ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

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

1 adsorbed on aluminium phosphate 0.5 milligram Al$^{3+}$
2 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein 9-16 micrograms
3 conjugated to tetanus toxoid carrier protein 5-10 micrograms
4 conjugated to diphtheria toxoid carrier protein 3-6 micrograms

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against invasive disease and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 2 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and method of administration

Method of administration

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

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

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

The primary vaccination schedule consists of three doses of 0.5 ml with an interval of at least 1 month between doses. (see sections 4.4 and 5.1)

A booster dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age. (see section 4.4)

**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. (see section 4.4)

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

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients, or to any of the carrier proteins.

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

**4.4 Special warnings and precautions for use**

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

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

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

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

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

There is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine or against non-typeable *Haemophilus influenzae*. Synflorix does not provide protection against other micro-organisms.
As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease or otitis media caused by the serotypes in the vaccine. Protection against otitis media caused by pneumococcal serotypes in the vaccine is expected to be substantially lower than protection against invasive disease. In addition, as otitis media is caused by many micro-organisms other than the Streptococcus pneumoniae serotypes represented in the vaccine, the overall protection against otitis media is expected to be limited (see section 5.1).

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

Synflorix is indicated for use in children aged from 6 weeks up to 2 years. Children should receive the dose regimen of Synflorix that is appropriate to their age at the time of commencing the vaccination series (see section 4.2). Safety and immunogenicity data are not yet available in children above 2 years of age.

The immune response elicited after two doses of Synflorix in children 12-23 months of age is comparable to the response elicited after three doses in infants (see section 5.1). The immune response to a booster dose after two doses in children aged 12-23 months has not been evaluated, but a booster dose may be needed to ensure optimal individual protection.

However, a 2-dose schedule in children aged 12-23 months with high risk of pneumococcal disease (such as children with sickle-cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) may not be sufficient to provide optimal protection. In these children, a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age, whenever recommended. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.

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 vaccination.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. However, data suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix remains unknown.

The use of prophylactic antipyretic medicinal products is recommended:
- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.
Antipyretic treatment should be initiated according to local treatment guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines
Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). 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.

*Use with systemic immunosuppressive medicinal products*

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

*Use with prophylactic administration of antipyretics*

See section 4.4.

### 4.6 Pregnancy and lactation

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

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

Not relevant.

### 4.8 Undesirable effects

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 ≥38°C and >39°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: \((\geq 1/100 \text{ to } <1/10)\)
Uncommon: \((\geq 1/1,000 \text{ to } <1/100)\)
Rare: \((\geq 1/10,000 \text{ to } <1/1,000)\)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Very common: drowsiness
Rare: febrile and non-febrile convulsions

Respiratory, thoracic and mediastinal disorders
Uncommon: apnoea in very premature infants (\(\leq 28\) 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 (\(\geq 38^\circ\)C rectally)
Common: injection site induration, fever (\(>39^\circ\)C rectally)
Uncommon: injection site haematoma, haemorrhage and nodule, fever (\(>40^\circ\)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

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines, ATC code: J07AL52

Epidemiological data

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

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and Non-Typeable *Haemophilus influenzae* (NTHi) are the most common causes of bacterial AOM worldwide.

1. Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

The protective efficacy of Synflorix against IPD has not been studied. 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 (upper limit of the 96.5% CI around the difference between groups >10%) (Table 1). 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%).

Table 1: Comparative analysis between 7-valent Prevenar and Synflorix in percentage of subjects with antibody concentrations \( \geq 0.20 \mu\text{g/ml} \) one month post-dose 3

<table>
<thead>
<tr>
<th>Antibody</th>
<th>SYNFLORIX</th>
<th>7-valent Prevenar</th>
<th>Difference in % ( \geq 0.20 \mu\text{g/ml} ) (7-valent Prevenar minus SYNFLORIX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Anti-4</td>
<td>1106</td>
<td>97.1</td>
<td>373</td>
</tr>
<tr>
<td>Anti-6B</td>
<td>1100</td>
<td>65.9</td>
<td>372</td>
</tr>
<tr>
<td>Anti-9V</td>
<td>1103</td>
<td>98.1</td>
<td>374</td>
</tr>
<tr>
<td>Anti-14</td>
<td>1100</td>
<td>99.5</td>
<td>374</td>
</tr>
<tr>
<td>Anti-18C</td>
<td>1102</td>
<td>96.0</td>
<td>374</td>
</tr>
<tr>
<td>Anti-19F</td>
<td>1104</td>
<td>95.4</td>
<td>375</td>
</tr>
<tr>
<td>Anti-23F</td>
<td>1102</td>
<td>81.4</td>
<td>374</td>
</tr>
</tbody>
</table>

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by 7-valent Prevenar. Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines. After the booster dose the GMCs elicited by Synflorix were lower for most serotypes in common with 7-valent Prevenar.

In the same study, Synflorix was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87.7% to 100% of Synflorix vaccinees and 92.1% to 100% of
7-valent Prevenar vaccinees reached an OPA titre ≥ 8 one month after the third dose. The difference between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was <5% for all serotypes in common, including 6B and 23F. Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by Synflorix were lower than those elicited by 7-valent Prevenar for the seven shared serotypes, except for serotype 19F. For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre ≥ 8 were respectively 65.7%, 90.9% and 99.6% after the primary vaccination course and 91.0%, 96.3% and 100% after the booster dose. The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

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. 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

In total eight studies, conducted in various countries across Europe, in Chile and in the Philippines, have evaluated the immunogenicity of Synflorix after a three-dose primary series (N=3,089) according to different vaccination schedules (6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age). A fourth (booster) dose was given in six clinical studies to 1,976 subjects. In general, comparable vaccine responses were observed for the different schedules, although somewhat higher immune responses were noted for the 2-4-6 month schedule.

In addition to the 3-dose primary schedule, the immunogenicity of Synflorix was evaluated in a 2-dose primary vaccination schedule in subjects less than 6 months of age. Although there was no significant impact on subjects with antibody concentration ≥ 0.20 μg/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. Overall, post-primary ELISA antibody GMCs and OPA GMTs were lower in the 2-dose primary group, as was the persistence of the immune response until the booster at 11 months of age. In both schedules, a booster response indicative of immunological priming was observed, even though lower percentage of subjects with OPA titers ≥ 8 was still observed in the 2-dose schedule for some serotypes. The clinical consequences of the lower post-primary and post-
booster immune responses observed after the two-dose primary schedule are not known. The 3-dose primary schedule is recommended to ensure optimal protection.

One clinical study evaluated vaccination in children 7-11 months of age and 12-23 months of age. 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 for which responses were higher in the 12-23 months children. The need for a booster dose after two doses in children aged 12-23 months has not been established.

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

In a clinical study, it has been demonstrated that Synflorix can be safely administered as a booster dose in the second year of life to children who had received 3 primary doses of 7-valent Prevenar. This study has shown that the immune responses against the 7 common serotypes were comparable to those elicited by a booster dose of 7-valent Prevenar. However, children who received 7-valent Prevenar for the primary series would not be primed against the additional serotypes contained in Synflorix (1, 5, 7F). Therefore the degree and duration of protection against invasive pneumococcal disease and otitis media due to these three serotypes in children of this age group following a single dose of Synflorix cannot be predicted.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not available for vaccines.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adsorbent, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

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.

6.5  Nature and contents of container

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

Not all pack sizes may be marketed.

6.6  Special precautions for disposal and other handling

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

The content of the pre-filled syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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

The vaccine should be well shaken before use.

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

7.  MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l’Institut 89
B-1330 Rixensart, Belgium

8.  MARKETING AUTHORISATION NUMBER(S)

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.  DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) [http://www.emea.europa.eu/](http://www.emea.europa.eu/).
1. NAME OF THE MEDICINAL PRODUCT

Synflorix suspension for injection
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

- Pneumococcal polysaccharide serotype 1\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 4\(^1,2\) 3 micrograms
- Pneumococcal polysaccharide serotype 5\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 6B\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 7F\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 9V\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 14\(^1,2\) 1 microgram
- Pneumococcal polysaccharide serotype 18C\(^1,3\) 3 micrograms
- Pneumococcal polysaccharide serotype 19F\(^1,4\) 3 micrograms
- Pneumococcal polysaccharide serotype 23F\(^1,2\) 1 microgram

\(^1\) adsorbed on aluminium phosphate 0.5 milligram Al\(^{3+}\)
\(^2\) conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein 9-16 micrograms
\(^3\) conjugated to tetanus toxoid carrier protein 5-10 micrograms
\(^4\) conjugated to diphtheria toxoid carrier protein 3-6 micrograms

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 2 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and method of administration

*Method of administration*

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

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

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

The primary vaccination schedule consists of three doses of 0.5 ml with an interval of at least 1 month between doses. (see sections 4.4 and 5.1)

A booster dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age. (see section 4.4)

**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. (see section 4.4)

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

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients, or to any of the carrier proteins.

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

**4.4 Special warnings and precautions for use**

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

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

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

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

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

There is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine or against non-typeable *Haemophilus influenzae*. Synflorix does not provide protection against other micro-organisms.
As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease or otitis media caused by the serotypes in the vaccine. Protection against otitis media caused by pneumococcal serotypes in the vaccine is expected to be substantially lower than protection against invasive disease. In addition, as otitis media is caused by many micro-organisms other than the *Streptococcus pneumoniae* serotypes represented in the vaccine, the overall protection against otitis media is expected to be limited (see section 5.1).

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

Synflorix is indicated for use in children aged from 6 weeks up to 2 years. Children should receive the dose regimen of Synflorix that is appropriate to their age at the time of commencing the vaccination series (see section 4.2). Safety and immunogenicity data are not yet available in children above 2 years of age.

The immune response elicited after two doses of Synflorix in children 12-23 months of age is comparable to the response elicited after three doses in infants (see section 5.1). The immune response to a booster dose after two doses in children aged 12-23 months has not been evaluated, but a booster dose may be needed to ensure optimal individual protection.

However, a 2-dose schedule in children aged 12-23 months with high risk of pneumococcal disease (such as children with sickle-cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) may not be sufficient to provide optimal protection. In these children, a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age, whenever recommended. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.

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 vaccination.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. However, data suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix remains unknown.

The use of prophylactic antipyretic medicinal products is recommended:
- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.

Antipyretic treatment should be initiated according to local treatment guidelines.

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

*Use with other vaccines*
Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). 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.

*Use with systemic immunosuppressive medicinal products*

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

*Use with prophylactic administration of antipyretics*

See section 4.4.

**4.6 Pregnancy and lactation**

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

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

Not relevant.

**4.8 Undesirable effects**

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 ≥38°C and >39°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 $<1/1,000)$

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Nervous system disorders**
- Very common: drowsiness
- Rare: febrile and non-febrile convulsions

**Respiratory, thoracic and mediastinal disorders**
- Uncommon: apnoea in very premature infants ($\leq 28$ 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 ($\geq 38^\circ C$ rectally)
- Common: injection site induration, fever ($>39^\circ C$ rectally)
- Uncommon: injection site haematoma, haemorrhage and nodule, fever ($>40^\circ C$ 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

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines, ATC code: J07AL52

**Epidemiological data**

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

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and Non-Typeable *Haemophilus influenzae* (NTHi) are the most common causes of bacterial AOM worldwide.

1. Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

The protective efficacy of Synflorix against IPD has not been studied. 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 (upper limit of the 96.5% CI around the difference between groups >10%) (Table 1). 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%).

**Table 1: Comparative analysis between 7-valent Prevenar and Synflorix in percentage of subjects with antibody concentrations > 0.20 µg/ml one month post-dose 3**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>SYNFLORIX</th>
<th>7-VALENT PREVENAR</th>
<th>Difference in %≥0.20 µg/ml (7-VALENT PREVENAR minus SYNFLORIX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Anti-4</td>
<td>1106</td>
<td>97.1</td>
<td>373</td>
</tr>
<tr>
<td>Anti-6B</td>
<td>1100</td>
<td>65.9</td>
<td>372</td>
</tr>
<tr>
<td>Anti-9V</td>
<td>1103</td>
<td>98.1</td>
<td>374</td>
</tr>
<tr>
<td>Anti-14</td>
<td>1100</td>
<td>99.5</td>
<td>374</td>
</tr>
<tr>
<td>Anti-18C</td>
<td>1102</td>
<td>96.0</td>
<td>374</td>
</tr>
<tr>
<td>Anti-19F</td>
<td>1104</td>
<td>95.4</td>
<td>375</td>
</tr>
<tr>
<td>Anti-23F</td>
<td>1102</td>
<td>81.4</td>
<td>374</td>
</tr>
</tbody>
</table>

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by 7-valent Prevenar. Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines. After the booster dose the GMCs elicited by Synflorix were lower for most serotypes in common with 7-valent Prevenar.

In the same study, Synflorix was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87.7% to 100% of Synflorix vaccinees and 92.1% to 100% of 7-valent Prevenar vaccinees reached an OPA titre ≥ 8 one month after the third dose. The difference
between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was <5% for all serotypes in common, including 6B and 23F. Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by Synflorix were lower than those elicited by 7-valent Prevenar for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre ≥ 8 were respectively 65.7%, 90.9% and 99.6% after the primary vaccination course and 91.0%, 96.3% and 100% after the booster dose. The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

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. 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

In total eight studies, conducted in various countries across Europe, in Chile and in the Philippines, have evaluated the immunogenicity of Synflorix after a three-dose primary series (N=3,089) according to different vaccination schedules (6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age). A fourth (booster) dose was given in six clinical studies to 1,976 subjects. In general, comparable vaccine responses were observed for the different schedules, although somewhat higher immune responses were noted for the 2-4-6 month schedule.

In addition to the 3-dose primary schedule, the immunogenicity of Synflorix was evaluated in a 2-dose primary vaccination schedule in subjects less than 6 months of age. Although there was no significant impact on subjects with antibody concentration ≥ 0.20 μg/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. Overall, post-primary ELISA antibody GMCs and OPA GMTs were lower in the 2-dose primary group, as was the persistence of the immune response until the booster at 11 months of age. In both schedules, a booster response indicative of immunological priming was observed, even though lower percentage of subjects with OPA titers ≥ 8 was still observed in the 2-dose schedule for some serotypes. The clinical consequences of the lower post-primary and post-
booster immune responses observed after the two-dose primary schedule are not known. The 3-dose primary schedule is recommended to ensure optimal protection.

One clinical study evaluated vaccination in children 7-11 months of age and 12-23 months of age. 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 for which responses were higher in the 12-23 months children. The need for a booster dose after two doses in children aged 12-23 months has not been established.

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

In a clinical study, it has been demonstrated that Synflorix can be safely administered as a booster dose in the second year of life to children who had received 3 primary doses of 7-valent Prevenar. This study has shown that the immune responses against the 7 common serotypes were comparable to those elicited by a booster dose of 7-valent Prevenar. However, children who received 7-valent Prevenar for the primary series would not be primed against the additional serotypes contained in Synflorix (1, 5, 7F). Therefore the degree and duration of protection against invasive pneumococcal disease and otitis media due to these three serotypes in children of this age group following a single dose of Synflorix cannot be predicted.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not available for vaccines.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adsorbent, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

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.

6.5  Nature and contents of container

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

Not all pack sizes may be marketed.

6.6  Special precautions for disposal and other handling

A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. 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 allowed to reach room temperature before use.

The vaccine should be well shaken before use.

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

7.  MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l’Institut 89
B-1330 Rixensart, Belgium

8.  MARKETING AUTHORISATION NUMBER(S)

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.  DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.
1. NAME OF THE MEDICINAL PRODUCT

Synflorix suspension for injection in multidose container
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

- Pneumococcal polysaccharide serotype 1\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 4\textsuperscript{1,2} 3 micrograms
- Pneumococcal polysaccharide serotype 5\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 6B\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 7F\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 9V\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 14\textsuperscript{1,2} 1 microgram
- Pneumococcal polysaccharide serotype 18C\textsuperscript{1,3} 3 micrograms
- Pneumococcal polysaccharide serotype 19F\textsuperscript{1,4} 3 micrograms
- Pneumococcal polysaccharide serotype 23F\textsuperscript{1,2} 1 microgram

\textsuperscript{1} adsorbed on aluminium phosphate 0.5 milligram Al\textsuperscript{3+}
\textsuperscript{2} conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein 9-16 micrograms
\textsuperscript{3} conjugated to tetanus toxoid carrier protein 5-10 micrograms
\textsuperscript{4} conjugated to diphtheria toxoid carrier protein 3-6 micrograms

This is a multidose container. See section 6.5 for the number of doses per vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against invasive disease and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 2 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different areas.

4.2 Posology and method of administration

Method of administration

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

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

Infants from 6 weeks to 6 months of age

The primary vaccination schedule consists of three doses of 0.5 ml with an interval of at least 1 month between doses. (see sections 4.4 and 5.1)

A booster dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age. (see section 4.4)

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. (see section 4.4)

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients, or to any of the carrier proteins.

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

4.4 Special warnings and precautions for use

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

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

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

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

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

There is insufficient evidence that Synflorix provides protection against pneumococcal serotypes not contained in the vaccine or against non-typeable *Haemophilus influenzae*. Synflorix does not provide protection against other micro-organisms.
As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease or otitis media caused by the serotypes in the vaccine. Protection against otitis media caused by pneumococcal serotypes in the vaccine is expected to be substantially lower than protection against invasive disease. In addition, as otitis media is caused by many micro-organisms other than the *Streptococcus pneumoniae* serotypes represented in the vaccine, the overall protection against otitis media is expected to be limited (see section 5.1).

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

Synflorix is indicated for use in children aged from 6 weeks up to 2 years. Children should receive the dose regimen of Synflorix that is appropriate to their age at the time of commencing the vaccination series (see section 4.2). Safety and immunogenicity data are not yet available in children above 2 years of age.

The immune response elicited after two doses of Synflorix in children 12-23 months of age is comparable to the response elicited after three doses in infants (see section 5.1). The immune response to a booster dose after two doses in children aged 12-23 months has not been evaluated, but a booster dose may be needed to ensure optimal individual protection.

However, a 2-dose schedule in children aged 12-23 months with high risk of pneumococcal disease (such as children with sickle-cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) may not be sufficient to provide optimal protection. In these children, a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age, whenever recommended. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.

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 vaccination.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. However, data suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix remains unknown.

The use of prophylactic antipyretic medicinal products is recommended:
- for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8).
- for children with seizure disorders or with a prior history of febrile seizures.
Antipyretic treatment should be initiated according to local treatment guidelines.

4.5 Interaction with other medicinal products and other forms of interaction
Use with other vaccines

Synflorix can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). 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.

Use with systemic immunosuppressive medicinal products

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

Use with prophylactic administration of antipyretics

See section 4.4.

4.6 Pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 ≥38°C and >39°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:  (≥ 1/10)
 Common:  (≥1/100 to <1/10)
 Uncommon:  (≥1/1,000 to <1/100)
 Rare:  (≥1/10,000 to <1/1,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (≥38°C rectally)
 Common:  injection site induration, fever (>39°C rectally)
 Uncommon:  injection site haematoma, haemorrhage and nodule, fever (>40°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

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pneumococcal vaccines, ATC code: J07AL52

Epidemiological data

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

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and Non-Typeable *Haemophilus influenzae* (NTHi) are the most common causes of bacterial AOM worldwide.

1. Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

The protective efficacy of Synflorix against IPD has not been studied. 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 (upper limit of the 96.5% CI around the difference between groups >10%) (Table 1). 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%).

Table 1: Comparative analysis between 7-valent Prevenar and Synflorix in percentage of subjects with antibody concentrations > 0.20 µg/ml one month post-dose 3

<table>
<thead>
<tr>
<th>Antibody</th>
<th>SYNFLORIX</th>
<th>7-VALENT PREVENAR</th>
<th>Difference in %≥0.20µg/ml (7-VALENT PREVENAR minus SYNFLORIX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Anti-4</td>
<td>1106</td>
<td>97.1</td>
<td>373</td>
</tr>
<tr>
<td>Anti-6B</td>
<td>1100</td>
<td>65.9</td>
<td>372</td>
</tr>
<tr>
<td>Anti-9V</td>
<td>1103</td>
<td>98.1</td>
<td>374</td>
</tr>
<tr>
<td>Anti-14</td>
<td>1100</td>
<td>99.5</td>
<td>374</td>
</tr>
<tr>
<td>Anti-18C</td>
<td>1102</td>
<td>96.0</td>
<td>374</td>
</tr>
<tr>
<td>Anti-19F</td>
<td>1104</td>
<td>95.4</td>
<td>375</td>
</tr>
<tr>
<td>Anti-23F</td>
<td>1102</td>
<td>81.4</td>
<td>374</td>
</tr>
</tbody>
</table>

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by 7-valent Prevenar. Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines. After the booster dose the GMCs elicited by Synflorix were lower for most serotypes in common with 7-valent Prevenar.

In the same study, Synflorix was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87.7% to 100% of Synflorix vaccinees and 92.1% to 100% of 7-valent Prevenar vaccinees reached an OPA titre ≥ 8 one month after the third dose. The difference
between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was <5% for all serotypes in common, including 6B and 23F. Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by Synflorix were lower than those elicited by 7-valent Prevenar for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre ≥ 8 were respectively 65.7%, 90.9% and 99.6% after the primary vaccination course and 91.0%, 96.3% and 100% after the booster dose. The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

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. 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

In total eight studies, conducted in various countries across Europe, in Chile and in the Philippines, have evaluated the immunogenicity of Synflorix after a three-dose primary series (N=3,089) according to different vaccination schedules (6-10-14 weeks, 2-3-4, 3-4-5 or 2-4-6 months of age). A fourth (booster) dose was given in six clinical studies to 1,976 subjects. In general, comparable vaccine responses were observed for the different schedules, although somewhat higher immune responses were noted for the 2-4-6 month schedule.

In addition to the 3-dose primary schedule, the immunogenicity of Synflorix was evaluated in a 2-dose primary vaccination schedule in subjects less than 6 months of age. Although there was no significant impact on subjects with antibody concentration ≥ 0.20 μg/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. Overall, post-primary ELISA antibody GMCs and OPA GMTs were lower in the 2-dose primary group, as was the persistence of the immune response until the booster at 11 months of age. In both schedules, a booster response indicative of immunological priming was observed, even though lower percentage of subjects with OPA titers ≥ 8 was still observed in the 2-dose schedule for some serotypes. The clinical consequences of the lower post-primary and post-
booster immune responses observed after the two-dose primary schedule are not known. The 3-dose primary schedule is recommended to ensure optimal protection.

One clinical study evaluated vaccination in children 7-11 months of age and 12-23 months of age. 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 for which responses were higher in the 12-23 months children. The need for a booster dose after two doses in children aged 12-23 months has not been established.

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

In a clinical study, it has been demonstrated that Synflorix can be safely administered as a booster dose in the second year of life to children who had received 3 primary doses of 7-valent Prevenar. This study has shown that the immune responses against the 7 common serotypes were comparable to those elicited by a booster dose of 7-valent Prevenar. However, children who received 7-valent Prevenar for the primary series would not be primed against the additional serotypes contained in Synflorix (1, 5, 7F). Therefore the degree and duration of protection against invasive pneumococcal disease and otitis media due to these serotypes in children of this age group following a single dose of Synflorix cannot be predicted.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not available for vaccines.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adsorbent, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After first opening of the multidose vial, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.
6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

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 allowed to reach room temperature before use.

The vaccine should be well shaken before use.

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

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l’Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.
ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

GlaxoSmithKline Biologicals S.A.
Parc de la Noire Epine
Rue Fleming 20
B-1300 Wavre
Belgium

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
BE-1330 Rixensart
Belgium

GlaxoSmithKline Biologicals Kft.
HU-2100 Gödöllő
Tânesics Mihály út 82.
Hungary

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
BE-1330 Rixensart
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

• OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 3 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.
As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

• When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
• Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
• At the request of the EMEA

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON OF PRE-FILLED SYRINGE WITH OR WITHOUT NEEDLE, PACK OF 1, 10

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Sodium chloride  
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection  
1 pre-filled syringe  
1 dose (0.5 ml)

| 10 pre-filled syringes 10 doses (0.5 ml) |
| 1 pre-filled syringe + 1 needle 1 dose (0.5 ml) |
| 10 pre-filled syringes + 10 needles 10 x 1 dose (0.5 ml) |
| 1 pre-filled syringe + 2 needles 1 dose (0.5 ml) |

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use  
Intramuscular use  
The vaccine should be allowed to reach room temperature before use.  
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 – pack of 1 without needle
EU/0/00/000/000 – pack of 10 without needle
EU/0/00/000/000 – pack of 1 with 1 needle
EU/0/00/000/000 – pack of 10 with 10 needles
EU/0/00/000/000 – pack of 1 with 2 needles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
Justification for not including Braille accepted
### Minimum Particulars to Appear on Small Immediate Packaging Units

**Pre-Filled Syringe Label**

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td><strong>1. Name of the Medicinal Product and Route(s) of Administration</strong></td>
<td>Synflorix suspension for injection in pre-filled syringe IM</td>
</tr>
<tr>
<td><strong>2. Method of Administration</strong></td>
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<td><strong>3. Expiry Date</strong></td>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. Batch Number</strong></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. Contents by Weight, by Volume or by Unit</strong></td>
<td>1 dose (0.5 ml)</td>
</tr>
<tr>
<td><strong>6. Other</strong></td>
<td></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL, PACK OF 1, 10, 100

1. NAME OF THE MEDICINAL PRODUCT

Synflorix suspension for injection
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
1 dose (0.5 ml)

10 vials
10 x 1 dose (0.5 ml)

100 vials
100 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
The vaccine should be allowed to reach room temperature before use
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
9. **SPECIAL STORAGE CONDITIONS**

Store in a refrigerator  
Do not freeze  
Store in the original package in order to protect from light

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose of in accordance with local regulations.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000 – pack of 1  
EU/0/00/000/000 – pack of 10  
EU/0/00/000/000 – pack of 100

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted
<p>| | |</p>
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| **1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION** | Synflorix suspension for injection  
IM                                                               |
| **2. METHOD OF ADMINISTRATION**                                    |                                                                 |
| **3. EXPIRY DATE**                                                 | EXP                                                              |
| **4. BATCH NUMBER**                                                | Lot                                                              |
| **5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**                    | 1 dose (0.5 ml)                                                   |
| **6. OTHER**                                                       |                                                                 |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL MULTIDOSE (2 DOSES), PACK OF 100

1. NAME OF THE MEDICINAL PRODUCT

Synflorix suspension for injection in multidose container
Pneumococcal polysaccharide conjugate vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
100 MULTIDOSE vials (2 doses per vial – 0.5 ml per dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
The vaccine should be allowed to reach room temperature before use
Shake well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light
Should be used within 6 hours after first broaching of the vial

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL MULTIDOSE (2 DOSES)</th>
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<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>Synflorix injection IM</td>
</tr>
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<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
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<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
</tr>
<tr>
<td>2 doses (0.5 ml per dose)</td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
Read all of this leaflet carefully before your child receives this vaccine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This vaccine has been prescribed for your child. Do not pass it on to others.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Synflorix is and what it is used for
2. Before your child receives Synflorix
3. How Synflorix is given
4. Possible side effects
5. How to store Synflorix
6. Further information

1. WHAT SYNFLORIX IS AND WHAT IT IS USED FOR

Synflorix is a pneumococcal conjugate vaccine. Your doctor or nurse will inject your child with this vaccine.

It is used to help protect your child from 6 weeks up to 2 years of age against:
a bacteria called ‘Streptococcus pneumoniae’. This bacteria can cause serious illnesses including meningitis, sepsis or bacteraemia (bacteria in blood stream) or ear infection and pneumonia.

How the vaccine works

Synflorix helps your body to make its own antibodies. The antibodies form a part of the immune system that will protect your child against these diseases.

2. BEFORE YOUR CHILD RECEIVES SYNFLORIX

Synflorix should not be given if:
• your child has ever had an allergic reaction (is hypersensitive) to the active substance, or any of the other ingredients in this vaccine (listed in Section 6). Signs of an allergic reaction may include itchy skin rash, being short of breath and swelling of the face or tongue.
• your child has a severe infection with a high temperature (over 38°C). If this applies to your child then the vaccination will be postponed until your child is feeling better. A minor infection such as a cold should not be a problem. However, talk to your doctor first.

Synflorix should not be given to your child if any of the above applies to them. If you are not sure, talk to your doctor or pharmacist before they receive Synflorix.

Take special care with Synflorix:

Check with your doctor or pharmacist before giving this vaccine if:
• your child has a bleeding problem or bruises easily.
As with all vaccines, Synflorix may not fully protect all children who are vaccinated.

Synflorix will only protect against infections caused by the bacteria for which the vaccine has been developed.

Children with a weakened immune system (such as due to HIV infection) may not get the full benefit from Synflorix.

If you are not sure, talk to your doctor or pharmacist before having Synflorix.

**Using other medicines**

Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicines. This includes medicines obtained without a prescription or if they have recently received any other vaccine. Synflorix may not work as well if your child is taking medicines that affect the immune system to fight infection.

Synflorix can be given at the same time as other childhood vaccines such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, oral or inactivated polio, hepatitis B, measles-mumps-rubella, varicella, oral rotavirus vaccines as well as meningococcal serogroup C conjugate vaccines. A different place for the injection will be used for each vaccine.

Your doctor may ask you to give your child paracetamol or other medicines that lower fever before Synflorix is given. This will help to lower some of the side effects of Synflorix. However if your child has paracetamol, their protection against pneumococcal diseases may not be as good.

**Important information about some of the ingredients of Synflorix**

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

### 3. HOW SYNFLORIX IS GIVEN

**How the vaccine is given**

Synflorix is always injected into a muscle. This is usually in the thigh or upper arm.

**How much is given**

Usually, your child will receive a course of 3 injections according to official recommendations or an alternative schedule may be used by the health care professional. It is important to follow the instructions from the doctor or nurse to complete the courses of injections.

- Each injection will be given at least one month apart.
- The first injection can be given from the age of 6 weeks onwards.
- If additional injections (boosters) are necessary, the doctor will tell you. You will be told when your child should come back for their next injection.

Infants aged 7 to 11 months will receive 2 injections. Each injection will be given at least one month apart. A third injection will be given in the second year of life with at least two months apart.

Children aged 12 to 23 months will receive 2 injections. Each injection will be given at least two months apart.

**If your child misses an injection**

If your child misses an injection, it is important that you make another appointment. This is so that you and your doctor can talk about what steps need to be taken to protect your child.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Synflorix can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Very common** (these may occur with more than 1 in 10 doses of the vaccine)
- pain, redness and swelling where the injection is given
- high temperature of 38°C or higher (fever)
- feeling sleepy
- feeling irritable
- loss of appetite.

**Common** (these may occur with up to 1 in 10 doses of the vaccine)
- hardness where the injection is given.

**Uncommon** (these may occur with up to 1 in 100 doses of the vaccine)
- blood clot, bleeding or a small lump where the injection is given
- diarrhoea or feeling sick (vomiting)
- unusual crying.
- temporarily stopping breathing (apnoea) if your child is born prematurely (before or at 28 weeks of pregnancy).

**Rare** (these may occur with up to 1 in 1,000 doses of the vaccine)
- fits without temperature or due to high temperature (fever)
- rash, hives, allergic reactions such as skin rash or allergies

Booster doses of Synflorix may increase the risk of side effects.

In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SYNFLORIX

Keep out of the reach and sight of children.

- Do not use Synflorix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Do not freeze.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Synflorix contains

- The active substances are:
One 0.5 ml dose contains:

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

1 adsorbed on aluminium phosphate 0.5 milligram Al$^{3+}$
2 conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein 9-16 micrograms
3 conjugated to tetanus toxoid carrier protein 5-10 micrograms
4 conjugated to diphtheria toxoid carrier protein 3-6 micrograms

- The other ingredients are: sodium chloride and water for injections

**What Synflorix looks like and contents of the pack**

- Suspension for injection in pre-filled syringe
- Synflorix is a turbid white suspension.
- Synflorix is available in pre-filled syringes with or without needles in packs of 1 or 10.
- Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

GlaxoSmithKline Biologicals s.a.
Rue de l’Institut 89
B-1330 Rixensart
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

**Luxembourg/Luxemburg**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

**България**
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

**Magyarország**
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

**Česká republika**
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

**Malta**
GlaxoSmithKline Malta
Tel: + 356 21 238131

**Danmark**
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00

**Nederland**
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich
GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Polska
GlaxoSmithKline Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal
GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: + 40 (0)21 3028 208

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0) 2 48 26 11 11
recepcia.sk@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

This leaflet was last approved in {MM/YYYY}.
Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

The following information is intended for medical or healthcare professionals only:

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

The content of the pre-filled syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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

The vaccine should be well shaken before use.

The vaccine is for intramuscular use only. Do not administer intravascularly.

If Synflorix is co-administered with other vaccines, different injection sites should be used.

Synflorix should not be mixed with other vaccines. If a vaccine dose is withdrawn into a syringe for injection, the needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

Any unused product or waste material should be disposed of in accordance with local requirements.
Read all of this leaflet carefully before your child receives this vaccine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Synflorix is and what it is used for
2. Before your child receives Synflorix
3. How Synflorix is given
4. Possible side effects
5. How to store Synflorix
6. Further information

1. WHAT SYNFLORIX IS AND WHAT IT IS USED FOR

Synflorix is a pneumococcal conjugate vaccine. Your doctor or nurse will inject your child with this vaccine.

It is used to help protect your child from 6 weeks up to 2 years of age against: a bacteria called ‘Streptococcus pneumoniae’. This bacteria can cause serious illnesses including meningitis, sepsis or bacteraemia (bacteria in blood stream) or ear infection and pneumonia.

How the vaccine works

Synflorix helps your body to make its own antibodies. The antibodies form a part of the immune system that will protect your child against these diseases.

2. BEFORE YOUR CHILD RECEIVES SYNFLORIX

Synflorix should not be given if:

- your child has ever had an allergic reaction (is hypersensitive) to the active substance, or any of the other ingredients in this vaccine (listed in Section 6). Signs of an allergic reaction may include itchy skin rash, being short of breath and swelling of the face or tongue.
- your child has a severe infection with a high temperature (over 38°C). If this applies to your child then the vaccination will be postponed until your child is feeling better. A minor infection such as a cold should not be a problem. However, talk to your doctor first.

Synflorix should not be given to your child if any of the above applies to them. If you are not sure, talk to your doctor or pharmacist before they receive Synflorix.

Take special care with Synflorix:

Check with your doctor or pharmacist before giving this vaccine if:

- your child has a bleeding problem or bruises easily.
As with all vaccines, Synflorix may not fully protect all children who are vaccinated.

Synflorix will only protect against infections caused by the bacteria for which the vaccine has been developed.

Children with a weakened immune system (such as due to HIV infection) may not get the full benefit from Synflorix.

If you are not sure, talk to your doctor or pharmacist before having Synflorix.

**Using other medicines**
Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicines. This includes medicines obtained without a prescription or if they have recently received any other vaccine. Synflorix may not work as well if your child is taking medicines that affect the immune system to fight infection.

Synflorix can be given at the same time as other childhood vaccines such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, oral or inactivated polio, hepatitis B, measles-mumps-rubella, varicella, oral rotavirus vaccines as well as meningococcal serogroup C conjugate vaccines. A different place for the injection will be used for each vaccine.

Your doctor may ask you to give your child paracetamol or other medicines that lower fever before Synflorix is given. This will help to lower some of the side effects of Synflorix. However if your child has paracetamol, their protection against pneumococcal diseases may not be as good.

**Important information about some of the ingredients of Synflorix**
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

3. **HOW SYNFLORIX IS GIVEN**

**How the vaccine is given**

Synflorix is always injected into a muscle. This is usually in the thigh or upper arm.

**How much is given**

Usually, your child will receive a course of 3 injections according to official recommendations or an alternative schedule may be used by the health care professional. It is important to follow the instructions from the doctor or nurse to complete the courses of injections.

- Each injection will be given at least one month apart.
- The first injection can be given from the age of 6 weeks onwards.
- If additional injections (boosters) are necessary, the doctor will tell you. You will be told when your child should come back for their next injection.

Infants aged 7 to 11 months will receive 2 injections. Each injection will be given at least one month apart. A third injection will be given in the second year of life with at least two months apart.

Children aged 12 to 23 months will receive 2 injections. Each injection will be given at least two months apart.

**If your child misses an injection**

If your child misses an injection, it is important that you make another appointment. This is so that you and your doctor can talk about what steps need to be taken to protect your child.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Synflorix can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Very common** (these may occur with more than 1 in 10 doses of the vaccine)
- pain, redness and swelling where the injection is given
- high temperature of 38°C or higher (fever)
- feeling sleepy
- feeling irritable
- loss of appetite.

**Common** (these may occur with up to 1 in 10 doses of the vaccine)
- hardness where the injection is given.

**Uncommon** (these may occur with up to 1 in 100 doses of the vaccine)
- blood clot, bleeding or a small lump where the injection is given
- diarrhoea or feeling sick (vomiting)
- unusual crying.
- temporarily stopping breathing (apnoea) if your child is born prematurely (before or at 28 weeks of pregnancy).

**Rare** (these may occur with up to 1 in 1,000 doses of the vaccine)
- fits without temperature or due to high temperature (fever)
- rash, hives, allergic reactions such as skin rash or allergies

Booster doses of Synflorix may increase the risk of side effects.

In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SYNFLORIX

Keep out of the reach and sight of children.

- Do not use Synflorix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Do not freeze.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Synflorix contains

- The active substances are:
One 0.5 ml dose contains:

1. Pneumococcal polysaccharide serotype 1\textsuperscript{1,2} 1 microgram
2. Pneumococcal polysaccharide serotype 4\textsuperscript{1,2} 3 micrograms
3. Pneumococcal polysaccharide serotype 5\textsuperscript{1,2} 1 microgram
4. Pneumococcal polysaccharide serotype 6B\textsuperscript{1,2} 1 microgram
5. Pneumococcal polysaccharide serotype 7F\textsuperscript{1,2} 1 microgram
6. Pneumococcal polysaccharide serotype 9V\textsuperscript{1,2} 1 microgram
7. Pneumococcal polysaccharide serotype 14\textsuperscript{1,2} 1 microgram
8. Pneumococcal polysaccharide serotype 18C\textsuperscript{1,3} 3 micrograms
9. Pneumococcal polysaccharide serotype 19F\textsuperscript{1,4} 3 micrograms
10. Pneumococcal polysaccharide serotype 23F\textsuperscript{1,2} 1 microgram

\textsuperscript{1} adsorbed on aluminium phosphate 0.5 milligram Al\textsuperscript{3+}
\textsuperscript{2} conjugated to protein D (derived from non-typeable \textit{Haemophilus influenzae}) carrier protein 9-16 micrograms
\textsuperscript{3} conjugated to tetanus toxoid carrier protein 5-10 micrograms
\textsuperscript{4} conjugated to diphtheria toxoid carrier protein 3-6 micrograms

- The other ingredients are: sodium chloride and water for injections

\textbf{What Synflorix looks like and contents of the pack}

- Suspension for injection
- Synflorix is a turbid white suspension.
- Synflorix is available in vials in packs of 1, 10 or 100
- Not all pack sizes may be marketed.

\textbf{Marketing Authorisation Holder and Manufacturer}

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B-1330 Rixensart
Belgium

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\textbf{België/Belgique/Belgien}
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

\textbf{България}
ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

\textbf{Česká republika}
GlaxoSmithKline s.r.o.
Tel: +420 2 22 00 11 11
gsk.czmail@gsk.com

\textbf{Danmark}
GlaxoSmithKline Pharma A/S
Tlf: +45 36 35 91 00

\textbf{Luxembourg/Luxemburg}
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

\textbf{Magyarország}
GlaxoSmithKline Kft.
Tel.: +36-1-2255300

\textbf{Malta}
GlaxoSmithKline Malta
Tel: +356 21 238131

\textbf{Nederland}
GlaxoSmithKline BV
Tel: +31 (0)30 69 38 100
info@glaxosmithkline.dk

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Eesti
GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Ελλάδα
GlaxoSmithKline A.E.B.E
Τηλ.: + 30 210 68 82 100

España
GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 (0) 1 39 17 84 44
diam@gsk.com

Ireland
GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Ísland
GlaxoSmithKline ehf.
Sími: +354-530 3700

Italia
GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος
GlaxoSmithKline Cyprus Ltd
Τηλ.: + 357 22 39 70 00

Latvia
GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

Lietuva
GlaxoSmithKline Lietuva UAB
Tel. +370 5 264 90 00
info.lt@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich
GlaxoSmithKline Pharma GmbH.
Tel: +43 1 970 75-0
at.info@gsk.com

Polska
GlaxoSmithKline Commercial Sp. z o.o.
Tel.: + 48 (22) 576 9000

Portugal
GlaxoSmithKline, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: + 40 (0)21 3028 208

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 (0) 1 280 25 00
medical.x.si@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0) 2 48 26 11 11
recepcia.sk@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: +44 (0)808 100 9997
customercontactuk@gsk.com

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

The following information is intended for medical or healthcare professionals only:

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 allowed to reach room temperature before use.

The vaccine should be well shaken before use.

The vaccine is for intramuscular use only. Do not administer intravascularly.

If Synflorix is co-administered with other vaccines, different injection sites should be used.

Synflorix should not be mixed with other vaccines. If a vaccine dose is withdrawn into a syringe for injection, the needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

Any unused product or waste material should be disposed of in accordance with local requirements.
1. **WHAT SYNFLORIX IS AND WHAT IT IS USED FOR**

Synflorix is a pneumococcal conjugate vaccine. Your doctor or nurse will inject your child with this vaccine.

It is used to help protect your child from 6 weeks up to 2 years of age against:

a bacteria called ‘Streptococcus pneumoniae’. This bacteria can cause serious illnesses including meningitis, sepsis or bacteraemia (bacteria in blood stream) or ear infection and pneumonia.

**How the vaccine works**

Synflorix helps your body to make its own antibodies. The antibodies form a part of the immune system that will protect your child against these diseases.

2. **BEFORE YOUR CHILD RECEIVES SYNFLORIX**

Synflorix should not be given if:

- your child has ever had an allergic reaction (is hypersensitive) to the active substance, or any of the other ingredients in this vaccine (listed in Section 6).
  Signs of an allergic reaction may include itchy skin rash, being short of breath and swelling of the face or tongue.
- your child has a severe infection with a high temperature (over 38°C). If this applies to your child then the vaccination will be postponed until your child is feeling better. A minor infection such as a cold should not be a problem. However, talk to your doctor first.

Synflorix should not be given to your child if any of the above applies to them. If you are not sure, talk to your doctor or pharmacist before they receive Synflorix.

**Take special care with Synflorix:**

Check with your doctor or pharmacist before giving this vaccine if:

- your child has a bleeding problem or bruises easily.
As with all vaccines, Synflorix may not fully protect all children who are vaccinated.

Synflorix will only protect against infections caused by the bacteria for which the vaccine has been developed.

Children with a weakened immune system (such as due to HIV infection) may not get the full benefit from Synflorix.

If you are not sure, talk to your doctor or pharmacist before having Synflorix.

Using other medicines
Please tell your doctor or pharmacist if your child is taking or has recently taken any other medicines. This includes medicines obtained without a prescription or if they have recently received any other vaccine. Synflorix may not work as well if your child is taking medicines that affect the immune system to fight infection.

Synflorix can be given at the same time as other childhood vaccines such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, oral or inactivated polio, hepatitis B, measles-mumps-rubella, varicella, oral rotavirus vaccines as well as meningococcal serogroup C conjugate vaccines. A different place for the injection will be used for each vaccine.

Your doctor may ask you to give your child paracetamol or other medicines that lower fever before Synflorix is given. This will help to lower some of the side effects of Synflorix. However if your child has paracetamol, their protection against pneumococcal diseases may not be as good.

Important information about some of the ingredients of Synflorix
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

3. HOW SYNFLORIX IS GIVEN

How the vaccine is given
Synflorix is always injected into a muscle. This is usually in the thigh or upper arm.

How much is given
Usually, your child will receive a course of 3 injections according to official recommendations or an alternative schedule may be used by the health care professional. It is important to follow the instructions from the doctor or nurse to complete the courses of injections.

- Each injection will be given at least one month apart.
- The first injection can be given from the age of 6 weeks onwards.
- If additional injections (boosters) are necessary, the doctor will tell you. You will be told when your child should come back for their next injection.

Infants aged 7 to 11 months will receive 2 injections. Each injection will be given at least one month apart. A third injection will be given in the second year of life with at least two months apart.

Children aged 12 to 23 months will receive 2 injections. Each injection will be given at least two months apart.

If your child misses an injection
If your child misses an injection, it is important that you make another appointment. This is so that you and your doctor can talk about what steps need to be taken to protect your child.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Synflorix can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Very common** (these may occur with more than 1 in 10 doses of the vaccine)
- pain, redness and swelling where the injection is given
- high temperature of 38°C or higher (fever)
- feeling sleepy
- feeling irritable
- loss of appetite.

**Common** (these may occur with up to 1 in 10 doses of the vaccine)
- hardness where the injection is given.

**Uncommon** (these may occur with up to 1 in 100 doses of the vaccine)
- blood clot, bleeding or a small lump where the injection is given
- diarrhoea or feeling sick (vomiting)
- unusual crying.
- temporarily stopping breathing (apnoea) if your child is born prematurely (before or at 28 weeks of pregnancy).

**Rare** (these may occur with up to 1 in 1,000 doses of the vaccine)
- fits without temperature or due to high temperature (fever)
- rash, hives, allergic reactions such as skin rash or allergies.

Booster doses of Synflorix may increase the risk of side effects.

In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SYNFLORIX

Keep out of the reach and sight of children.

- Do not use Synflorix after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Do not freeze.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Synflorix contains

- The active substances are:
One 0.5 ml dose contains:

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

1 adsorbed on aluminium phosphate 0.5 milligram Al^{3+}
2 conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein 9-16 micrograms
3 conjugated to tetanus toxoid carrier protein 5-10 micrograms
4 conjugated to diphtheria toxoid carrier protein 3-6 micrograms

- The other ingredients are: sodium chloride and water for injections

**What Synflorix looks like and contents of the pack**

- Suspension for injection in multidose container
- Synflorix is a turbid white suspension.
- Synflorix is available in vials for 2 doses in a pack of 100.

**Marketing Authorisation Holder and Manufacturer**

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Rue de l’Institut 89
B-1330 Rixensart
Belgium

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**België/Belgique/Belgien**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

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GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

**Česká republika**
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

**Danmark**
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

**Luxembourg/Luxemburg**
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

**Malta**
GlaxoSmithKline Malta
Tel: + 356 21 238131

**Nederland**
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com
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The following information is intended for medical or healthcare professionals only:

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 allowed to reach room temperature before use.

The vaccine should be well shaken before use. 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.

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

The vaccine is for intramuscular use only. Do not administer intravascularly.

If Synflorix is co-administered with other vaccines, different injection sites should be used.

Synflorix should not be mixed with other vaccines. If a vaccine dose is withdrawn into a syringe for injection, the needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

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