Synflorix
Version GDSv17/IPIv17
Pneumococcal polysaccharide and Non-Typeable
Haemophilus influenzae (NTHi) protein D conjugate
vaccine, absorbed

Qualitative and Quantitative Composition

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

1 adsorbed on aluminium phosphate 0.5 milligram 
2 conjugated to protein D (derived from NTHi) carrier protein 13 micrograms 
3 conjugated to tetanus toxoid carrier protein 8 micrograms 
4 conjugated to diphtheria toxoid carrier protein 5 micrograms

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

Pharmaceutical Form

Suspension for injection.

Clinical Particulars

Indications

Active 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.

Doseage and Administration

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

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 Pharmacodynamics).

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 Pharmacodynamics).

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 Pharmacodynamics).

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 Human Immunodeficiency Virus (HIV) infection, sickle cell disease (SCD) or splenic dysfunction) SYNFLORIX may be given according to the above mentioned schedules, except that a 3-dose schedule should be given as primary vaccination in infants starting vaccination from 6 weeks to 6 months of age (see Warnings and Precautions and Pharmacodynamics).

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 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 intravenously or intradermally. No data are available on the intravenous 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 thymocytopenia or any coagulation disorder since bleeding may follow occurring an intramuscular administration to those 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 Adverse reactions and Pharmacodynamics).

As with any vaccine, the administration of SYNFLORIX should be postponed in subjects with thymocytopenia or any coagulation disorder since bleeding may follow occurring an intramuscular administration to those subjects.

Adverse reactions reported (for all age groups):

- Anaphylactic/anaphylactoid reactions (≥1/10000)
- Very rare:
  - Angioedema, Kawasaki disease
  - Fever ≥38°C rectally (age ≥ 2 years)
  - Hypotonic hyporesponsive episode

- Rare:
  - Convulsions
  - Diarrhoea
  - Injection site reactions like injection site induration, fever >39°C rectally (age < 2 years)

- Uncommon following catch-up vaccination in children 12 to 23 months of age:
  - Allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema), convulsions (including febrile convulsions, urticaria)

- Very rare:
  - Pruritus, diffuse swelling of the injected limb

- Uncommon:
  - Fever <38°C rectally (age < 2 years)

- Post-marketing experience:
  - Anaphylaxis

(1) Uncommon following catch-up vaccination in children 12 to 23 months of age.

(2) Fever ≥38°C rectally (age ≥ 2 years)

(3) Contraindicated for subjects with known hypersensitivity to any component of the vaccine.
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 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 6-12 weeks received either SYNFLORIX or the control vaccine according to a 3+1 schedule (2-4.5 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>SYNFLORIX 2+1 schedule</th>
<th>SYNFLORIX 3+1 schedule</th>
<th>Control (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>VE (95% CI)</td>
<td>No. of cases</td>
<td>VE (95% CI)</td>
</tr>
<tr>
<td>N 1027</td>
<td>100% (82.8; 100)</td>
<td>N 11798</td>
<td>100% (77.3; 100)</td>
</tr>
<tr>
<td>0</td>
<td>91.8(4) (58.3; 89.5)</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>1</td>
<td>51.5% (15.9; 88)</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Any serotype</td>
<td>100% (85.6; 100)</td>
<td>100% (89.5; 100)</td>
<td>0</td>
</tr>
</tbody>
</table>

1.2. Pneumonia

Vaccine efficacy of SYNFLORIX against likely bacterial Community Acquired Pneumonia (CAP), i.e. radiologically confirmed CAP cases with either alveolar consolidation/plural 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 vaccine serotypes (Table 2).

Table 2: Vaccine Efficacy Against AOM(2) in COMPAS (ATP(2); 5989 Subjects)

<table>
<thead>
<tr>
<th>Type of cause of AOM</th>
<th>Vaccine efficacy</th>
<th>95% CI</th>
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<tr>
<td>Clinical AOM regardless of aetiology</td>
<td>33.6%</td>
<td>20.8; 46.3</td>
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<tr>
<td>Any pneumococcal serotype</td>
<td>51.5%</td>
<td>25.4; 76.3</td>
</tr>
<tr>
<td>10 pneumococcal serotypes in common with SYNFLORIX</td>
<td>67.9%</td>
<td>53.3; 82.5</td>
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<tr>
<td>Vaccine-related pneumococcal serotypes</td>
<td>65.5%</td>
<td>22.8; 84.1</td>
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<td>Non-vaccine/non-vaccine related pneumococcal serotypes</td>
<td>8.5%</td>
<td>21.1; 51.5</td>
</tr>
<tr>
<td>NTHs</td>
<td>15.0%</td>
<td>38.3; 60.7</td>
</tr>
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</table>

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.

1.3. Acute Otitis Media (AOM)

Table 2: Vaccine Efficacy Against AOM(2) in COMPAS (ATP(2); 5989 Subjects)

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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.

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: 69.9; 92.3)) and IPD due to serotype 19A (82.2% (95% CI: 70.0; 90.3)).

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 55 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: 72.8; 85)), any vaccine serotype IPD (92% (95% CI: 86.3; 98)) and IPD due to serotype 19A (92% (95% CI: 80.2; 98)).

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 uncertain. 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 was high (≥ 87%) with the exception of serotypes 1 and 19A for SYNFLORIX post-boost (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, 3-4, 5-6 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 serotype 19A in 2-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed for each vaccine serotype and serotype 19A.

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

4. Implications

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.

5. 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.

6. Conclusion

SYNFLORIX demonstrated to be both efficacious in preventing culture-confirmed IPD and vaccine serotypes (Table 1).

- Vaccine effectiveness (in FinIP) or efficacy (in COMPAS) was demonstrated in preventing culture-confirmed IPD due to vaccine serotypes (Table 1).
- Vaccine efficacy of SYNFLORIX against likely bacterial Community Acquired Pneumonia (CAP), i.e. radiologically confirmed CAP cases with either alveolar consolidation/plural 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 vaccine serotypes (Table 2).
- In all studies, SYNFLORIX significantly reduced vaccine type carriage (combined and 6B, 19F and 23F individually) with a trend for increase after booster injection in 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 = 110), 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).

7. Acknowledgments

The authors thank the participating centres and families and the data management teams of FinIP and COMPAS. The study was supported by AstraZeneca. The authors thank the participating centres and families and the data management teams of FinIP and COMPAS. The study was supported by AstraZeneca.
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 for 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 found 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 dysfuntion 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.

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

Pharmaceutical Particulars
List of Excipients
Sodium chloride, water for injections

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

Shelf Life
The expiry date is indicated on the label and packaging.

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

After first opening of the 2-dose 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 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 (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.

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