)

Type of IPD	FinIP					COMPAS		
	No. of cases			VE (95% CI)		No. of 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 (1)	0	1	12	100%(3) (82.8; 100)	91.8%(4) (58.3; 99.6)	0	18	100% (77.3;100)
Serotype 6B	0	0	5	100% (54.9; 100)	100% (54.5; 100)	0	2	-
Serotype 14	0	0	4	100% (39.6; 100)	100% (43.3; 100)	0	9	100% (49.5;100)
Any serotype	0	2	14	100%(5) (85.6;100)	85.8%(5) (49.1;97.8)	7	21	66.7% (21.8;85.9)

IPD: Invasive Pneumococcal Disease
VE: Vaccine effectiveness (FinIP) or efficacy (COMPAS)
N: number of subjects per group; CI: Confidence Interval
(1) In FinIP, the other vaccine serotypes causing IPD were 7F (1case 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 also detected in control group in addition to serotypes 6B and 14.
(2) the 2 groups of control clusters of infants were pooled
(3) p-value<0.0001
(4) p-value=0.0009
(5) 93.0% (95% CI, 74.9;98.9; 2 versus 14 cases) regardless of the primary schedule

<u>Catch-up cohorts</u>
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 months cohort and serotypes 3, 4, 6B, 15C and 19F in the 12-18 months cohort).

<u>1.2. Pneumonia</u>

Vaccine efficacy of ***Synflorix™*** against likely bacterial Community Acquired Pneumonia (CAP) was demonstrated in the according-to-protocol (ATP) cohort (immunized with at least the 3-dose primary series) as the primary objective of COMPAS during a follow up of 38 months from study start: 22.0% (95% CI: 7.7; 34.2); P value ≤ 0.002; 240 cases/10,295 subjects in the ***Synflorix™*** group versus 304 cases/10,201 subjects in the control group.

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.

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, 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.

1.3. Acute Otitis Media (AOM)

AOM efficacy was evaluated in COMPAS.

Table 2: Vaccine efficacy against AOM(1) in COMPAS (ATP(2): 5,989 subjects)

Type or cause of AOM	Vaccine efficacy	95% CI
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
NTHi	15.0%	-83.8;60.7

CI Confidence Interval
(1) First episode
(2) Follow up period for a maximum of 40 months from 2 weeks after third primary dose
(3) Not statistically significant by pre-defined criteria (One sided p=0.032). However, in TVC cohort, vaccine efficacy against clinical AOM episodes was 19% (95% CI: 4.4; 31.4)

In another large randomised double-blind trial (POET) conducted in the Czech Republic and Slovakia, infants received either an 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of ***Synflorix™*** (along with serotype 3 for which efficacy was not demonstrated), or a control vaccine, according to a 3, 4, 5 and 12-15 months vaccination schedule.

Table 3: Vaccine efficacy against AOM(1) in POET (ATP(2): 4907 subjects)

Type or cause of AOM	Vaccine efficacy	95% CI
Clinical AOM regardless of aetiology	33.6%	20.8; 44.3
Any pneumococcal serotype	51.5%	36.8; 62.9
10 pneumococcal serotypes in common with ***Synflorix™***	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
NTHi	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

In POET, efficacy of the 11Pn-PD vaccine against the first occurrence of vaccine serotype AOM episode was 52.6% (95% CI: 35.0; 65.5). Serotype specific efficacy against the first AOM episodes due to 6B, 14, 19F and 23F was demonstrated.

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.

Impact on antimicrobial prescriptions

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

1.4 Impact on nasopharyngeal carriage (NPC)

The effect of ***Synflorix™*** on NPC was studied in the nested study of FinIP (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.

2. Effectiveness in post-marketing surveillance

In Brazil, ***Synflorix™*** was introduced into the national immunization program (NIP) in March 2010, using a 3+1 schedule in infants 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 (83.8% (95% CI: 65.9;92.3)) and IPD due to serotype 19A (82.2% (95% CI: 10.7;96.4)).

In Finland, ***Synflorix™*** was introduced into NIP in September 2010, with a 2+1 schedule in infants without catch-up campaign. The relative rate reduction of IPD incidence in children of ≤5 years of age during the first 3 years after NIP introduction was evaluated. Before and after NIP comparison suggests a significant decrease in the incidence of any culture confirmed IPD (80% (95% CI: 72;85)), any vaccine serotype IPD (92% (95% CI: 86;95)) and IPD due to serotype 19A (62% (95% CI: 20;85)).

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.

3. Immunogenicity data

3.1 Immunologic non-inferiority to 7-valent PCV

In a head-to-head comparative trial with 7-valent PCV, non-inferiority of the immune response to ***Synflorix™*** measured by ELISA was demonstrated for all serotypes, except for 6B and 23F. For serotypes 6B and 23F, respectively, 65.9% and 81.4% of infants vaccinated at 2, 3 and 4 months reached the ELISA antibody threshold (i.e. 0.20 µg/ml) one month after the third dose of ***Synflorix™*** versus 79.0% and 94.1% respectively, after 3 doses of 7-valent PCV. The clinical relevance of these differences is unclear, as ***Synflorix™*** was observed to be effective against IPD caused by serotype 6B in a clinical study (see Table 1). The percentage of vaccinees reaching the threshold for serotypes 1, 5 and 7F in ***Synflorix™*** was at least as good as the aggregate 7-valent PCV response against the 7 common serotypes.

In the same study, the proportion of functional antibody responders (OPA titre ≥ 8) to all serotypes contained in each vaccine were high (> 87.7%) with the exception of serotype 1 for ***Synflorix™*** post-primary (65.7%).
The administration of a fourth dose (booster dose) in the second year of life elicited an anamnestic antibody response for all vaccine serotypes demonstrating the induction of immune memory after the primary course.
It has also been demonstrated that ***Synflorix™*** induces an immune response to the cross-reactive serotype 19A with 6.1 fold increases in both GMC and OPA GMT observed 1 month after a booster dose compared to pre-booster concentrations.

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

3-dose primary schedule

The immunogenicity of ***Synflorix™*** has been evaluated in various clinical studies across Africa, Asia, Europe and Latin America according to different schedules (6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age). A booster dose was given in multiple clinical studies.

2-dose primary schedule

A clinical study evaluated the immunogenicity of ***Synflorix™*** after a 2-dose or a 3-dose primary vaccination schedule. Although there was no significant difference between the two groups in the percentages of subjects reaching ELISA antibody threshold, a lower percentage of subjects reaching OPA threshold was observed for some vaccine serotypes 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.

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

Immune memory

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 serotype 19A. Anamnestic immune responses to protein D were shown with both schedules.

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

In studies in previously unvaccinated 7-11 months children (2+1 schedule) and children 12 months up to 5 years of age (2 dose schedule), ELISA antibody GMCs and OPA GMTs for vaccine serotypes and the cross-reactive serotype 19A were similar or higher than those induced by 3-dose primary infant series. A similar immune response was observed for protein D in 2 to 5 years old children and infants after a 3-dose primary series.

3.4 Immunogenicity in preterm infants

Immunogenicity of ***Synflorix™*** in very preterm and preterm (gestation period of 27-30 weeks and 31-36 weeks respectively) as well as full term infants was evaluated (3 primary doses at 2 4, 6 months of age with a booster dose at 15-18 months of age).

After primary vaccination, for each vaccine serotype the proportion of subjects with ELISA antibody concentrations ≥ 0.20 µg/ml and OPA titres ≥ 8 was similar regardless of maturity. With respect to full term, similar immunogenicity was observed in preterm groups except lower antibody GMCs for serotypes 4, 5, 9V and the cross-reactive serotype 19A and lower OPA GMT for serotype 5.

Immunological memory was shown for each vaccine serotype and the cross-reactive serotype 19A one month after the booster dose.

Pre-clinical Safety Data

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium chloride, water for injections

Incompatibilities

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

Shelf Life

The expiry date is indicated on the label and packaging.

Synflorix™ should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that ***Synflorix™*** remains stable and can be administered when the vaccine has been stored outside the refrigerator for up to 72 hours at temperatures between 8°C and 25°C.

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 – +8°C). If not used within 6 hours it should be discarded.

Special Precautions for Storage

Store at +2°C to +8°C (in a refrigerator).
Do not freeze.
Store in the original packaging in order to protect from light.

Nature and Contents of Container

Synflorix™ is presented:
- in pre-filled syringes (type I glass) for 1 dose (0.5 ml) with a plunger stopper (rubber butyl) with or without needles.
- in vials (type I glass) for 1 dose (0.5 ml) or 2 doses (1 ml) with a stopper (rubber butyl).

Instructions for Use/Handling

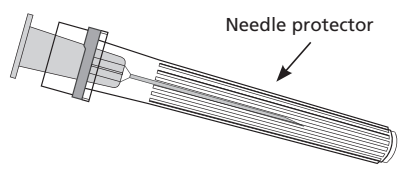
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

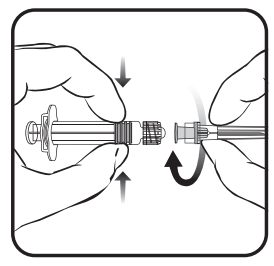
The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

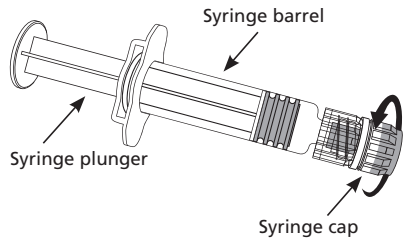
Instructions for administration of the vaccine presented in pre-filled syringe

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.

Not all presentations are available in every country.

***Synflorix* is a trade mark of the GSK group of companies.**

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ان هذا الدواء:
الدواء مستحضر يؤثر على صحتك واستهلاكه خلافاً للتعليمات يعرضك للخطر.
اتبع بدقة وصفة الطبيب وطريقة الاستعمال المنصوص عليها وتعليمات الصيدلاني الذي صرفها لك.
– فالطبيب والصيدلاني هما الخبيران بالدواء وبنفعه وضرره.
– لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
– لا تكرر صرف الدواء بدون وصفة طبية.
– لا تترك الأدوية في متناول أيدي الأطفال.
مجلس وزراء الصحة العرب
واتحاد الصيادلة العرب.

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

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