

# Synflorix™

## 1. NAME OF THE MEDICINAL PRODUCT

Synflorix™ suspension for injection in vial  
Synflorix™ suspension for injection in pre-filled syringe  
Synflorix™ suspension for injection in multidose container  
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Pneumococcal polysaccharide serotype 1 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 4 <sup>1,2</sup>	3 micrograms
Pneumococcal polysaccharide serotype 5 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 6B <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 7F <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 9V <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 14 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 18C <sup>1,3</sup>	3 micrograms
Pneumococcal polysaccharide serotype 19F <sup>1,4</sup>	3 micrograms
Pneumococcal polysaccharide serotype 23F <sup>1,2</sup>	1 microgram

<sup>1</sup> adsorbed on aluminium phosphate 0.5 milligram Al<sup>3+</sup>

<sup>2</sup> conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein 9-16 micrograms

<sup>3</sup> conjugated to tetanus toxoid carrier protein 5-10 micrograms

<sup>4</sup> conjugated to diphtheria toxoid carrier protein 3-6 micrograms

Multidose container - see section 6.5 for the number of doses per vial.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection (injection).  
The vaccine is a turbid white suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Active immunisation against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F 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.

## **4.2 Posology and method of administration**

### Posology

The immunisation schedules for Synflorix should be based on official recommendations.

#### **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 (fourth) dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age (see sections 4.4 and 5.1).

#### **Preterm newborn infants (born between 27-36 weeks gestation)**

In 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 given at 2 months of age and with an interval of at least 1 month between doses. A booster (fourth) dose is recommended at least 6 months after the last primary dose (see sections 4.4 and 5.1).

#### **Unvaccinated infants and children $\geq$ 7 months of age**

- infants aged 7-11 months: The vaccination schedule consists of two primary doses of 0.5 ml with an interval of at least 1 month between doses. A booster (third) dose is recommended in the second year of life with an interval of at least 2 months after the last primary dose.
- children aged 12 months - 5 years: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

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

### **Paediatric population**

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

### 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 young children.

## **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to any of the carrier proteins.

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.

#### 4.4 Special warnings and precautions for use

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born  $\leq 28$  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 should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Synflorix.

In children as of 2 years of age, 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.

Official recommendations for the immunisation against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

There is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine except the cross-reactive serotype 19A (see section 5.1) or against non-typeable *Haemophilus influenzae*. Synflorix does not provide protection against other micro-organisms.

As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease, pneumonia or otitis media caused by the serotypes in the vaccine and the cross-reactive serotype 19A. In addition, as otitis media and pneumonia are caused by many micro-organisms other than the *Streptococcus pneumoniae* serotypes represented by the vaccine, the overall protection against these diseases is expected to be limited and substantially lower than protection against invasive disease caused by the serotypes in the vaccine and serotype 19A (see section 5.1).

In clinical trials Synflorix elicited an immune response to all ten serotypes included in the vaccine, but the magnitude of the responses varied between serotypes. The functional immune response to serotypes 1 and 5 was lower in magnitude than the response against all other vaccine serotypes. It is not known whether this lower functional immune response against serotypes 1 and 5 will result in lower protective efficacy against invasive disease, pneumonia or otitis media caused by these serotypes (see section 5.1).

Synflorix is indicated for use in children aged from 6 weeks up to 5 years. Children should receive the dose regimen of Synflorix that is appropriate to their age at the time of commencing the vaccination series (see section 4.2). Safety and immunogenicity data are not yet available in children above 5 years of age.

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 vaccination.

Safety and immunogenicity data in children with increased risk for pneumococcal infections (e.g. sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not yet available for Synflorix. Vaccination in high-risk groups should be considered on an individual basis (see section 4.2).

Children younger than 2 years old should receive the appropriate-for-age Synflorix vaccination series (see section 4.2). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children  $\geq 2$  years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immunocompromised) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are  $\geq 24$  months of age and already primed with Synflorix should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. Clinical data generated with paracetamol and ibuprofen suggest that the prophylactic use of paracetamol might reduce the fever rate, while prophylactic use of ibuprofen showed a limited effect in reducing fever rate. The clinical data suggest that paracetamol might reduce the immune response to Synflorix. However, the clinical relevance of this observation is not known.

The use of prophylactic antipyretic medicinal products is recommended:

- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.

Antipyretic treatment should be initiated according to local treatment guidelines.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### Use with other vaccines

Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM<sub>197</sub> and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral polio vaccine (OPV) and oral 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 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 the above observations is unknown.

### Use with systemic immunosuppressive medicinal products

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

### Use with prophylactic administration of antipyretics

See section 4.4.

#### **4.6 Fertility, pregnancy and lactation**

Synflorix is not intended for use in adults. Human data on the use during pregnancy or lactation and animal reproduction studies are not available.

#### **4.7 Effects on ability to drive and use machines**

Not relevant.

#### **4.8 Undesirable effects**

##### ***Summary of the safety profile***

Safety assessment of Synflorix was based on clinical trials involving the administration of 63,905 doses of Synflorix to 22,429 healthy children and 137 preterm infants as primary vaccination. Furthermore, 19,466 children and 116 preterm infants received a booster dose of Synflorix in the second year of life.

Safety was also assessed in 435 previously unvaccinated children from 2 to 5 years old of which 285 subjects received 2 doses of Synflorix.

In all trials, Synflorix was administered concurrently with the recommended childhood vaccines.

In infants, 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.

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

Local reactogenicity of primary vaccination course was similar in infants < 12 months of age and in children > 12 months of age except for injection site pain for which the incidence increased with increasing age: pain was reported by more than 39% of the infants < 12 months of age and by more than 58% of the children > 12 months of age.

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.

Reactogenicity was higher in children receiving whole cell pertussis vaccines concomitantly. In a clinical study children received either Synflorix (N=603) or 7-valent Prevenar (N=203) concomitantly with a DTPw containing vaccine. After the primary vaccination course, fever  $\geq 38^{\circ}\text{C}$  and  $> 39^{\circ}\text{C}$  was reported respectively in 86.1% and 14.7% of children receiving Synflorix and in 82.9% and 11.6% of children vaccinated with 7-valent Prevenar.

In comparative clinical studies, the incidence of local and general adverse events reported within 4 days after each vaccination dose was within the same range as after vaccination with 7-valent Prevenar.

##### ***Tabulated list of adverse reactions***

Adverse reactions (for all age groups) considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:

Very common: ( $\geq 1/10$ )

Common: ( $\geq 1/100$  to  $< 1/10$ )

Uncommon: ( $\geq 1/1,000$  to  $< 1/100$ )

Rare: ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare: ( $< 1/10,000$ )

System Organ Class	Frequency	Adverse reactions
<b>Clinical trials</b>		
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 in very premature infants ( $\leq 28$ weeks of gestation) (see section 4.4)
Gastrointestinal disorders	Uncommon	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Urticaria
General disorders and administration site conditions	Very common	Pain, redness, swelling at the injection site, fever $\geq 38^{\circ}\text{C}$ rectally (age $< 2$ years)
	Common	Injection site reactions like injection site induration, fever $> 39^{\circ}\text{C}$ rectally (age $< 2$ years)
	Uncommon	Injection site reactions like injection site haematoma, haemorrhage and nodule
<i>Adverse reactions additionally reported after booster vaccination of primary series and/or catch-up vaccination:</i>		
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 $\geq 38^{\circ}\text{C}$ rectally (age 2 to 5 years)
	Uncommon	Injection site reactions like pruritus, fever $> 40^{\circ}\text{C}$ rectally (age $< 2$ years), fever $> 39^{\circ}\text{C}$ rectally (age 2 to 5 years), diffuse swelling of the injected limb, sometimes involving the adjacent joint
<b>Post-marketing experience</b>		
Immune system disorders	Very rare	Anaphylaxis
Nervous system disorders	Rare	Hypotonic-hyporesponsive episode

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

Additionally, you should also report to GSK Israel ([il.safety@gsk.com](mailto:il.safety@gsk.com))

## 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines, ATC code: J07AL52

#### **1. Epidemiological data**

The 10 pneumococcal serotypes included in this vaccine represent the major disease-causing serotypes in Europe covering approximately 56% to 90% of invasive pneumococcal disease (IPD) in children <5 years of age. In this age group, serotypes 1, 5 and 7F account for 3.3% to 24.1% of IPD depending on the country and time period studied.

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 pneumonia cases.

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and Non-Typeable *Haemophilus influenzae* (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 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 (2/3<sup>rd</sup> of clusters) or hepatitis vaccines as control (1/3<sup>rd</sup> 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 and hospital-diagnosed pneumonia. In a nested study, infants were followed up till approximately 21 months of age to assess impact on nasopharyngeal carriage and physician-diagnosed AOM reported by parents.

In a large-scale phase III, randomized, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS) conducted in Argentina, Panama and Colombia, 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. Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)**

*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 N 10,273	Synflorix 2+1 schedule N 10,054	Control <sup>(2)</sup> N 10,200	3+1 schedule	2+1 schedule	Synflorix 3+1 schedule N 11,798	Control N 11,799	3+1 schedule
Vaccine serotype IPD <sup>(1)</sup>	0	1	12	100% <sup>(3)</sup> (82.8; 100)	91.8% <sup>(4)</sup> (58.3; 99.6)	0	18	100% <sup>(5)</sup> (77.3;100)
Serotype 6B IPD	0	0	5	100% (54.9; 100)	100% (54.5; 100)	0	2	-
Serotype 14 IPD	0	0	4	100% (39.6; 100)	100% (43.3; 100)	0	9	100% (49.5;100)

IPD Invasive Pneumococcal Disease

VE Vaccine effectiveness (FinIP) or efficacy (COMPAS)

N number of subjects per group

CI Confidence Interval

- (1) In FinIP apart from serotypes 6B and 14, culture-confirmed vaccine serotype IPD cases included 7F (1 case in the Synflorix 2+1 clusters), 18C, 19F and 23F (1 case of each in the control clusters). In COMPAS, serotypes 5 (2 cases), 18C (4 cases) and 23F (1 case) were detected in control group in addition to serotypes 6B and 14.
- (2) the 2 groups of control clusters of infants were pooled
- (3) p-value<0.0001
- (4) p-value=0.0009
- (5) in the ATP cohort VE was 100% (95% CI: 74.3-100; 0 versus 16 cases)

In FinIP the overall observed VE against culture-confirmed IPD 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 5 vaccine serotype IPD cases were observed in the control groups (serotypes 4, 6B, 7F, 14 and 19F).

## **2.2 Pneumonia**

Efficacy against pneumonia was assessed in COMPAS. The mean duration follow-up from 2 weeks post-dose 3 in the ATP cohort was 23 months (range from 0 to 34 months) for the interim analysis (IA) and 30 months (range from 0 to 44 months) for the end-of-study analysis. At the end of this IA or end-of-study ATP follow-up period, the mean age was 29 months (range from 4 to 41 months) and 36 months (range from 4 to 50 months), respectively. The proportion of subjects who received the booster dose in the ATP cohort was 92.3% in both analyses.

Efficacy of Synflorix against first episodes of likely bacterial Community Acquired Pneumonia (CAP) occurring from 2 weeks after the administration of the 3rd dose was demonstrated in the ATP cohort (P value ≤ 0.002) in the interim analysis (event-driven; primary objective).

Likely bacterial CAP (B-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 B-CAP observed at the interim analysis is presented below (table 2).



**Table 2: Numbers and percentages of subjects with first episodes of B-CAP occurring from 2 weeks after the administration of the 3rd dose of Synflorix or control vaccine and vaccine efficacy (ATP cohort)**

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/percentage of subjects reporting a first episode of B-CAP anytime from 2 weeks after the administration of the 3<sup>rd</sup> dose

CI Confidence Interval

In the interim analysis (ATP cohort), the vaccine efficacy against first episodes of CAP with alveolar consolidation or pleural effusion (C-CAP, WHO definition) was 25.7% (95% CI: 8.4; 39.6) and against first episodes of clinically suspected CAP referred for X-ray was 6.7% (95% CI: 0.7; 12.3).

At the end-of-study analysis (ATP cohort), the vaccine efficacy (first episodes) against B-CAP was 18.2% (95% CI: 4.1; 30.3), against C-CAP 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). Efficacy was 100% (95% CI: 41.9; 100) against bacteraemic pneumococcal pneumonia or empyema due to vaccine serotypes. The protection against B-CAP before booster dose and at the time or after booster dose was 13.6% (95% CI: -11.3; 33.0) and 21.7% (95% CI: 3.4; 36.5) respectively. For C-CAP it was 15.1% (95% CI: -15.5; 37.6) and 26.3% (95% CI: 4.4; 43.2) respectively.

The reduction in B-CAP and C-CAP was greatest in children < 36 months of age (vaccine efficacy of 20.6% (95% CI: 6.5; 32.6) and 24.2% (95% CI: 7.4; 38.0) respectively). Vaccine efficacy results in children > 36 months of age suggest a waning of protection. The persistence of protection against B-CAP and C-CAP beyond the age of 36 months is currently not established.

The results of the COMPAS study, which was performed in Latin America, should be interpreted with caution due to possible differences in epidemiology of pneumonia in different geographical locations.

In the FinIP study, vaccine effectiveness in reducing hospital-diagnosed pneumonia cases (identified based on the ICD 10 codes for pneumonia) was 26.7% (95% CI: 4.9; 43.5) in the 3+1 infant schedule and 29.3% (95% CI: 7.5; 46.3) in the 2+1 infant schedule. For catch-up vaccination, vaccine effectiveness was 33.2% (95% CI: 3.0; 53.4) in the 7-11 month cohort and 22.4% (95% CI: -8.7; 44.8) in the 12-18 month cohort.

### **2.3. Acute Otitis Media (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<sup>(1)</sup> in COMPAS**

Type or cause of AOM	Vaccine efficacy (95% CI)
	ATP <sup>(2)</sup>
Clinical AOM	16.1% (-1.1;30.4) <sup>(3)</sup>
Any pneumococcal serotype	56.1% (13.4;77.8)
10 pneumococcal vaccine serotypes	67.1%

	(17.0; 86.9)
Non-typeable <i>Haemophilus influenzae</i> (NTHi)	15.0% <sup>(4)</sup> (-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 first clinical AOM episode was 19% (95% CI: 4.4;31.4).
- (4) Not statistically significant.

In another large randomised double-blind trial (POET) conducted in the Czech Republic and in Slovakia, 4,907 infants (ATP cohort) received either the 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of Synflorix (along with serotype 3 for which efficacy was not demonstrated) or a control vaccine (hepatitis A vaccine) according to a 3, 4, 5 and 12-15 months vaccination schedule.

Efficacy of the 11 Pn-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 episode was demonstrated for serotypes 6B (86.5%, 95% CI: 54.9;96.0), 14 (94.8%, 95% CI: 61.0;99.3), 19F (43.3%, 95% CI: 6.3;65.4) and 23F (70.8%, 95% CI: 20.8;89.2). For other vaccine serotypes, the number of AOM cases was too limited to allow any efficacy conclusion to be drawn. Efficacy against any AOM episode due to any pneumococcal serotype was 51.5% (95% CI: 36.8;62.9). The vaccine efficacy against the first episode of NTHi AOM was 31.1% (95% CI: -3.7; 54.2, not significant). Efficacy against any NTHi AOM episode was 35.3% (95% CI: 1.8; 57.4). The estimated vaccine efficacy against any clinical episodes of otitis media regardless of aetiology was 33.6% (95% CI: 20.8; 44.3).

Based on immunological bridging of the functional vaccine response (OPA) of Synflorix with the 11-valent formulation used within POET, it is expected that Synflorix provides similar protective efficacy against pneumococcal AOM.

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

Effectiveness against physician-diagnosed AOM reported by parents was studied in the nested study within the FinIP trial. Vaccine effectiveness was 6.1% (95% CI: -2.7; 14.1) for the 3+1 schedule and 7.4% (95% CI -2.8; 16.6) for 2+1 schedule for this AOM endpoint in the infant vaccinated cohort.

## **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 (5,023 subjects) and in COMPAS (1,700 subjects).

In both COMPAS and the nested Finnish study, Synflorix reduced vaccine type carriage with an apparent increase in non-vaccine (excluding vaccine-related) serotypes observed after booster. The results were not statistically significant across all analyses in COMPAS. However, taken together there was a trend for decrease in overall pneumococcal carriage.

In both studies there were significant decrease of individual serotypes 6B and 19F. In the nested Finnish study, a significant reduction was also observed for individual serotypes 14, 23F and, in the 3 dose primary schedule, for the cross-reactive serotype 19A.

## **3. Effectiveness in post-marketing surveillance**

In Brazil, Synflorix was introduced into the national immunization programme (NIP) 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 4: Summary of effectiveness of Synflorix for IPD in Brazil**

<b>Types of IPD<sup>(1)</sup></b>	<b>Adjusted Effectiveness<sup>(2)</sup> % (95% CI)</b>
Any vaccine serotype IPD <sup>(3)</sup>	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 <sup>(4)</sup>	
- 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 the effectiveness analysis controlling for confounding factors (no adjustment for multiplicity performed).

In Finland, Synflorix was introduced into NIP 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 5: Rates of IPD and the corresponding rate reductions in Finland**

<b>IPD</b>	<b>Incidence per 100,000 person years</b>		<b>Relative rate reduction<sup>(1)</sup> % (95% CI)</b>
	<b>Before NIP</b>	<b>After NIP</b>	
Any culture confirmed	62.9	12.9	80% (72;85)
Any vaccine serotype <sup>(2)</sup>	49.1	4.2	92% (86;95)
Serotype 19A	5.5	2.1	62% (20;85)

(1) The relative rate reduction indicates how much the incidence of IPD in children of ≤5 years of age was reduced in the Synflorix cohort (followed for 3 years after NIP introduction) versus age and season matched non-vaccinated historical cohorts (each followed for 3 year periods before introduction of Synflorix into NIP).

(2) 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 Prevenar. 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. Overall, the incidence of IPD was 35/100,000 person-years in those cohorts exposed to Synflorix, and 64/100,000 person-years in those exposed to 7-valent Prevenar, representing a statistically significant difference ( $p = 0.03$ ). No direct cause-and-effect can be inferred from observational studies of this type.

## 4. Immunogenicity data

### 4.1 Immunologic non-inferiority to 7-valent Prevenar

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 Prevenar), as recommended by the WHO. Immune responses to the extra three serotypes in Synflorix were also measured.

In a head-to-head comparative trial with 7-valent Prevenar, 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%) (Table 56). 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 7-valent Prevenar. 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, cluster-randomized 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 Prevenar response against the 7 common serotypes (95.8%).

**Table 6: Comparative analysis between 7-valent Prevenar and Synflorix in percentage of subjects with antibody concentrations  $\geq 0.20$  µg/ml one month post-dose 3**

Antibody	SYNFLORIX		7-valent Prevenar		Difference in % $\geq 0.20$ µg/ml (7-valent Prevenar minus SYNFLORIX)		
	N	%	N	%	%	96.5% CI	
Anti-4	1106	97.1	373	100	2.89	1.71	4.16
Anti-6B	1100	65.9	372	79.0	13.12	7.53	18.28
Anti-9V	1103	98.1	374	99.5	1.37	-0.28	2.56
Anti-14	1100	99.5	374	99.5	-0.08	-1.66	0.71
Anti-18C	1102	96.0	374	98.9	2.92	0.88	4.57
Anti-19F	1104	95.4	375	99.2	3.83	1.87	5.50
Anti-23F	1102	81.4	374	94.1	12.72	8.89	16.13

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by 7-valent Prevenar. 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 7-valent Prevenar.

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 Prevenar vaccinees reached an OPA titre  $\geq 8$  one month after the third dose. The difference between both vaccines in terms of percentage of subjects with OPA titres  $\geq 8$  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 7-valent Prevenar for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre  $\geq 8$  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.

It has also been demonstrated that Synflorix induces an immune response to the cross-reactive serotype 19A with 48.8% (95% CI: 42.9;54.7) of vaccinees reaching an OPA titre  $\geq 8$  one month after a booster dose.

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 vaccine serotypes and the cross-reactive serotype 19A demonstrating the induction of immune memory after the three-dose primary course.

## 4.2 Additional immunogenicity data

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

In total eight studies, conducted in various countries across Europe, in Chile and in the Philippines, have evaluated the immunogenicity of Synflorix after a three-dose primary series (N=3,089) 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 six clinical studies to 1,976 subjects. In general, comparable vaccine responses were observed for the different schedules, although somewhat higher immune responses were noted for the 2-4-6 month schedule.

The immunogenicity of Synflorix following a 2-dose or 3-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  $\geq 0.20$   $\mu\text{g/mL}$  (ELISA), the percentages of subjects for serotypes 6B and 23F were lower than for the other vaccine serotypes (Table 7 and Table 8). The percentage of subjects with OPA titres  $\geq 8$  in 2-dose primed subjects compared to 3-dose primed subjects were lower for serotypes 6B, 18C and 23F (74.4%, 82.8%, 86.3% respectively for the 2-dose schedule and 88.9%, 96.2%, 97.7% respectively for the 3-dose schedule). Overall, the persistence of the immune response until the booster at 11 months of age was lower in the 2-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed for each vaccine serotype (Table 7 and Table 8). After the booster dose a lower percentage of subjects with OPA titres  $\geq 8$  was observed in the 2-dose schedule for serotypes 5 (87.2% versus 97.5% for the 3-dose primed subjects) and 6B (81.1% versus 90.3%), all other responses were comparable.

**Table 7: Percentage of 2-dose primed subjects with antibody concentrations  $\geq 0.20$   $\mu\text{g/mL}$  one month post-primary and one month post-booster**

Antibody	$\geq 0.2\mu\text{g/mL}$ (ELISA)					
	Post-primary			Post-booster		
	%	95% CI		%	95% CI	
Anti-1	97.4	93.4	99.3	99.4	96.5	100
Anti-4	98.0	94.4	99.6	100	97.6	100
Anti-5	96.1	91.6	98.5	100	97.6	100
Anti-6B	55.7	47.3	63.8	88.5	82.4	93.0
Anti-7F	96.7	92.5	98.9	100	97.7	100
Anti-9V	93.4	88.2	96.8	99.4	96.5	100
Anti-14	96.1	91.6	98.5	99.4	96.5	100
Anti-18C	96.1	91.6	98.5	100	97.7	100
Anti-19F	92.8	87.4	96.3	96.2	91.8	98.6
Anti-23F	69.3	61.3	76.5	96.1	91.7	98.6

**Table 8: Percentage of 3-dose primed subjects with antibody concentrations  $\geq 0.20$   $\mu\text{g/mL}$  one month post-primary and one month post-booster**

Antibody	$\geq 0.2\mu\text{g/mL}$ (ELISA)
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	Post-primary			Post-booster		
	%	95% CI		%	95% CI	
Anti-1	98.7	95.3	99.8	100	97.5	100
Anti-4	99.3	96.4	100	100	97.5	100
Anti-5	100	97.6	100	100	97.5	100
Anti-6B	63.1	54.8	70.8	96.6	92.2	98.9
Anti-7F	99.3	96.4	100	100	97.5	100
Anti-9V	99.3	96.4	100	100	97.5	100
Anti-14	100	97.6	100	98.6	95.2	99.8
Anti-18C	99.3	96.4	100	99.3	96.3	100
Anti-19F	96.1	91.6	98.5	98.0	94.2	99.6
Anti-23F	77.6	70.2	84.0	95.9	91.3	98.5

For the cross-reactive serotype 19A, similar ELISA antibody GMCs were observed post-primary and post-booster for the 2 dose schedule (0.14 µg/ml (95% CI: 0.12;0.17) and 0.73 µg/ml (95% CI: 0.58;0.92)) and the 3 dose schedule (0.19 µg/ml (95% CI: 0.16;0.24) and 0.87 µg/ml (95% CI: 0.69;1.11)). The percentage of subjects with OPA titres  $\geq 8$  and GMTs observed post-primary and post-booster were lower in the 2 dose schedule than that in the 3 dose schedule. In both schedules, a booster response indicative of immunological priming was observed.

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

#### *Immune memory*

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 subjects that had received a 2-dose primary series followed by a booster dose with at least 83.7% of subjects remaining seropositive for vaccine serotypes and the cross-reactive serotype 19A. In subjects that had received a 3-dose primary series followed by a booster dose, at least 96.5% of the subjects remained seropositive for vaccine serotypes and 86.4% for serotype 19A. After a single dose of Synflorix, administered during the 4th year of life, as a challenge dose, the fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, was similar in 2-dose primed subjects to that in 3-dose primed subjects. These results are indicative of immunological memory in primed subjects for all vaccine serotypes and the cross-reactive serotype 19A.

#### Unvaccinated infants and children $\geq 7$ months of age

The immune responses elicited by Synflorix in previously unvaccinated older children were evaluated in three clinical studies.

The first clinical study evaluated the immune responses for vaccine serotypes and the cross-reactive serotype 19A in children aged 7-11 months, 12-23 months and 2 to 5 years:

- Children aged 7-11 months received 2 primary doses followed by a booster dose in the second year of life. The immune responses after the booster dose in this age group were generally similar to those observed after the booster dose in infants who had been primed with 3 doses below 6 months of age.
- In children aged 12-23 months, the immune responses elicited after two doses were comparable to the responses elicited after three doses in infants below 6 months of age, except for vaccine serotypes 18C and 19F as well as serotype 19A for which responses were higher in the 12-23 months children.
- In children aged 2 to 5 years that received 1 dose, the ELISA antibody GMCs were similar for 6 vaccine serotypes as well as serotype 19A than those achieved following a 3-dose vaccination schedule in infants below 6 months of age while they were lower for 4 vaccine serotypes (serotypes 1, 5, 14 and 23F). The OPA GMTs were similar or higher

following a single dose than a 3 dose primary course in infants below 6 months of age, except for serotype 5.

In the second clinical study, a single dose administered four months after two catch-up doses at 12-20 months of age elicited a marked increase of ELISA GMCs and OPA GMTs (when comparing the responses pre and post the last dose), indicating that two catch-up doses provide adequate priming.

The third clinical study showed that 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. The proportion of subjects with an ELISA antibody concentration  $\geq 0.20 \mu\text{g/mL}$  or an OPA titre  $\geq 8$  for each vaccine serotype was comparable or higher in the catch-up group than in the 3-dose primed infants.

Long-term persistence of antibodies has not been investigated after administration of a primary series in infants plus booster or after a two-dose priming in older children.

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 Prevenar. This study has shown that the immune responses against the 7 common serotypes were comparable to those elicited by a booster dose of 7-valent Prevenar. However, children who received 7-valent Prevenar for the primary series would not be primed against the additional serotypes contained in Synflorix (1, 5, 7F). Therefore the degree and duration of protection against invasive pneumococcal disease and otitis media due to these three serotypes in children of this age group following a single dose of Synflorix cannot be predicted.

#### **4.3. Immunogenicity data in preterm infants**

Immunogenicity of Synflorix in very preterm (gestation period of 27-30 weeks) (N=42), preterm (gestation period of 31-36 weeks) (N=82) and full term (gestation period > 36 weeks) (N=132) infants was evaluated following a 3 dose primary vaccination course at 2, 4, 6 months of age. Immunogenicity following a fourth dose (booster dose) at 15 to 18 months of age was evaluated in 44 very preterm, 69 preterm and 127 full term infants.

One month after primary vaccination (i.e. after the third dose), for each vaccine serotype at least 92.7% of subjects achieved ELISA antibody concentrations  $\geq 0.2 \mu\text{g/mL}$  and at least 81.7% achieved OPA titres  $\geq 8$  except serotype 1 (at least 58.8% with OPA titres  $\geq 8$ ). 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. The clinical relevance of these differences is not known.

One month after the booster dose increases of ELISA antibody GMCs and OPA GMTs were seen for each vaccine serotype and the cross-reactive serotype 19A, 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  $\geq 0.2 \mu\text{g/mL}$  and at least 91.9% achieved OPA titres  $\geq 8$ .

The European Medicines Agency has deferred the obligation to submit the results of studies with Synflorix in one or more subsets of the paediatric population in diseases caused by *Streptococcus pneumoniae* and in acute otitis media caused by *Haemophilus influenzae* (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not available for vaccines.

### **5.3 Preclinical safety data**

Studies with an 11-valent vaccine formulation representative for Synflorix revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride  
Water for injections

For adsorbent, see section 2.

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

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

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.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).

Do not freeze.

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

Multidose vial

For storage conditions after first opening of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

#### **Pre-filled syringe:**

0.5 ml suspension in a pre-filled syringe (type I glass) with a stopper (butyl rubber) with or without needles. Pack size of 1 or 10.

#### **Vial:**

0.5 ml suspension in a vial (type I glass) with a stopper (butyl rubber). Pack size of 1, 10 or 100.

#### **Multidose vial:**

1 ml suspension in a vial (type I glass) with a stopper (butyl rubber) for 2 doses. Pack size x 100.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

The content of the vial or the pre-filled syringe 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.



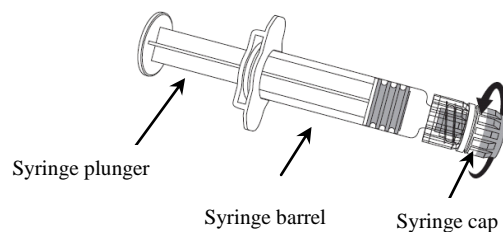
The vaccine should be allowed to reach room temperature before use.

The vaccine should be well shaken before use.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

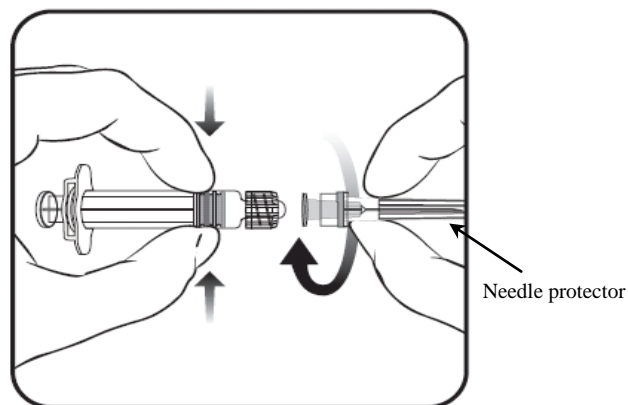
### Instructions for administration of the vaccine presented in pre-filled syringe

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock.

3. Remove the needle protector, which on occasion can be a little stiff.



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

### **7. MANUFACTURER**

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium.

### **8. LICENSE HOLDER**

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

### **9. LICENSE NUMBER**

142-81-32006

*Syn DR v6*