SYNFLORIX™

Pneumococcal Polysaccharide and Non-Typeable *Haemophilus influenzae* (NTHi) Protein D Conjugate Vaccine, adsorbed

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

1 adsorbed on aluminium phosphate 0.5 milligram Al\(^{3+}\)

2 conjugated to protein D (derived from Non-Typeable *Haemophilus influenzae*) carrier protein ~13 micrograms

3 conjugated to tetanus toxoid carrier protein ~8 micrograms

4 conjugated to diphtheria toxoid carrier protein ~5 micrograms

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and Method of Administration

**Posology**

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

*Three-dose primary series*

The recommended immunisation series to ensure optimal protection consists of four doses, each of 0.5 ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A booster dose is recommended at least 6 months after the last primary dose at 15-18 months. (*see section Pharmacodynamic Properties*)

Official recommendations should be taken into account when immunising with *SYNFLORIX™*.

It is recommended that subjects who receive a first dose of *SYNFLORIX™* complete the full vaccination course with *SYNFLORIX™*. 
The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children.

**Contraindications**

SYNFLORIX™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see sections Qualitative and Quantitative Composition and List of excipients).

**Special Warnings and Special 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™.

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

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

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

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

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

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

- the appropriate-for-age SYNFLORIX™ vaccination series should be given below 2 years
• a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age.

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

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

Interaction with Other Medicaments 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), oral polio vaccine (OPV) and rotavirus vaccine. Different injectable vaccines should always be given at different injections sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 responses, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known. No negative interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM197 and TT conjugates). Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed.

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

Pregnancy and Lactation

As SYNFLORIX™ is not intended for use in adults, adequate human data on use during pregnancy and lactation and adequate animal reproduction studies are not available.

Effects on Ability to Drive and Use Machines

Not relevant.

Undesirable Effects

Clinical trials involved the administration of approximately 12,800 doses of SYNFLORIX™ to approximately 4,500 healthy children as primary vaccination. Furthermore, approximately 3,800 children received a booster dose of SYNFLORIX™ in the second year of life. Safety
was also assessed in approximately 200 children from 2 years 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.

An increase in injection site reactions was reported in children > 12 months of age compared to the rates observed in infants during the primary series with SYNFLORIX™.

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

The most common adverse reactions observed after primary vaccination were redness at the injection site and irritability which occurred after 38.3% and 52.3% of all doses respectively. Following booster vaccination, these adverse reactions occurred at 52.6% and 55.4% respectively. The majority of these reactions were of mild to moderate severity and were not long lasting.

Adverse reactions (following primary immunisation or booster dose for all age groups) considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:

- Very common: (≥ 1/10)
- Common: (≥1/100 to <1/10)
- Uncommon: (≥1/1,000 to <1/100)
- Rare: (≥1/10,000 to <1/1,000)

**Immune system disorders:**

- Rare : allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema)

**Metabolism and nutrition disorders:**

- Very common : appetite lost

**Psychiatric disorders:**

- Very common : irritability
- Uncommon : crying abnormal

**Nervous system disorders:**

- Very common : drowsiness
- Rare : febrile and non-febrile convulsions

**Respiratory, thoracic and mediastinal disorders:**

- Uncommon : apnoea (see section “Special Warnings and Special Precautions for Use” for apnoea in very premature infants (≤ 28 weeks of gestation)

**Gastro-intestinal disorders:**

- Uncommon : diarrhoea, vomiting

**Skin and subcutaneous tissue disorders:**
Rare: rash, urticaria

**General disorders and administration site conditions:**

Very common: pain, redness, swelling at the injection site, fever (≥ 38°C rectally) (age < 2 years)

Common: injection site induration, fever (> 39°C rectally) (age < 2 years), fever ≥ 38°C rectally (age 2 to 5 years)

Uncommon: injection site haematoma, haemorrhage and nodule, fever (> 40°C rectally)* (age < 2 years), fever >39°C rectally (age 2 to 5 years)

*reported following booster vaccination of primary series

**Overdose**

Insufficient data are available

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

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

**1. Efficacy against invasive pneumococcal disease** (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

As recommended by WHO, the assessment of potential efficacy against IPD has been 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™). Immune responses to the extra three serotypes in *SYNFLORIX™* have also been 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. 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 not known.

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%).

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 ≥ 8 one month after the third dose.

For serotypes 1, 5 and 7F, the percentages of *SYNFLORIX™* vaccinees reaching an OPA titre ≥ 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 administration of a fourth dose (booster dose) in the second year of life elicited an anamnestic antibody response as measured by ELISA and OPA for the 10 serotypes included in the vaccine demonstrating the induction of immune memory after the three-dose primary course.

2. Efficacy against Acute Otitis Media (AOM)

In a large randomised double-blind Pneumococcal Otitis Media Efficacy Trial (POET) conducted in the Czech Republic and in Slovakia, 4,968 infants received an 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of SYNFLORIX™ (along with serotype 3 for which efficacy was not demonstrated) 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). No increase in the incidence of AOM due to other bacterial pathogens or non-vaccine serotypes was observed in this study. 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.

3. Additional immunogenicity data

3-dose primary schedule

In total eight studies, conducted in various European countries, 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 the clinical study where infants were vaccinated at 6, 10, 14 weeks, the percentage of SYNFLORIX™ vaccinees with antibody concentrations ≥ 0.20 µg/ml and with an OPA titre ≥ 8 was in the same range as the percentage of Prevenar™ vaccinees for the seven serotypes in common. The observed differences in the percentage of subjects with OPA titre ≥8 were below 5% for all serotypes except 19F (percentage was higher in the SYNFLORIX™ group).

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™.

2-dose primary schedule

In addition to the 3-dose primary schedule, the immunogenicity of SYNFLORIX™ following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in two clinical studies.
In the first study, the immunogenicity 2 months after the second dose of SYNFLORIX™ was compared with 7-valent Prevenar™ and the percentage of subjects with ELISA antibody concentration ≥ 0.2 µg/ml was within the same range for each of the serotypes common to both vaccines with the exception of serotypes 6B (higher for SYNFLORIX™) and 18C (higher for 7-valent Prevenar™). Similarly, the percentage of subjects reaching OPA titres ≥ 8 was within the same range for each of the serotypes common to both vaccines.

In the second study, the immunogenicity after two or three doses of SYNFLORIX™ were compared. Although there was no significant impact on subjects with antibody concentration ≥ 0.2µg/ml (ELISA), a lower percentage of subjects with OPA titers ≥8 was observed for some serotypes in 2-dose primed subjects compared to 3-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed. Following the booster, a lower percentage of subjects with OPA titers ≥8 was observed for some serotypes in 2-dose primed subjects compared to 3-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed. Following the booster, a lower percentage of subjects with OPA titers ≥8 was observed for some serotypes in 2-dose primed subjects compared to 3-dose primed subjects. While the clinical relevance of these observations remains unknown, the persistence of the immune response was evaluated in a follow-up of this second study. In this follow-up study, the persistence of antibodies at 36-46 months of age was demonstrated in 2-dose primed subjects (at least 83.7% of subjects remaining seropositive for vaccine serotypes i.e. detectable antibody ≥ 0.05 µg/ml). A single dose of SYNFLORIX™ administered during the 4th year of life, as a challenge dose, elicited higher ELISA antibody GMCs 7-10 days following vaccination in 2-dose and 3-dose primed subjects compared to unprimed subjects. This was indicative of an anamnestic immune response in primed subjects for all vaccine serotypes. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, in 2-dose primed subjects was similar to that in 3-dose primed subjects.

A 3-dose primary schedule has shown higher response against protein D compared to a 2-dose primary schedule. Anamnestic immune responses to protein D were shown with both schedules. However, the clinical relevance of these observations remains unknown.

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

**Catch-up**

The immune responses in previously unvaccinated older children were evaluated in two clinical studies.

The first study evaluated vaccination in children aged 7-11 months, 12-23 months and 2 to 5 years.

In the 7-11 months group, children received 2 primary doses followed by a booster dose in the second year of life. The immune responses after the booster dose of SYNFLORIX™ 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.

The immune response elicited after two doses of SYNFLORIX™ in children 12-23 months of age was comparable to the response elicited after three doses in infants, except for 18C and 19F.

In the 2 to 5 years group, where children received 1 dose of SYNFLORIX™, the ELISA antibody GMCs for vaccine serotypes were similar to those achieved following a 3 dose
vaccination schedule in infants except for serotypes 1, 5, 14 and 23F and for anti-protein D. The OPA GMTs were similar or higher following a single dose than a 3 dose primary course in infants, except for serotype 5.

The second clinical study showed that 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 a similar immune response for protein D.

Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

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.

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

36 months.

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

Special Precautions for Storage

Store at +2°C to +8°C (in a refrigerator).

Do not freeze.

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

Nature and Contents of Container

SYNFLORIX™ is presented:

- In pre-filled syringes for 1 dose (0.5 ml) with a plunger stopper (rubber butyl) with or without needles. Pack sizes of 1 or 10.

- In vials for 1 dose (0.5 ml) with a stopper (rubber butyl). Pack sizes of 1, 10 or 100.
- In vials for 2 doses (1 ml) with a stopper (rubber butyl). Pack size of 100.

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

Not all pack sizes / presentations may be marketed in India.

**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.

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

**Needle**

![Needle diagram](image)

**Syringe**

![Syringe diagram](image)

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.

For further information, please contact the manufacturer.

**Manufactured by:**
GlaxoSmithKline Biologicals s.a.
Rue de l’Institut, 89,
B-1330 Rixensart, Belgium

**Imported by:**
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