Synflorix®

NAME OF THE MEDICINAL PRODUCT

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

PRODUCT DESCRIPTION

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

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Pharmaco-therapeutic group: pneumococcal vaccines, ATC code: J07AL52
Synflorix® is a pneumococcal polysaccharide conjugate vaccine using protein D as the main carrier protein. Protein D is derived from Non-Typeable *Haemophilus influenzae* and is highly conserved in all *Haemophilus influenzae* strains.
1. Efficacy and effectiveness against Invasive Pneumococcal Disease (IPD) (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)
a) Immunologic non-inferiority to 7-valent pneumococcal conjugate vaccine (PCV)
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 7-valent PCV for which protective efficacy was evaluated previously. Immune responses to the extra three serotypes in *Synflorix®* were also measured.
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 three doses of 7-valent PCV. The clinical relevance of these differences is unclear, as was *Synflorix®* observed to be effective against IPD caused by serotype 6B (see Table 1) in a double-blind randomized clinical study.
The percentage of vaccinees reaching the threshold for the three additional serotypes in *Synflorix®* (1, 5 and 7F) was at least as good as the aggregate 7-valent PCV response against the 7 common serotypes (95.8%).
In the same study, *Synflorix®* and 7-valent PCV were shown to elicit functional antibodies to all serotypes contained in each vaccine with 87.7% to 100% of vaccinees reaching an OPA threshold (opsonophagocytic assay titre ≥ 8) one month post-primary or post-booster with the sole 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 as measured by ELISA and OPA for the 10 serotypes included in the vaccine demonstrating the induction of immune memory after the three-dose primary course.
b) Protective effectiveness against IPD in a clinical trial
In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), 30,528 infants less than 7 months of age at enrolment and 15,449 children aged 7 months to 18 months at enrolment were followed for invasive disease for an average of 25 and 28 months respectively and included in the analysis of effectiveness. Children were enrolled into 78 study clusters. Clusters were randomised into 4 groups according to the two infant vaccination schedules (2-dose or 3-dose primary schedule followed by a booster dose: 2+1 or 3+1 schedule) to receive either *Synflorix®* (52 clusters) or hepatitis vaccines as control (26 clusters).
Effectiveness in infant cohort below 7 months of age at enrolment
Vaccine effectiveness (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 (see Table 1).
Table 1: Number of vaccine serotype IPD cases and vaccine effectiveness in infants below 7 months of age at enrolment receiving at least one vaccine dose (Infant total vaccinated cohort)

Type of IPD	No. of IPD cases			VE (95% CI)	
	Synflorix® 3+1 schedule (N=10,273)	*Synflorix®* 2+1 schedule (N=10,054)	Control (HBV)[(2)] (N=10,201)	3+1 schedule	2+1 schedule
Vaccine serotype IPD[(1)]	0	1	12	100%[(3)](82.8;100)	91.8%[(4)] (58.3;99.6)
Serotype 6B IPD	0	0	5	100% (54.9;100)	100% (54.5;100)
Serotype 14 IPD	0	0	4	100% (39.6;100)	100% (43.3;100)

IPD Invasive Pneumococcal Disease
VE Vaccine Effectiveness
N number of subjects per group
CI Confidence Interval
(1) 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).
(2) the 2 groups of control clusters of infants were pooled
(3) p-value<0.0001
(4) p-value=0.0009
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.
Effectiveness following catch-up immunization
In the catch-up cohorts, children between 7-11 months of age at first vaccine dose received *Synflorix®* or hepatitis B 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. Among the 15,449 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).

a) Protective effectiveness against IPD in post-marketing surveillance

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 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.

2. Efficacy against Pneumonia

Efficacy against pneumonia was assessed in a large-scale randomised, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS). 23,738 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.

Efficacy of *Synflorix*® against likely bacterial Community Acquired Pneumonia (CAP) was demonstrated in the according-to-protocol (ATP) cohort (immunized with at least the three-dose primary series) (P value ≤ 0.002) as the primary objective of the study.

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
n	% (n/N)	n	% (n/N)	
240	2.3%	304	3.0%	22.0% (95% CI: 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 (observation period of 38 months), 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).

3. Efficacy against Acute Otitis Media (AOM)

In a large randomised double-blind Pneumococcal Otitis Media Efficacy Trial (POET) conducted in the Czech Republic and in Slovakia, 2,489 infants received an 11-valent investigational vaccine (11Pn-PD), containing the 10 serotypes of Synflorix along with serotype 3 for which efficacy was not demonstrated, according to a 3, 4, 5 and 12-15 months vaccination schedule.

In this study, the vaccine efficacy against AOM episodes was as follows:

Type or cause of AOM	Vaccine efficacy
Clinical AOM episodes regardless of etiology	33.6 % (95% CI: 20.8; 44.3)
AOM episodes due to any pneumococcal serotype	51.5%(95% CI: 36.8;62.9)
AOM episodes due to pneumococcal serotypes covered by the 11Pn-PD vaccine	57.6% (95% CI: 41.4;69.3)
AOM episodes due to pneumococcal serotypes covered by Synflorix	67.9% (95% CI: 53.0;78.1)
AOM episodes due to vaccine related pneumococcal serotypes	65.5% (95 % CI: 22.4;84.7)
AOM episodes caused by Hi (including NTHi)	35.6% (95% CI: 3.8; 57.0)
AOM episodes caused by NTHi only	35.3%(95% CI: 1.8;57.4)

Serotype specific efficacy against AOM episodes due to 6B, 14, 19F and 23F was demonstrated. No increase in the incidence of AOM due to other bacterial pathogens or non-vaccine serotype was observed.

4. Additional immunogenicity data

a) 3-dose primary schedule

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

In a clinical study, it has been demonstrated that *Synflorix*® can be safely administered as a booster dose in the second year of life to children who had received 3 primary doses of 7-valent PCV.

Preterm infants

Immunogenicity of *Synflorix*® in very preterm (born after a gestation period of 27-30 weeks), preterm (born after a gestation period of 31-36 weeks) and full term (born after a gestation period of more than 36 weeks) infants was evaluated following a three dose primary vaccination course at 2, 4, 6 months of age and following a booster dose at 15 to 18 months of age.

Regardless of maturity, one month after primary vaccination, at least 92.7% of subjects achieved ELISA antibody concentrations ≥ 0.2 µg/ml and at least 81.7% achieved OPA titres ≥ 8 for all vaccine serotypes, except serotype 1 (at least 58.8% with OPA titres ≥ 8). Similar antibody geometric mean concentrations (GMCs) and OPA antibody geometric mean titres (GMTs) were observed for all infants except lower antibody GMCs for serotypes 4, 5 and 9V in very preterms and serotype 9V in preterms and lower OPA GMT for serotype 5 in very preterms.

Increases of ELISA antibody GMCs and OPA GMTs were seen for all serotypes one month after the booster dose, indicative of immunological memory.

Protein D immune responses post-primary and booster vaccination were similar regardless of maturity.

b) 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 two clinical studies.

In the first study, the immunogenicity 2 months after the second dose of *Synflorix®* was compared with 7-valent PCV. The percentages of subjects reaching the ELISA antibody and OPA thresholds were within the same range for each of the 7 common serotypes except for 6B (higher for *Synflorix®)* and 18C (higher for 7-valent PCV) for the ELISA threshold.

In the second study, the immunogenicity after two or three doses of *Synflorix®* was compared. Although there was no significant impact on subjects reaching ELISA antibody threshold, a lower percentage of subjects reaching OPA threshold was observed for some serotypes in 2-dose primed subjects compared to 3-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed. In the follow-up study, the persistence of antibodies at 36-46 months of age was demonstrated in 2-dose primed subjects (at least 83.7% still had detectable antibody ≥ 0.05 µg/ml). A single challenge dose of *Synflorix®* administered during the 4th year of life, elicited higher ELISA antibody GMCs 7-10 days following vaccination in 2-dose and 3-dose primed subjects compared to unprimed subjects, indicative of an anamnestic immune response in primed subjects for all vaccine serotypes. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, in 2-dose and 3-dose primed subjects were similar.
For the vaccine-related serotypes 6A and 19A, induction of immune memory was demonstrated. For serotype 6A, a 4 fold-increase in ELISA GMCs was observed for both 2-dose and 3-dose primed subjects and for OPA GMTs, a 25 fold and a 15 fold-increase were observed in the 2 dose and the 3 dose primed subjects respectively. In unprimed subjects, there was a 1.4 fold increase in antibody GMCs and a 11 fold increase in OPA GMTs. For serotype 19A, a 11 fold and a 14 fold increase in ELISA GMCs were observed in the 2 dose and the 3 dose primed subjects respectively while for OPA GMTs, a 99 fold and a 217 fold increase were observed in 2-dose and 3-dose primed subjects respectively. In unprimed subjects, there was a 2.5 fold increase in antibody GMCs and a 39 fold increase in OPA GMTs.
A 3-dose primary schedule has shown higher response against protein D compared to a 2-dose primary schedule. Anamnestic immune responses to protein D were shown with both schedules. However, the clinical relevance of these observations remains unknown.
The clinical consequences of the lower post-primary and post-booster immune responses observed after the two-dose primary schedule are not known.
c) Catch-up
The immune responses in previously unvaccinated older children were evaluated in two clinical studies.
The first study evaluated vaccination in children aged 7-11 months, 12-23 months and 2 to 5 years.
In the 7-11 months group, children received 2 primary doses followed by a booster dose in the second year of life. The immune responses after the booster dose of *Synflorix®* were generally similar to those observed after the booster dose in infants primed with 3 doses below 6 months of age.
The immune response elicited after two doses of *Synflorix®* in children 12-23 months of age was comparable to the response elicited after three doses in infants, except for 18C and 19F.
In the 2 to 5 years group, where children received 1 dose of *Synflorix®*, the ELISA antibody GMCs for vaccine serotypes were similar to those achieved following a 3 dose vaccination schedule in infants except for 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.
The second clinical study showed that 2 doses of *Synflorix®* 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 a similar immune response for protein D.

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.

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

DOSAGE AND ADMINISTRATION
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 section Pharmacodynamics).
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 section Pharmacodynamics).

Preterm infants born after at least 27 weeks of gestational age
The recommended immunisation series consists of four doses, each of 0.5ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. A booster dose is recommended at least 6 months after the last primary dose (see section Pharmacodynamics).
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 12-23 months**: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses. The need for a booster dose after this immunisation schedule has not been established.
- **children aged 24 months – 5 years:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

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®*.
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 sections *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 vaccines. Official recommendations for the immunisations against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.
As with any vaccine, a protective immune response may not be elicited in all vaccinees.
Safety and immunogenicity data in children with increased risk for pneumococcal infections (sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.
Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.
For children at high-risk for pneumococcal disease (such as children with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised),

- the appropriate-for-age *Synflorix*® vaccination series should be given below 2 years of age (see section *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.

DRUG 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), 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%). The clinical relevance of this observation is not known. No negative interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM_{197} and TT conjugates). Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed.
As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.

ADVERSE EFFECTS

Clinical trials involved the administration of approximately 21,000 doses of *Synflorix*® to approximately 7,000 healthy children and 137 preterm infants as primary vaccination. Furthermore, approximately 5,800 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 after primary or booster vaccination were pain at the injection site and irritability. 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	Apnoea in very premature infants (≤28 weeks of gestation) (see section Warnings and Precautions), diarrhoea, vomiting, injection site reactions like injection site haematoma, haemorrhage and nodule
Rare	Allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema), crying abnormal, convulsions (including febrile convulsions), rash, urticaria
Very rare	Angioedema
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 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

Following booster vaccination, children > 12 months of age are more likely to experience injection site reactions such as rash (uncommon) and crying abnormal (uncommon) compared to the rates observed in infants during the primary series with *Synflorix*®.

STORAGE CONDITION

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

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.

Multidose vials

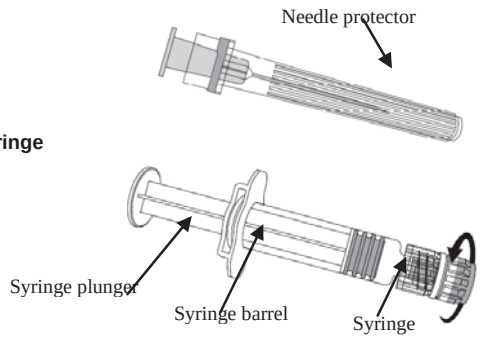
After first opening of the multidose vial, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (+2°C – +8°C). If not used within 6 hours it should be discarded.

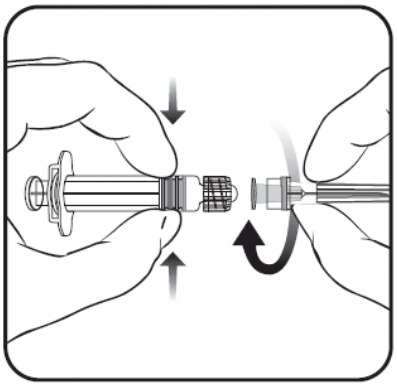
INSTRUCTIONS FOR USE/HANDLING

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





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.

AVAILABILITY

Synflorix® is presented:
- in pre-filled syringes for 1 dose (0.5 ml) with a plunger stopper (rubber butyl) with or without needles. Pack sizes of 1.
- in vials for 1 dose (0.5 ml) with a stopper (rubber butyl). Pack sizes of 10.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to US Pharmacopoeia requirements

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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GlaxoSmithKline

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