**Synflorix™**

1. **NAME OF THE MEDICINAL PRODUCT**

1.1 **Product Name**

*Synflorix™*

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

1.2 **Pharmaceutical Dosage Form**

Suspension for injection.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One dose (0.5 ml) contains 1 microgram of polysaccharide for serotypes 1\(^1\), 2\(^1\), 5\(^1\), 6B\(^1\), 7F\(^1\), 9V\(^1\), 14\(^1\), and 23F\(^1\), and 3 micrograms for serotypes 4\(^1\), 18C\(^1\), and 19F\(^1\).

1. adsorbed on aluminium phosphate

2. conjugated to protein D (derived from NTHi) carrier protein

3. conjugated to tetanus toxoid carrier protein

4. conjugated to diphtheria toxoid carrier protein

3. **PHARMACEUTICAL FORM**

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

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

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

4.2 **Posology and Method of Administration**

Official recommendations should be taken into account when immunizing with *Synflorix™*.

**Posology**

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

3-dose primary series

An immunization series of 4 doses, each of 0.5 ml, is recommended to ensure optimal protection: 3 primary doses with an interval of at least 1 month between doses and a booster dose at least 6 months after the last primary dose. The first dose may be given as early as 6
weeks of age and the booster dose from the age of 9 months onwards (see section 5.1 Pharmacodynamic properties).

2-dose primary series
Alternatively, when Synflorix™ is given as part of a routine infant immunization programme, a series of 3 doses, each of 0.5 ml, may be given: 2 primary doses given 2 months apart and a booster dose at least 6 months after the last primary dose. The first dose may be given as early as 6 weeks of age and the booster dose from the age of 9 months onwards (see section 5.1 Pharmacodynamic properties).

Preterm infants born after at least 27 weeks of gestational age
An immunization series of 4 doses, each of 0.5 ml, is recommended: 3 primary doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses with a booster dose at least 6 months after the last primary dose (see section 5.1 Pharmacodynamic properties).

Previously unvaccinated older infants and children:
- 7-11 months of age: 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.
- 12 months-5 years of age: 2 doses of 0.5 ml with an interval of at least 2 months between doses.

Special populations:
In individuals who have underlying conditions predisposing them to invasive pneumococcal disease (such as sickle cell disease (SCD), HIV infection or splenic dysfunction) Synflorix™ may be given (see section 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties):
- in infants as described under “Three-dose primary series” above.
- in unvaccinated children ≥7 months of age and under 2 years of age as described under “Previously unvaccinated older infants and children” above.

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

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

4.3 Contra-indications
Synflorix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see sections 2. Qualitative and quantitative composition and 6.1 List of excipients).
4.4 Special Warnings and Precautions for Use

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

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

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

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

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

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

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 are available for HIV infected infants, children with SCD and children with splenic dysfunction (see sections 4.6 Undesirable Effects and 5.1 Pharmacodynamic properties). Safety and immunogenicity data for Synflorix™ are not available for individuals in other specific immunocompromised groups and vaccination should be considered on an individual basis.

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

For children at high-risk for pneumococcal disease (such as children with SCD, asplenia, HIV infection, chronic illness or those who have other immunocompromising conditions),

- the appropriate-for-age Synflorix™ vaccination series should be given below 2 years of age (see section 4.2 Posology and method of administration).
• a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age according to local recommendations.

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Synflorix™ can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine, meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (MenACWY-TT), 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 (seroprotection ranging from 78% to 100% across studies) and MenACWY-TT vaccine when co-administered with a booster dose of Synflorix™ following a 3 doses primary series (lower antibody geometric mean concentration (GMC) and opsonophagocytic assay geometric mean titre (OPA GMT) for pneumococcal 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.

4.6 Undesirable Effects

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.

Adverse reactions reported (for all age groups) are listed according to the following frequency:

Very common: \( \geq \frac{1}{10} \)
Common: \( \geq \frac{1}{100} \) to \( < \frac{1}{10} \)
Uncommon: \( \geq \frac{1}{1,000} \) to \( < \frac{1}{100} \)
Rare: \( \geq \frac{1}{10,000} \) to \( < \frac{1}{1,000} \)
Very rare: \( < \frac{1}{10,000} \)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Appetite lost, irritability, drowsiness, pain, redness, swelling at the injection site, fever ( \geq 38^\circ )C rectally (age ( &lt; 2 ) years)</td>
</tr>
<tr>
<td>Common</td>
<td>Injection site reactions like injection site induration, fever ( &gt; 39^\circ )C rectally (age ( &lt; 2 ) years)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Crying abnormal, apnoea in very premature infants (( \leq 28 ) weeks of gestation) (see section 4.4 Special warnings and precautions for use), diarrhoea, vomiting, rash, injection site reactions like injection site haematoma, haemorrhage and nodule</td>
</tr>
<tr>
<td>Rare</td>
<td>Allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema), convulsions (including febrile convulsions), urticaria(1)</td>
</tr>
<tr>
<td>Very rare</td>
<td>Angioedema, Kawasaki disease</td>
</tr>
</tbody>
</table>

Adverse reactions additionally reported after booster vaccination of primary series and/or catch-up vaccination:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Fever ( \geq 38^\circ )C rectally (age 2 to 5 years)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Injection site reactions(2) like pruritus, diffuse swelling of the injected limb, sometimes involving the adjacent joint; age ( &lt; 2 ) years: fever ( &gt; 40^\circ )C rectally; age 2 to 5 years: headache, nausea and fever ( &gt; 39^\circ )C rectally</td>
</tr>
</tbody>
</table>

Post-marketing experience

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Hypotonic-hyporesponsive episode</td>
</tr>
<tr>
<td>Very rare</td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

(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.

Safety of *Synflorix™* was assessed in 83 HIV positive infants, 101 HIV negative infants born from an HIV positive mother and 150 children with SCD. Results suggest comparable
reactogenicity and safety profile of Synflorix™ between these high risk groups and healthy children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

1. Efficacy and effectiveness in clinical trials

In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), children received either Synflorix™ or control vaccines according to a 3+1 or 2+1 infant schedule (3-4-5 months of age or 3-5 months of age with booster at 11 months).

In the catch-up cohorts, children 7-11 months of age or 12-18 months of age at first vaccine dose received either Synflorix™ or control vaccines according to the appropriate-for-age Synflorix™ vaccination schedule.

In a large-scale phase III, randomized, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS), infants aged 6 to 16 weeks received either Synflorix™ or the control vaccine according to a 3+1 schedule (2-4-6 months of age with booster at 15-18 months).

1.1 Invasive Pneumococcal Disease (IPD)

Infant cohort below 7 months of age at enrolment

Vaccine effectiveness (in FinIP) or efficacy (in COMPAS) was demonstrated in preventing culture-confirmed IPD due to vaccine serotypes (Table 1).

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

<table>
<thead>
<tr>
<th>Type of IPD</th>
<th>No. of cases</th>
<th>FinIP</th>
<th></th>
<th></th>
<th></th>
<th>COMPAS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synflorix™</td>
<td>Synflorix™</td>
<td>Control(2)</td>
<td></td>
<td></td>
<td>Synflorix™</td>
<td>Control(2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3+1 schedule</td>
<td>2+1 schedule</td>
<td></td>
<td></td>
<td></td>
<td>3+1 schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Vaccine serotype (1)</td>
<td>10,273</td>
<td>10,054</td>
<td>10,200</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
</tr>
<tr>
<td>3+1 schedule</td>
<td>10,273</td>
<td>10,054</td>
<td>10,200</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
</tr>
<tr>
<td>2+1 schedule</td>
<td>10,054</td>
<td>10,054</td>
<td>10,200</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
<td>11,799</td>
<td>11,798</td>
</tr>
<tr>
<td>100%(3)</td>
<td>91.8%(4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(82.8;100)</td>
<td>(58.3;99.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(77.3;100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotype 6B</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(54.9;100)</td>
<td>(54.5;100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(49.5;100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotype 14</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(39.6;100)</td>
<td>(43.3;100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(49.5;100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serotype</td>
<td>0</td>
<td>2</td>
<td>14</td>
<td>7</td>
<td>21</td>
<td>66.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%(5)</td>
<td>85.8%(5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(21.8;85.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(85.6;100)</td>
<td>(49.1;97.8)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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 (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 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

**Catch-up cohorts**

Among the 15,447 children in the catch-up cohorts, there were no culture-confirmed IPD cases in the Synflorix™ groups while 7 IPD cases were observed in the control groups (2 and 5 cases in the 7-11 months and 12-18 months cohorts respectively).

**1.2. Pneumonia**

Vaccine efficacy of Synflorix™ against likely bacterial Community Acquired Pneumonia (CAP), ie. 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, 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.

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 an 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. 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)**

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

<table>
<thead>
<tr>
<th>Type or cause of AOM</th>
<th>Vaccine efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AOM regardless of aetiology</td>
<td>16.1%</td>
<td>-1.1; 30.4(3)</td>
</tr>
<tr>
<td>Any pneumococcal serotype</td>
<td>56.1%</td>
<td>13.4; 77.8</td>
</tr>
<tr>
<td>10 pneumococcal vaccine serotypes</td>
<td>67.1%</td>
<td>17.0; 86.9</td>
</tr>
<tr>
<td>Vaccine-related pneumococcal serotypes</td>
<td>25.7%</td>
<td>-232.2; 83.4</td>
</tr>
<tr>
<td>Non-vaccine/non-vaccine related pneumococcal serotypes</td>
<td>25.7%</td>
<td>-231.9; 83.4</td>
</tr>
<tr>
<td>NTHi</td>
<td>15.0%</td>
<td>-83.8; 60.7</td>
</tr>
</tbody>
</table>

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

Table 3: Vaccine efficacy against AOM\(^{(2)}\) in POET\(^{(1)}\) (ATP\(^{(3)}\); 4,907 subjects)

<table>
<thead>
<tr>
<th>Type or cause of AOM</th>
<th>Vaccine efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AOM regardless of aetiology</td>
<td>33.6%</td>
<td>20.8;44.3</td>
</tr>
<tr>
<td>Any pneumococcal serotype</td>
<td>51.5%</td>
<td>36.8;62.9</td>
</tr>
<tr>
<td>10 pneumococcal serotypes in common with Synflorix™</td>
<td>67.9%</td>
<td>53.0;78.1</td>
</tr>
<tr>
<td>Vaccine-related pneumococcal serotypes</td>
<td>65.5%</td>
<td>22.4;84.7</td>
</tr>
<tr>
<td>Non-vaccine/non-vaccine related pneumococcal serotypes</td>
<td>8.5%</td>
<td>-64.2;49.0</td>
</tr>
<tr>
<td>NTHi</td>
<td>35.3%</td>
<td>1.8;57.4</td>
</tr>
</tbody>
</table>

CI: Confidence Interval
\(^{(1)}\) Large randomised double-blind trial in the Czech Republic and Slovakia where infants received either an 11-valent investigational vaccine 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 schedule.
\(^{(2)}\) All episodes
\(^{(3)}\) Follow up period for a maximum of 24 months from 2 weeks after third primary dose

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

**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 serotype 19A.

In a clinical study assessing NPC in HIV positive infants (HIV+/+, N = 83) and HIV negative infants born from an HIV positive mother (HIV+/-, N = 101), the HIV exposure or infection did not appear to alter the effect of Synflorix™ on pneumococcal carriage when compared to the effect in HIV negative infants born from an HIV negative mother (HIV-/-, N = 100).
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 ≤ 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 ≤ 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. 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 ELISA antibody threshold (i.e. 0.20 µg/ml) 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.

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%).

Immunological memory was shown for all vaccine serotypes after a booster dose in the second year of life.

It has also been demonstrated that **Synflorix™** induces an immune response to serotype 19A with 6.1 fold increases in both antibody 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

In clinical trials, the immunogenicity of Synflorix™ was evaluated after a 2- or 3-dose primary course according to different schedules (6-14 weeks, 2-4, 3-5 months of age or 6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age) and after a booster dose given at least 6 months after the last primary dose and from the age of 9 months onwards.

In a clinical study which evaluated the immunogenicity of Synflorix™ in 2-dose or 3-dose primed subjects, 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 and serotypes 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.

A study in South Africa assessed the immunogenicity of Synflorix™ given as a booster dose at 9 to 10 months of age after a 3-dose (6-10-14 weeks of age) or 2-dose (6-14 weeks of age) priming. The booster dose induced marked increases in antibody GMCs and OPA GMTs for each vaccine serotype and serotype 19A in both groups, indicative of immunological priming.

Immune memory

After a single challenge dose of Synflorix™ in the 4th year of life, similar anamnestic immune response was observed for all vaccine serotypes and 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), antibody GMCs and OPA GMTs for vaccine serotypes and 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 vaccine serotypes 4, 5, 9V and serotype 19A and lower OPA GMT for serotype 5.

Immunological memory was shown for each vaccine serotype and serotype 19A one month after the booster dose.
3.5 Immunogenicity in special populations.

In a clinical study in South Africa, Synflorix™ was given to HIV+/+ (asymptomatic or mild disease), HIV+- and HIV-/- infants (3 primary doses at 6-10-14 weeks of age with a booster dose at 9-10 months of age). Group comparisons (HIV+/+ and HIV+- versus HIV-/-) suggest comparable immune responses for most vaccine serotypes, serotype 19A and protein D, except a trend for lower post primary OPA response in HIV+/+ group for most vaccine serotypes with unknown clinical relevance. Immunological memory was shown for each vaccine serotype and serotype 19A after the booster dose.

A clinical study in Burkina Faso in children with or without SCD receiving vaccination according to their age (<6 months, 7-11 months, 12-23 months of age) suggests that the immunogenicity of Synflorix™ is not influenced by SCD.

Immunogenicity and safety of Synflorix™ were assessed in a limited number of subjects with congenital or acquired asplenia, splenic dysfunction or complement deficiencies: 6 subjects 2-5 years of age and 40 subjects 6-17 years of age (Synflorix™ is indicated up to 5 years of age). Synflorix™ was shown to be immunogenic and no new safety concerns were observed in this study.

5.2 Preclinical Safety Data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, water for injections

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 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.

6.4 Special Precautions for Storage

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

6.5 **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 (butyl rubber) with or without needles.
- in vials (type I glass) for 1 dose (0.5 ml) or 2 doses (1 ml) with a stopper (butyl rubber).

Not all presentations are available in every country.

6.6 **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.
7. MARKETING AUTHORIZATION HOLDER
GlaxoSmithKline (Thailand) Ltd.

8. MARKETING AUTHORIZATION NUMBER
2C 7/53 (NB)

9. DATE OF AUTHORIZATION
29 December 2010 (conditional license)
19 May 2015 (unconditional license)

Synflorix is a trademark of the GSK group of companies.

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<th>Version number: GDS016/IPI016 / Date of issue: 25 January 2017</th>
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<tbody>
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GlaxoSmithKline