

WHO PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Synflorix™
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

¹ adsorbed on aluminium phosphate	0.5 milligram Al ³⁺
² conjugated to protein D (derived from Non-Typeable <i>Haemophilus influenzae</i>) carrier protein	~13 micrograms
³ conjugated to tetanus toxoid carrier protein	~8 micrograms
⁴ conjugated to diphtheria toxoid carrier protein	~5 micrograms

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Synflorix™ is a turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 2 years of age.

4.2 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 priming dose (see section 5.1)

Two-dose primary series

Alternatively, when Synflorix is given as part of a routine infant immunisation programme, a series consisting of three doses, each of 0.5 ml may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. A booster dose is recommended at least 6 months after the last primary dose (see section 5.1).

Previously unvaccinated older infants and children:

- **infants aged 7-11 months:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 1 month between doses. A third dose is recommended in the second year of life with an interval of at least 2 months between doses.

- **children aged 12-23 months:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses. The need for a booster dose after this immunisation schedule has not been established.

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™.

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 Contraindications

Synflorix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see sections 2 and 6.1).

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™.

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 (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 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.

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

- the appropriate-for-age Synflorix™ vaccination series should be given below 2 years of age (see section 4.2)
- 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.

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

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known. No 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.

4.6 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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Clinical trials involved the administration of 12,879 doses of Synflorix™ to 4,595 healthy children as primary vaccination. Furthermore, 3,870 children received a booster dose of Synflorix™ in the second year of life. In all trials, Synflorix™ was administered concurrently with the recommended childhood vaccines.

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.

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

An increase in reactogenicity was reported after booster vaccination compared to the doses of the primary course with Synflorix™.

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.

Adverse reactions (following primary immunisation or booster dose) 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 $<1/1,000$)

Nervous system disorders:

Very common: drowsiness

Rare: febrile and non-febrile convulsions

Respiratory, thoracic and mediastinal disorders

Uncommon: apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

Gastro-intestinal disorders:

Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:

Rare: rash, urticaria

Metabolism and nutrition disorders:

Very common: appetite lost

General disorders and administration site conditions:

Very common: pain, redness, swelling at the injection site, fever ($\geq 38^{\circ}\text{C}$ rectally)

Common: injection site induration, fever ($>39^{\circ}\text{C}$ rectally)

Uncommon: injection site haematoma, haemorrhage and nodule, fever ($>40^{\circ}\text{C}$ rectally)*

Immune system disorders

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

Psychiatric disorders:

Very common: irritability

Uncommon: crying abnormal

*reported following booster vaccination

4.9 Overdose

Insufficient data are available

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

1. 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. 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.

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 $\mu\text{g/ml}$ 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 titres ≥ 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

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, in a post hoc analysis, the immunogenicity 2 months after the second dose of Synflorix was compared with 7-valent Prevenar. For each of the serotypes common to both vaccines, the percentage of subjects with ELISA antibody concentration ≥ 0.2 $\mu\text{g/ml}$ was within the same range except for serotypes 6B (higher for Synflorix) and 18C (higher for 7-valent Prevenar). Similarly, the percentage of subjects reaching OPA titres ≥ 8 was also within the same range in the two groups for each of the serotypes common to both vaccines, except for higher responses for 6B and 19F in the Synflorix group.

In the second study, the immunogenicity after two or three doses of Synflorix was compared and there was no significant difference in percentage of subjects with antibody concentration ≥ 0.2 $\mu\text{g/ml}$ (ELISA) although for serotypes 6B and 23F the percentages were lower in the two-dose primed subjects. A lower percentage of subjects with OPA titres ≥ 8 was observed for serotypes 6B, 18C and 23F in 2-dose primed subjects compared to 3-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed for each serotype. After the booster dose, a lower percentage of subjects with OPA titres ≥ 8 was observed in the two-dose primed subjects for serotypes 5 and 6B.

In the follow-up of the second study, the persistence of antibodies at 36-46 months of age was demonstrated in 2-dose and 3-dose primed subjects. A single challenge dose of Synflorix, during the 4th year of life, elicited similar ELISA antibody GMCs 7-10 days after challenge in 2-dose primed subjects and 3-dose primed subjects. ELISA antibody GMCs were higher than those seen after a challenge of unprimed subjects. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, was also 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.

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 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 of the vaccine is indicated on the label and packaging.

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.

Synflorix should be administered as soon as possible after being removed from the refrigerator.

After first opening of the multidose vial, immediate use is recommended.

If not used immediately, the multidose vial must be discarded at the end of each immunization session or after 6 hours from first opening, whichever comes first.

6.5 Nature and contents of container

Synflorix™ is presented:

- 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 are made of neutral glass type I, which conforms to US Pharmacopoeia requirements.

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. This does not constitute a sign of deterioration.

The content of the 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.

When using a multidose vial, each dose should be drawn with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under aseptic conditions and precautions taken to avoid contamination of the contents. The remaining vaccine should be maintained between +2°C to +8°C and protected from the sunlight.

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

6.7 Vaccine Vial Monitor (see VVM pictogram at the end of the leaflet)

The Vaccine Vial Monitor (VVM) is either part of the label or the vial cap used for all Synflorix™ batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial for 1 dose (0.5 ml) or on the vial cap for 2 doses (1 ml) of vaccine is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the glass container should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event Synflorix™ has not been stored in compliance with those storage instructions. Furthermore, GlaxoSmithKline Biologicals assumes no responsibility in case a VVM is defective for any reason.



Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**



At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**



Discard point: Inner square matches colour of outer circle. **DO NOT use the vaccine.**



Beyond the discard point: Inner square darker than outer ring. **DO NOT use the vaccine.**

For further information, please contact the manufacturer.

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WHO Package Insert

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