

## PRODUCT MONOGRAPH

### **SYNFLORIX™**

Pneumococcal conjugate vaccine (Non-Typeable *Haemophilus influenzae* (NTHi)  
protein D, diphtheria or tetanus toxoid conjugates) adsorbed

Suspension for injection

Active immunizing agent

GlaxoSmithKline Inc.  
7333 Mississauga Road  
Mississauga, Ontario  
L5N 6L4

Date of Approval:  
May 5, 2009

Submission Control No:

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## DESCRIPTION

SYNFLORIX™ [(pneumococcal conjugate vaccine (Non-Typeable *Haemophilus influenzae* (NTHi) protein D, diphtheria or tetanus toxoid conjugates) adsorbed] is a 10-valent pneumococcal polysaccharide conjugate vaccine using protein D derived from Non-Typeable *Haemophilus influenzae* as a carrier protein for 8 out of the 10 serotypes (1, 4, 5, 6B, 7F, 9V, 14 and 23F). Serotypes 18C and 19F are conjugated to tetanus toxoid and to diphtheria toxoid, respectively. All conjugates are adsorbed onto aluminum phosphate.

## INDICATIONS AND CLINICAL USE

SYNFLORIX™ is indicated for active immunization of infants and children from 6 weeks up to 2 years of age against *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and invasive disease caused by these serotypes (including sepsis, meningitis, bacteraemic pneumonia, pleural empyema and bacteraemia). (see Part II, CLINICAL TRIALS)

### **Geriatrics (> 65 years of age):**

Studies have not been conducted in adults 65 years and older.

### **Pediatrics:**

See Part II, CLINICAL TRIALS.

## CONTRAINDICATIONS

SYNFLORIX™ should not be administered to subjects with known hypersensitivity to any component of the vaccine. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

## WARNINGS AND PRECAUTIONS

### **General**

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

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

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

SYNFLORIX™ will not protect against pneumococcal serogroups that are not included in the vaccine. The observed immune responses to the vaccine varied with each of the vaccine serotypes (see Part II, CLINICAL TRIALS). Although antibody response to diphtheria toxoid, tetanus toxoid and protein D (protein D is highly conserved in all *H. influenzae* strains including NTHi) occurs, immunization with SYNFLORIX™ does not substitute routine immunization with diphtheria, tetanus or *Haemophilus influenzae* type b vaccines. Official recommendations for the immunizations against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

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. Data however, suggest that the use of prophylactic acetaminophen might reduce the immune response to SYNFLORIX™. The clinical relevance of this observation as well as the impact of antipyretics other than acetaminophen remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born  $\leq 28$  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™ is indicated and intended for use in children up to 24 months of age. For appropriate usage of SYNFLORIX™ across age groups, children below 2 years of age should receive the appropriate-for-age SYNFLORIX™ vaccination series (see INDICATIONS AND CLINICAL USE).

### **Hematologic**

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.

### **Immune**

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

Syringe components contain latex.

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

### **Special Populations**

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

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

**Geriatrics (> 65 years of age):** Studies have not been conducted in adults 65 years and older.

## **ADVERSE REACTIONS**

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Clinical trials involved the administration of 12,879 doses of SYNFLORIX™ to 4,595 healthy children as primary vaccination. Three thousand, eight hundred and seventy infants received a booster dose of SYNFLORIX™ in the second year of life. In all trials, SYNFLORIX™ was administered concurrently with the recommended childhood vaccines.

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

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

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

Adverse reactions (following primary immunization or booster dose) considered as being at least possibly related to vaccination have been categorised by frequency (see Table 1).

**Table 1 Adverse reactions considered as being at least possibly related to vaccination**

| Frequency                                | Adverse Reactions   |
|--|---|
| Very common ( $\geq 1/10$ )              | drowsiness, appetite loss, pain, redness, swelling at the injection site, fever ( $\geq 38^{\circ}\text{C}$ rectally), irritability   |
| Common ( $\geq 1/100$ to $< 1/10$ )      | injection site induration, fever ( $> 39^{\circ}\text{C}$ rectally)   |
| Uncommon ( $\geq 1/1,000$ to $< 1/100$ ) | diarrhoea, vomiting, injection site haematoma, haemorrhage and nodule, fever ( $> 40^{\circ}\text{C}$ rectally)*, crying abnormal, apnoea in very premature infants ( $\leq 28$ weeks of gestation) |
| Rare ( $\geq 1/10,000$ to $< 1/1,000$ )  | febrile and non-febrile convulsions, rash, urticaria, allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema)   |

\*reported following booster vaccination

The incidence of solicited local and general adverse events reported within 4 days after each vaccination dose of SYNFLORIX™ was within the same range as after vaccination with PREVNAR® (see Table 2).

**Table 2 Percentage of subjects reporting local and general adverse events within 4 days (day 0-3) following each dose in primary vaccination course and after a booster dose of SYNFLORIX™ or PREVNAR® in primary study 10PN-PD-DIT-001 and subsequent booster study 10PN-PD-DIT-007**

|                                 | Dose 1     |          | Dose 2     |          | Dose 3     |          | Dose 4     |          |
|---------------------------------|------------|----------|------------|----------|------------|----------|------------|----------|
|                                 | SYNFLORIX™ | PREVNAR® | SYNFLORIX™ | PREVNAR® | SYNFLORIX™ | PREVNAR® | SYNFLORIX™ | PREVNAR® |
| <b>Local symptom</b>            | N = 1230   | N = 415  | N = 1217   | N = 414  | N = 1216   | N = 411  | N = 735    | N = 91   |
| Pain                            | 35.5       | 27.2     | 27.8       | 26.8     | 22.8       | 23.4     | 56.6       | 49.5     |
| Redness                         | 37.3       | 38.3     | 37.6       | 39.1     | 37.8       | 36.3     | 51.7       | 57.1     |
| Swelling                        | 28.9       | 26.0     | 30.1       | 27.8     | 28.3       | 24.6     | 36.9       | 38.5     |
| <b>General symptom</b>          |            |          |            |          |            |          |            |          |
| Fever $\geq 38^{\circ}\text{C}$ | 36.7       | 30.1     | 35.3       | 39.6     | 25.6       | 31.4     | 33.3       | 36.3     |
| Fever $> 39^{\circ}\text{C}$    | 2.0        | 1.4      | 2.2        | 2.4      | 1.8        | 2.4      | 3.3        | 7.7      |
| Irritability                    | 66.1       | 64.6     | 61.5       | 61.8     | 51.2       | 55.5     | 59.6       | 60.4     |
| Drowsiness                      | 58.0       | 54.7     | 47.5       | 45.2     | 33.1       | 35.3     | 41.2       | 52.7     |
| Loss of appetite                | 29.8       | 28.4     | 23.7       | 23.4     | 16.9       | 21.9     | 31.3       | 34.1     |

Study 10PN-PD-DIT-001 = 3 doses of SYNFLORIX™ or PREVNAR® + DTPa-HBV-IPV/Hib at 2, 3 and 4 months of age

Study 10PN-PD-DIT-007 = 1 dose of SYNFLORIX™ or PREVNAR® + DTPa-HBV-IPV/Hib at 12 to 18 months of age

### Swelling Reactions

In the clinical programme, the occurrence of large swelling reactions (i.e. swelling with a diameter  $> 50$  mm, noticeable diffuse swelling or noticeable increase of limb

circumference) was solicited in subjects  $\geq$  11 months of age, following booster or catch-up vaccination. Seven (out of 2086) subjects reported large swelling reactions after a booster dose at the SYNFLORIX™ injection site and four (out of 300) subjects reported a large swelling reaction after catch-up immunization. All swellings were local and limited to the injection site, all occurred within three days of vaccination, and all resolved within three days.

### **Serious Adverse Events (SAE)**

Five out of 4,145 subjects (0.1%) receiving primary vaccination with SYNFLORIX™ and two out of 1,072 PREVNAR® vaccinees (0.2%) experienced an SAE that was assessed by the investigator as causally related to vaccination. In booster studies four out of 3,725 subjects (0.1%) receiving a booster dose of SYNFLORIX™ and none of the 449 PREVNAR® vaccinees reported an SAE that was assessed by the investigator as causally related to vaccination.

### **Deaths**

In primary vaccination studies, two (out of 4,145) SYNFLORIX™ vaccinees (receiving 12,137 doses) experienced serious adverse events with a fatal outcome. These serious adverse events included one case of Sudden Infant Death Syndrome (SIDS) and one case of brain neoplasm. One out of 1,072 PREVNAR® vaccinees died due to muscle atrophy. None of the fatal cases were assessed by the investigator as causally related to vaccination. No fatal serious adverse events were reported in the completed booster and catch-up immunization studies.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

#### **Use with other vaccines**

SYNFLORIX™ can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), measles-mumps-rubella vaccine (MMR), varicella vaccine, meningococcal serogroup C conjugate vaccine (CRM<sub>197</sub> and TT conjugates), and rotavirus vaccine. Different injectable vaccines should always be given at different injections sites.

Clinical studies demonstrated that the immune responses 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 (CRM<sub>197</sub> and TT conjugates). Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed.

The safety profiles of the co-administered vaccines appeared unaffected.

**Use with systemic immunosuppressive medications**

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 WARNINGS AND PRECAUTIONS - GENERAL

**Drug-Food Interactions**

Interactions with food have not been established.

**Drug-Herb Interactions**

Interactions with herbal products have not been established.

**Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**

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

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

**Recommended Dose and Dosage Adjustment**

**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 Part II, CLINICAL TRIALS).

Results available to date suggest a 2-4-6 month schedule provides a better immune response as compared with 2-3-4 or 3-4-5 month schedules.

A booster dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age. (see Part II, CLINICAL TRIALS)

**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 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 Part II, CLINICAL TRIALS). 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 protection. A 2-dose schedule in 12-23 month children 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.

### **Administration**

Use of pre-filled syringes: see SPECIAL HANDLING INSTRUCTIONS.

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

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

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

Shake well before use.

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

## **OVERDOSAGE**

Insufficient data are available.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Epidemiological data**

#### **Invasive Pneumococcal Disease (IPD)**

IPD is a severe illness that occurs when bacteria invade normally sterile sites. *S. pneumoniae* is the primary cause of IPD, which manifests as bacteraemia, bacteraemic pneumonia and meningitis. IPD can result in serious morbidity and mortality,

particularly in children, even in developed countries with high standards of healthcare. Routine use of PREVNAR<sup>®</sup> has decreased the incidence of IPD considerably: a Calgary research team that collected population-based surveillance data from 1998 to 2004 found an 81.6% decrease in the overall incidence of IPD in children 23 months of age and younger (63.6 to 11.7 cases/100,000 population). However, there has been an emergence of cases in Canada and worldwide from serotypes not included in the vaccine. Rates of IPD due to serotypes 1, 7F and 19A have increased in children, while serotype 5 has led to IPD outbreaks in adults. The causes of this changing epidemiology are unknown.

### **Mechanism of Action**

SYNFLORIX<sup>™</sup> is a conjugate vaccine, adsorbed, composed of 10 active ingredients: the *S. pneumoniae* polysaccharide serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, each conjugated to a carrier protein (protein D (PD), tetanus toxoid (TT) or diphtheria toxoid (DT)).

The carrier proteins (PD, TT and DT) provide T-cell help to B-cells to produce a boostable antibody response of high affinity to the polysaccharide antigens, thereby providing protection against bacterial tract infections caused by *S. pneumoniae*.

The amount of pneumococcal capsular polysaccharide antibodies elicited by the vaccine is measured by enzyme-linked immunosorbent assay (ELISA). These antibodies help to protect the host by facilitating opsonization of pneumococci and thus facilitating phagocytosis. The ability of a serum sample to facilitate opsonization of bacteria can be measured by *in vitro* opsonophagocytosis assays. It is generally agreed that opsonophagocytic activity (OPA) is the best functional correlate of protection against IPD. (see Part II, CLINICAL TRIALS)

### **STORAGE AND STABILITY**

Store in a refrigerator (2°C - 8°C). Do not freeze. Discard the vaccine if frozen.

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

Do not use after the expiry date shown on the label.

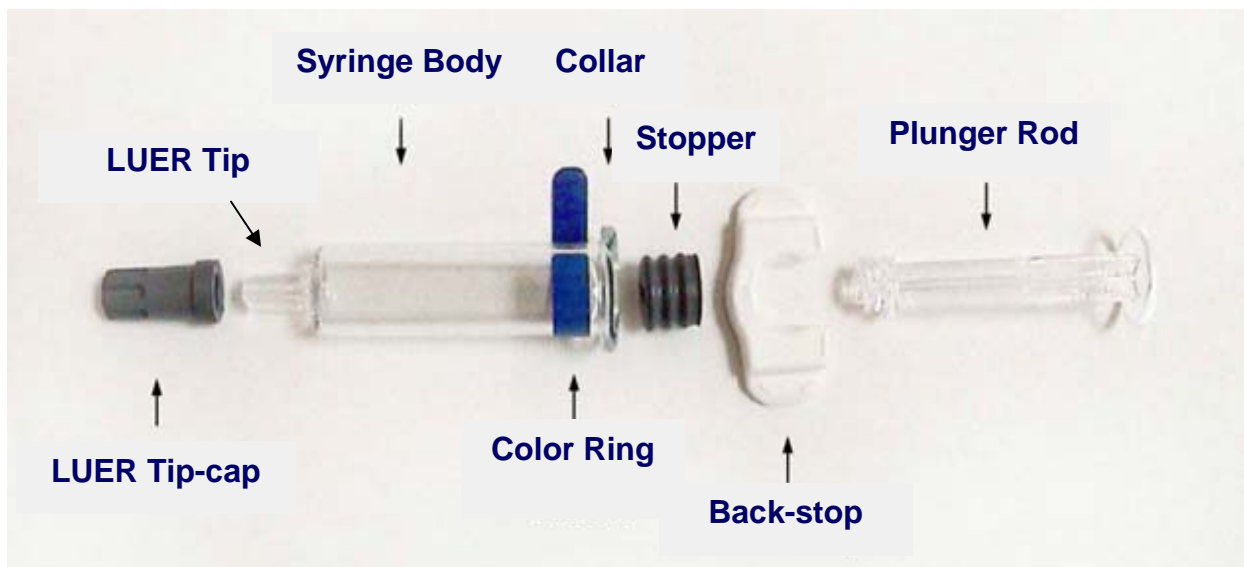
SYNFLORIX<sup>™</sup> should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that SYNFLORIX<sup>™</sup> remains stable and can be administered in case the vaccine has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C. These data are not recommendations for storage. If exposed to temperatures >37°C, discard vaccine.

## SPECIAL HANDLING INSTRUCTIONS

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

### Use of Pre-Filled Syringes

**Do not remove the white back-stop from the syringe.** Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. DO NOT over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Form

SYNFLORIX™ is available as a suspension for injection.

### Composition

One dose (0.5 mL) contains:

|  |                                |
|--|--------------------------------|
| Pneumococcal polysaccharide serotype 1 <sup>1,2</sup>  | 1 microgram                    |
| Pneumococcal polysaccharide serotype 4 <sup>1,2</sup>  | 3 micrograms                   |
| Pneumococcal polysaccharide serotype 5 <sup>1,2</sup>  | 1 microgram                    |
| Pneumococcal polysaccharide serotype 6B <sup>1,2</sup>   | 1 microgram                    |
| Pneumococcal polysaccharide serotype 7F <sup>1,2</sup>   | 1 microgram                    |
| Pneumococcal polysaccharide serotype 9V <sup>1,2</sup>   | 1 microgram                    |
| Pneumococcal polysaccharide serotype 14 <sup>1,2</sup>   | 1 microgram                    |
| Pneumococcal polysaccharide serotype 18C <sup>1,3</sup>  | 3 micrograms                   |
| Pneumococcal polysaccharide serotype 19F <sup>1,4</sup>  | 3 micrograms                   |
| Pneumococcal polysaccharide serotype 23F <sup>1,2</sup>  | 1 microgram                    |
| <sup>1</sup> adsorbed on aluminium phosphate   | 0.5 milligram Al <sup>3+</sup> |
| <sup>2</sup> conjugated to protein D (derived from Non-Typeable <i>H. influenzae</i> ) carrier protein | 9-16 micrograms                |
| <sup>3</sup> conjugated to tetanus toxoid carrier protein  | 5-10 micrograms                |
| <sup>4</sup> conjugated to diphtheria toxoid carrier protein   | 3-6 micrograms                 |

Additional Excipients: sodium chloride, water for injections

### Packaging

#### **Pre-filled Syringes**

SYNFLORIX™ is available as:

- 0.5 mL of suspension in a pre-filled syringe (type I glass) for 1 dose with a plunger stopper (rubber butyl) with or without needles in pack sizes of 1 or 10.

Syringe components contain latex.

#### **Vials**

SYNFLORIX™ is available as:

- 0.5 mL of suspension in a vial (type I glass) for 1 dose with a stopper (rubber butyl) in pack sizes of 1, 10 or 100.
- 1 mL of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl) in pack size of 100.

## **PART II: SCIENTIFIC INFORMATION**

### **PHARMACEUTICAL INFORMATION**

#### **Drug Substances**

- Pneumococcal polysaccharide serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated to Non-Typeable *Haemophilus influenzae* (NTHi) protein D
- Pneumococcal polysaccharide serotype 18C conjugated to tetanus toxoid carrier protein
- Pneumococcal polysaccharide serotype 19F conjugated to diphtheria toxoid carrier protein

All drug substances are individually adsorbed onto aluminum phosphate.

#### **Product Characteristics**

Individual polysaccharides, tetanus toxoid and diphtheria toxoid are prepared from fermentation, inactivation and purification of isolates.

Protein D is a 40kD cell-surface protein originally derived from Non-Typeable *H. influenzae* and now produced recombinantly.

Each polysaccharide serotype is conjugated and adsorbed onto aluminum phosphate as a monovalent preparation prior to mixing into the final vaccine formulation.

## CLINICAL TRIALS

**Table 3 Study demographics and trial design**

| Study No.                          | Trial design   | Vaccine schedule                           | No. of subjects <sup>†</sup>                  |
|------------------------------------|--|--|---|
| <b>Primary vaccination studies</b> |  |  |   |
| 10PN-PD-DIT-001                    | Multi-centre, single-blind, randomized, controlled           | 2, 3 and 4 months of age                   | SYNFLORIX™ = 1235<br>PREVNAR® = 415           |
| 10PN-PD-DIT-002*                   | Multi-centre, open, randomized                               | 2 and 4 months or 2, 3 and 4 months of age | SYNFLORIX™ = 351                              |
| 10PN-PD-DIT-003                    | Single centre, single-blind, randomized, controlled          | 2, 3 and 4 months of age                   | SYNFLORIX™ = 70<br>PREVNAR® = 64              |
| 10PN-PD-DIT-005                    | Single centre, observer-blind, randomized, controlled        | 2, 4 and 6 months of age                   | SYNFLORIX™ = 119<br>Hepatitis A vaccine = 121 |
| 10PN-PD-DIT-010                    | Single centre, open, randomized, controlled                  | 3, 4 and 5 months of age                   | SYNFLORIX™ = 459                              |
| 10PN-PD-DIT-011                    | Multi-centre, open, randomized, controlled                   | 2, 4, and 6 months of age                  | SYNFLORIX™ = 1158<br>PREVNAR® = 390           |
| 10PN-PD-DIT-013 <sup>§</sup>       | Single-centre, open, controlled                              | 3, 4 and 5 months of age                   | SYNFLORIX™ = 150                              |
| <b>Booster studies</b>             |  |  |   |
| 10PN-PD-DIT-002 <sup>¶</sup>       | Multi-centre, open, randomized                               | 11 months of age                           | SYNFLORIX™ = 345                              |
| 10PN-PD-DIT-007                    | Multi-centre, single-blind, partially randomized, controlled | 12-18 months of age                        | SYNFLORIX™ = 1020<br>PREVNAR® = 92            |
| 10PN-PD-DIT-022                    | Single centre, open, randomized, controlled                  | 12-16 months of age                        | SYNFLORIX™ = 324                              |

<sup>†</sup> Number of subjects represent total vaccinated cohort for safety.

\* Study 10PN-PD-DIT-002 evaluated both primary and booster vaccination: numbers of subjects are the numbers evaluated for the primary vaccination phase.

<sup>§</sup> Study 10PN-PD-DIT-013 evaluated primary, booster and catch-up vaccination: numbers of subjects is the number evaluated in the primary vaccination phase below 6 months of age.

<sup>¶</sup> Study 10PN-PD-DIT-002 evaluated both primary and booster vaccination: numbers of subjects are the numbers evaluated for the booster vaccination phase.

### ***Invasive Pneumococcal Disease (IPD)***

The indication against IPD, which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia, is based on World Health Organization (WHO) recommendations (see WHO Criteria). These recommendations state that approval of any new pneumococcal conjugate vaccines against IPD can be based on the demonstration of immunological non-inferiority to the licensed 7-valent CRM<sub>197</sub> conjugate vaccine (PREVNAR<sup>®</sup>). These immunological data are presented below. In line with WHO recommendations, no clinical study has evaluated the efficacy of SYNFLORIX<sup>™</sup> against IPD. However a study conducted with a different formulation demonstrated that the vaccine was able to confer protection against pneumococcal acute otitis media (see Part II, CLINICAL TRIALS, Efficacy Against AOM).

### ***WHO Criteria***

The WHO recommendations state that approval of any new pneumococcal conjugate vaccines against IPD can be based on the demonstration of immunological non-inferiority to PREVNAR<sup>®</sup> by measuring the total amount of anticapsular IgG with an enzyme-linked immunosorbent assay (ELISA).

According to these recommendations, the primary endpoint for demonstration of immunological non-inferiority is the percentage of subjects reaching a predetermined antibody threshold one month after three primary doses of pneumococcal conjugate vaccine. As serotype specific thresholds were not identified, the WHO recommended the use of a single antibody threshold for all serotypes. This threshold was derived from a pooled analysis of three efficacy trials conducted with pneumococcal conjugated vaccines and was found to be 0.35 µg/mL with the second generation ELISA available at that time. The chosen threshold does not represent an individual antibody protection level.

To increase specificity, third generation ELISAs including a 22F adsorption step have been developed. WHO recommendations state that third generation ELISAs must be bridged to the second generation ELISA. An antibody concentration of 0.2 µg/mL in the GSK third generation ELISA was shown in bridging experiments to be equivalent to the 0.35 µg/mL WHO reference threshold. The 0.2 µg/mL threshold was therefore used for the demonstration of immunological non-inferiority compared to PREVNAR<sup>®</sup> in a head-to-head comparative study.

The WHO also requires demonstration of functionality of the elicited antibodies. Opsonophagocytosis (antibody mediated killing of the bacteria) is recognized as the main mechanism of protection against pneumococcal disease. Measurement of the ability of the vaccine-elicited antibodies to opsonise and promote killing of the pneumococcus can be performed in vitro through an opsonophagocytosis activity assay (OPA). The percentage of subjects with an OPA titre  $\geq 8$  is used for comparison between vaccines, although the data to support the OPA titre  $\geq 8$  as a marker of protection are currently insufficient.

Finally, demonstration that vaccines induce immune memory is also required for registration.

In line with WHO recommendations, post-marketing studies will be undertaken to confirm the efficacy of any new pneumococcal conjugate vaccines.

## Results

Immunological non-inferiority compared to PREVNAR<sup>®</sup> was evaluated in the pivotal 10PN-PD-DIT-001 study in which infants were vaccinated according to a 2-3-4 months vaccination schedule. The study was randomized, controlled, multi-centric, conducted in Poland, France and Finland. Immunological non-inferiority was met when the upper limit of the 96.5% CI around the difference between groups (PREVNAR<sup>®</sup> minus SYNFLORIX<sup>™</sup>) in terms of subjects with antibody concentration  $\geq 0.2\mu\text{g/ml}$  was lower than 10%.

As shown in Table 4, SYNFLORIX<sup>™</sup> non inferiority was demonstrated by ELISA for all serotypes, except for 6B and 23F (upper limit of the 96.5% CI around the difference between groups  $> 10\%$ ). For serotypes 6B and 23F, respectively, 65.9% and 81.4% of vaccinees reached the threshold one month after the third primary dose (versus 79.0% and 94.1% for PREVNAR<sup>®</sup>). The clinical relevance of these differences is not known. For the other serotypes contained in each vaccine, 95.4% to 99.5% of vaccinees reached the threshold. The percentage of vaccinees reaching the threshold for the three additional serotypes (1, 5 and 7F) was respectively 97.3%, 99.0% and 99.5% and was at least as good as the aggregate PREVNAR<sup>®</sup> response against the 7 common serotypes (95.8%).

**Table 4 Study 10PN-PD-DIT-001: Non-inferiority analysis using ELISA**

| Antibody | SYNFLORIX <sup>™</sup> |      | PREVNAR <sup>®</sup> |      | Difference in $\% \geq 0.2\mu\text{g/ml}$ (PREVNAR <sup>®</sup> minus SYNFLORIX <sup>™</sup> ) |         |       |
|----------|------------------------|------|----------------------|------|--|---------|-------|
|          | N                      | %    | N                    | %    | %  | 96.5%CI |       |
| Anti-4   | 1106                   | 97.1 | 373                  | 100  | 2.89   | 1.71    | 4.16  |
| Anti-6B  | 1100                   | 65.9 | 372                  | 79.0 | 13.12  | 7.53    | 18.28 |
| Anti-9V  | 1103                   | 98.1 | 374                  | 99.5 | 1.37   | -0.28   | 2.56  |
| Anti-14  | 1100                   | 99.5 | 374                  | 99.5 | -0.08  | -1.66   | 0.71  |
| Anti-18C | 1102                   | 96.0 | 374                  | 98.9 | 2.92   | 0.88    | 4.57  |
| Anti-19F | 1104                   | 95.4 | 375                  | 99.2 | 3.83   | 1.87    | 5.50  |
| Anti-23F | 1102                   | 81.4 | 374                  | 94.1 | 12.72  | 8.89    | 16.13 |

Table 5 presents the percentages of subjects reaching the non-inferiority threshold and the geometric mean concentrations (GMCs) of pneumococcal antibodies following the third primary dose (2-3-4 months schedule), prior to and after the booster dose (12-18 months) of SYNFLORIX<sup>™</sup> or PREVNAR<sup>®</sup> in the pivotal non-inferiority study (10PN-PD-DIT-001) and its booster phase (10PN-PD-DIT-007).

Post-primary GMCs elicited by SYNFLORIX<sup>™</sup> against the seven serotypes in common were lower than those elicited by PREVNAR<sup>®</sup>. However, antibody persistence 8 to 12 months after the last primary dose was similar or higher in SYNFLORIX<sup>™</sup> vaccinees compared to PREVNAR<sup>®</sup> vaccinees for all serotypes, except serotype 14. After the booster dose, the GMCs elicited by SYNFLORIX<sup>™</sup> remained lower for most serotypes

in common with PREVNAR<sup>®</sup> (see Table 5), however the percentages of subjects reaching the 0.2 µg/mL threshold were similar for both vaccines.

In the same study, SYNFLORIX<sup>™</sup> was shown to elicit functional antibodies to all vaccine serotypes. For each of the serotypes in common, 87.7% to 100% of SYNFLORIX<sup>™</sup> vaccinees and 92.1% to 100% of PREVNAR<sup>®</sup> 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 below 5% for all serotypes in common, including 6B and 23F.

For serotypes 1, 5 and 7F, the percentages of SYNFLORIX<sup>™</sup> 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. OPA responses for serotypes 1 and 5 were lower in magnitude than the responses against the other serotypes, especially after the primary course. This may result in a lower efficacy for these serotypes prior to the booster dose which induces an anamnestic response. The clinical relevance of this observation is unknown as in studied populations, the vast majority of serotype 1 and 5 IPD cases occur after one year of age. The response observed for serotype 7F was in the same range as for the seven serotypes in common.

**Table 5 Percentages of subjects reaching the non-inferiority threshold and antibody GMCs, one month post-primary vaccination, prior and one month after booster vaccination – 10PN-PD-DIT-001 and -007**

| Serotype | Timing       | SYNFLORIX <sup>™</sup> |                     | PREVNAR <sup>®</sup>  |                     |
|----------|--------------|------------------------|---------------------|-----------------------|---------------------|
|          |              | %≥0.2µg/ml             | GMC                 | %≥0.2µg/ml            | GMC                 |
| 1        | Post-primary | 97.3<br>(96.1;98.2)    | 1.05<br>(1.00;1.10) | 4.0<br>(2.3;6.6)      | 0.03<br>(0.03;0.03) |
|          | Pre-booster  | 36.4<br>(31.3;41.8)    | 0.14<br>(0.13;0.16) | 3.7<br>(0.8;10.3)     | 0.03<br>(0.03;0.04) |
|          | Post-booster | 99.4<br>(97.9;99.9)    | 1.53<br>(1.40;1.68) | 4.9<br>(1.4;12.2)     | 0.04<br>(0.03;0.05) |
| 4        | Post-primary | 97.1<br>(95.9;98.0)    | 1.45<br>(1.38;1.53) | 100.0<br>(99.0;100.0) | 2.78<br>(2.58;3.00) |
|          | Pre-booster  | 57.3<br>(51.9;62.6)    | 0.23<br>(0.21;0.26) | 67.9<br>(56.4;78.1)   | 0.30<br>(0.25;0.37) |
|          | Post-booster | 99.7<br>(98.4;100.0)   | 3.35<br>(3.06;3.67) | 100.0<br>(95.9;100.0) | 4.40<br>(3.75;5.15) |
| 5        | Post-primary | 99.0<br>(98.2; 99.5)   | 1.70<br>(1.62;1.78) | 1.9<br>(0.8;3.8)      | 0.03<br>(0.03;0.03) |
|          | Pre-booster  | 67.2<br>(61.9;72.1)    | 0.27<br>(0.25;0.30) | 6.0<br>(2.0;13.3)     | 0.04<br>(0.04;0.05) |
|          | Post-booster | 99.4<br>(97.9;99.9)    | 2.20<br>(2.00;2.42) | 6.1<br>(2.0;13.7)     | 0.05<br>(0.04;0.07) |
| 6B       | Post-primary | 65.9<br>(63.0;68.7)    | 0.33<br>(0.30;0.36) | 79.0<br>(74.5;83.1)   | 0.59<br>(0.51;0.67) |
|          | Pre-booster  | 67.0<br>(61.6;72.0)    | 0.31<br>(0.27;0.35) | 30.7<br>(20.5;42.4)   | 0.14<br>(0.11;0.19) |
|          | Post-booster | 96.5<br>(93.9;98.2)    | 1.94<br>(1.74;2.17) | 97.7<br>(91.9;99.7)   | 3.53<br>(2.83;4.41) |
| 7F       | Post-primary | 99.5                   | 1.72                | 4.5                   | 0.04                |

| Serotype | Timing       | SYNFLORIX™            |                     | PREVNAR®              |                      |
|----------|--------------|-----------------------|---------------------|-----------------------|----------------------|
|          |              | %≥0.2µg/ml            | GMC                 | %≥0.2µg/ml            | GMC                  |
|          |              | (98.8;99.8)           | (1.64;1.80)         | (2.7;7.2)             | (0.04;0.04)          |
|          | Pre-booster  | 90.6<br>(87.0;93.5)   | 0.57<br>(0.52;0.62) | 4.7<br>(1.3;11.6)     | 0.03<br>(0.03;0.04)  |
|          | Post-booster | 100.0<br>(98.9;100.0) | 3.50<br>(3.25;3.76) | 7.1<br>(2.6;14.7)     | 0.04<br>(0.03;0.05)  |
| 9V       | Post-primary | 98.1<br>(97.1;98.8)   | 1.32<br>(1.25;1.38) | 99.5<br>(98.1;99.9)   | 2.68<br>(2.47;2.91)  |
|          | Pre-booster  | 84.6<br>(80.3;88.2)   | 0.54<br>(0.48;0.60) | 90.9<br>(82.2;96.3)   | 0.62<br>(0.51;0.76)  |
|          | Post-booster | 100.0<br>(98.9;100.0) | 3.25<br>(2.99;3.53) | 100.0<br>(95.9;100.0) | 6.09<br>(5.19;7.15)  |
| 14       | Post-primary | 99.5<br>(98.9;99.9)   | 2.90<br>(2.75;3.05) | 99.5<br>(98.1;99.9)   | 4.49<br>(4.07;4.96)  |
|          | Pre-booster  | 79.8<br>(75.1;83.9)   | 0.66<br>(0.56;0.76) | 93.3<br>(85.1;97.8)   | 1.06<br>(0.82;1.38)  |
|          | Post-booster | 99.1<br>(97.4;99.8)   | 5.56<br>(5.01;6.18) | 100.0<br>(95.8;100.0) | 9.29<br>(7.85;10.99) |
| 18C      | Post-primary | 96.0<br>(94.7;97.1)   | 1.66<br>(1.56;1.77) | 98.9<br>(97.3;99.7)   | 2.46<br>(2.25;2.69)  |
|          | Pre-booster  | 70.4<br>(65.2;75.2)   | 0.30<br>(0.28;0.34) | 72.3<br>(61.4;81.6)   | 0.32<br>(0.26;0.39)  |
|          | Post-booster | 100.0<br>(98.9;100.0) | 5.01<br>(4.60;5.46) | 100.0<br>(95.8;100.0) | 5.21<br>(4.44;6.11)  |
| 19F      | Post-primary | 95.4<br>(94.0;96.5)   | 1.84<br>(1.71;1.98) | 99.2<br>(97.7;99.8)   | 3.42<br>(3.16;3.70)  |
|          | Pre-booster  | 78.4<br>(73.7;82.6)   | 0.53<br>(0.46;0.61) | 44.7<br>(33.9;55.9)   | 0.23<br>(0.17;0.31)  |
|          | Post-booster | 99.4<br>(97.9;99.9)   | 6.05<br>(5.46;6.71) | 100.0<br>(95.8;100.0) | 3.35<br>(2.83;3.97)  |
| 23F      | Post-primary | 81.4<br>(79.0;83.7)   | 0.53<br>(0.50;0.57) | 94.1<br>(91.2;96.3)   | 1.34<br>(1.18;1.52)  |
|          | Pre-booster  | 60.9<br>(55.5;66.2)   | 0.27<br>(0.23;0.31) | 55.8<br>(44.1;67.2)   | 0.24<br>(0.19;0.31)  |
|          | Post-booster | 97.4<br>(95.0;98.8)   | 2.38<br>(2.13;2.66) | 98.9<br>(93.8;100.0)  | 6.67<br>(5.38;8.26)  |

### Additional immunogenicity data

In clinical trials conducted in various countries across Europe (Finland, France, Poland, Germany, Denmark, Norway, Slovakia, Sweden, Spain and Czech Republic) and in Chile, more than 3,300 subjects received SYNFLORIX™ as a primary vaccination course according to different vaccination schedules, at either 2-3-4, 3-4-5 or 2-4-6 months of age.

In three clinical trials conducted in Europe (Denmark, Norway, Slovakia, Sweden, Finland, France and Poland) more than 1,600 subjects received a fourth (booster) dose of SYNFLORIX™ between 11 and 18 months of age. The administration of a 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. In one study, administration of unconjugated pneumococcal polysaccharides at 13 months of age, after the primary series

with SYNFLORIX™ was also followed by a sharp increase in antibody response for the 10 serotypes further confirming that SYNFLORIX™ induces immune memory.

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 PREVNAR®. This study has shown that the immune response against the 7 common serotypes was comparable after the booster dose. However, as these children were not primed by PREVNAR® against the additional serotypes contained in SYNFLORIX™ (1, 5, 7F), a lower level of protection is anticipated against diseases caused by these three serotypes compared to other serotypes.

***Infants less than 6 months of age:***

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  $\geq 0.2$   $\mu\text{g/mL}$  (ELISA), a lower percentage of subjects with OPA titers  $\geq 8$  was observed for some serotypes in 2-dose primed subjects compared to 3-dose primed subjects. In both schedules, a booster response indicative of immunological priming was observed, even though lower percentage of subjects with OPA titers  $\geq 8$  was still observed in the 2-dose schedule for some serotypes. Post-booster differences, however, were never greater than 10%. The clinical relevance of these observations remains unknown. The 3-dose schedule is recommended to ensure optimal protection. (see DOSAGE AND ADMINISTRATION)

***Children 7-11 or 12-23 months of age:***

One clinical study evaluated catch-up 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 than after the booster dose in infants 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.

***Hyporesponsiveness***

No evidence of hyporesponsiveness has been seen following a booster dose of SYNFLORIX™ or pneumococcal polysaccharide vaccine.

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.

### **Efficacy against AOM**

In a large randomized double-blind Pneumococcal Otitis Media Efficacy Trial (POET) conducted in the Czech Republic and in Slovakia, 2,489 infants received an 11-valent investigational vaccine (11Pn-PD) according to a 3, 4, 5 and 12-15 months vaccination schedule. The vaccine used in this study was composed of the 10 serotypes included in SYNFLORIX™ along with serotype 3 and contained 1µg of each polysaccharide conjugated to Protein D.

Serotype 3 was removed from the SYNFLORIX™ formulation based on the absence of protection against AOM caused by this serotype (see Table 6) and because the ELISA post-booster response was lower than the post-primary response. This was contrary to what was observed for other serotypes.

**Table 6 Protective efficacy of pneumococcal conjugate vaccine (11Pn-PD) for all clinical episodes of AOM and for AOM related to vaccine pneumococcal serotypes (ATP cohort for efficacy)**

| Type or cause of AOM                    | Number of Episodes |     | Vaccine Efficacy |                  | P-value |
|---|--------------------|-----|------------------|------------------|---------|
|   | 11Pn-PD<br>N=2455  | HAV | %                | 95% CI           |         |
| <b>Clinical AOM Episodes</b>            | 333                | 499 | 33.6             | 20.8 to 44.3     | < 0.001 |
| <b>^Vaccine pneumococcal serotypes:</b> |                    |     |                  |                  |         |
| All eleven serotypes                    | 60                 | 141 | 57.6             | 41.4 to 69.3     | < 0.001 |
| Serotype 1                              | 1                  | 1   | 0.2              | -149.5 to 93.6   | 0.999   |
| Serotype 3^                             | 20                 | 17  | -17.1            | -126.5 to 39.5   | 0.639   |
| Serotype 4                              | 0                  | 3   | 100.0            | -27.8* to 100.0  | -       |
| Serotype 5                              | 0                  | 0   | -                | -                | -       |
| Serotype 6B                             | 3                  | 24  | 87.6             | 58.4 to 96.3     | < 0.001 |
| Serotype 7F                             | 0                  | 1   | 100.0            | -283.6* to 100.0 | -       |
| Serotype 9V                             | 3                  | 8   | 62.6             | -40.8 to 90.1    | 0.146   |
| Serotype 14                             | 1                  | 22  | 95.5             | 66.0 to 99.4     | 0.003   |
| Serotype 18C                            | 3                  | 5   | 40.1             | -176.6 to 87.0   | 0.512   |
| Serotype 19F                            | 24                 | 43  | 44.4             | 8.3 to 66.3      | 0.021   |
| Serotype 23F                            | 5                  | 18  | 72.3             | 24.8 to 89.8     | 0.012   |

^ 11-valent investigational formulation containing serotype 3

\*Conservative approximation using Attack Rate definition (standardized asymptotic CI)

HAV = Hepatitis A vaccine

No increase in the incidence of AOM due to other bacterial pathogens was observed.

## **TOXICOLOGY**

### **Animal Pharmacology**

In primary pharmacodynamic studies, the proposed 10-valent vaccine or related 11-valent vaccines were shown to be immunogenic in mice, guinea pigs and rabbits. Several 11-valent related phase II formulations were developed. These formulations contained the same serotypes as the current 10Pn-PD-DiT vaccine and in addition serotype 3, and the

vaccine formulations differed in carrier protein (protein D- PD, tetanus toxoid – TT and diphtheria toxoid- DT). All vaccine formulations induced polysaccharide-specific IgG to all serotypes in the animal models tested. The predictivity of the animal models for human immunogenicity is not clear, and the assessment of comparability for immune response between vaccine formulations was further supported by clinical data. The clinical route of i.m. injection was used for immunogenicity analysis, and ELISA was used in all studies to determine serum antibody levels to each of the serotype. The sera of immunised mice and guinea pigs had functional (opsonophagocytic) activity *in vitro* against several test serotypes.

Two immunogenicity studies in mice showed the enhancing effect of the adjuvant on the antibody response for most of the serotypes. Further justification for the inclusion of aluminium phosphate as adjuvant in the vaccine was given by clinical data.

With respect to the non-clinical data for protein D, the carrier protein from *H influenzae*, a juvenile chinchilla otitis media model was used to demonstrate that passive inoculation with the sera of children administered the 10- or 11-valent vaccine conferred protection against otitis media caused by non-typeable *H influenzae*. The passively transferred sera provided ~34% protection against otitis media, and there were no significant differences between the 2 vaccines.

### **Animal Toxicology**

Although no toxicology studies have been performed with the final 10Pn-PD-DiT SYNFLORIX™ vaccine, toxicology studies were performed with similar 11-valent formulated vaccines containing higher amounts of antigen, carrier proteins or residues. The vaccine formulations used in these studies were immunogenic, well tolerated and without evidence of toxicity, other than injection site reactions which were reversible over time. The toxicity studies with similar 11-valent formulated vaccines are considered to be representative of the final 10-valent 10Pn-PD-DiT vaccine proposed for registration.

The potential side-effects of intramuscular administration of 11Pn-PD-DiT vaccine on cardiovascular and respiratory parameters in the anaesthetised male Wistar rat was studied and did not produce any treatment-related effects on any of the cardiovascular or respiratory parameters measured in the study.

Acute and repeat-dose toxicity studies in which rabbits were administered the full human dose of several 11-valent vaccines showed no systemic toxicity or target organ toxicity, providing overall evidence that the vaccine was safe and well tolerated in the studied animal species. A local inflammatory response was observed which tended to diminish over time with no long-term muscle damage or impairment being observed, consistent with other Aluminium-adjuvanted vaccines.

4-dimethylaminopyridine (DMAP) is an impurity resulting from the conjugation of the polysaccharide serotypes to their respective carrier proteins. The toxicity, mutagenicity and sensitisation potential of DMAP have been investigated. Since DMAP is not

mutagenic and only a moderate skin sensitizer in guinea pigs at very high doses as compared to the human vaccine dose, it does not present any hazard to vaccinated subjects.

### **Carcinogenesis and Mutagenesis**

SYNFLORIX™ has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

### **Reproductive Toxicology**

No studies on reproductive and developmental toxicity have been performed. This vaccine is not intended for women of child-bearing potential.

## **REFERENCES**

1. Bruce MG, Deeks SL, Zulz T, Bruden D, Navarro C, Lovgren M, et al. International Circumpolar Surveillance System for invasive pneumococcal disease, 1999-2005. *Emerg Infect Dis* 2008 Jan; 14(1): 25-33.
2. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I. *Clin Infect Dis* 2000; 30:100-121.
3. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, Part II. *Clin Infect Dis* 2000; 30:122-140.
4. Hausdorff WP, Brueggemann AB, Hackell J, Scott JAG. Pneumococcal serotype epidemiology. In: *Pneumococcal Vaccines: The Impact of Conjugate Vaccine* (eds: G.R. Siber, K. P. Klugman, P. H. Makela), ASM Press: Washington, D.C. (2008 - in press)
5. Henckaerts I., Goldblatt D., Ashton L., Poolman J. Critical differences between pneumococcal polysaccharide enzyme-linked immunosorbent assays with and without 22F inhibition at low antibody concentrations in pediatric sera. *Clin Vaccine Immunol* 2006; 13:356-360.
6. Jakobsen H, Sigurdsson VD, Sigurdardottir S, Schulz D, Jonsdottir I. Pneumococcal serotype 19F conjugate vaccine induces cross-protective immunity to serotype 19A in a murine pneumococcal pneumonia model. *Infect Immun* 2003; 71:2956-2959.
7. Kellner JD, Church DL, MacDonald J, Tyrrell GJ, Scheifele D. Progress in the prevention of pneumococcal infection. *CMAJ* 2005 Nov 8; 173(10): 1149-51.

8. Pelton SI, Huot H, Finkelstein JA, Bishop CJ, Hsu KK, Kellenberg J, et al. Emergence of 19A as virulent and multidrug resistant Pneumococcus in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007 Jun; 26(6): 468-72.
9. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomized double-blind efficacy study. *Lancet* 2006; 367:740-748.
10. Quataert S., Kirch C., Quackenbush Wiedl L., Phipps D., Strohmeyer S., et al. Assignment of weight-based antibody units to a human antipneumococcal standard reference serum, Lot 89-S. *Clin Diagn Lab Immunol* 1995; 2:590-597.
11. Romney MG, Hull MW, Gustafson R, Sandhu J, Champagne S, Wong T, et al. Large community outbreak of *Streptococcus pneumoniae* serotype 5 invasive infection in an impoverished, urban population. *Clin Infect Dis* 2008 Sep 15; 47(6): 768-74.
12. Vakevainen M, Eklund C, Eskola J, Kayhty H. Cross-reactivity of antibodies to type 6B and 6A polysaccharides of *Streptococcus pneumoniae*, evoked by pneumococcal conjugate vaccines, in infants. *J Infect Dis* 2001; 184:789-793.

**PART III: CONSUMER INFORMATION****SYNFLORIX™**

Pneumococcal conjugate vaccine (Non-Typeable *Haemophilus influenzae* (NTHi) protein D, diphtheria or tetanus toxoid conjugates) adsorbed

This leaflet is Part III of a three-part "Product Monograph" published when SYNFLORIX™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SYNFLORIX™. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for and what it does:**

SYNFLORIX™ is a vaccine that will help protect your child against diseases caused by some types of a bacteria called *Streptococcus pneumoniae*. This bacteria can cause serious illnesses including meningitis and blood infection.

SYNFLORIX™ works by helping the body to make its own antibodies, which protect your child against these diseases.

As with all vaccines, SYNFLORIX™ may not fully protect all children who are vaccinated.

SYNFLORIX™ will not protect against pneumococcal serogroups that are not include in the vaccine. Children with a weakened immune system, for example due to HIV infection, may not get the full benefit from SYNFLORIX™.

**When it should not be used:**

Please see Warnings and Precautions section.

**What the medicinal ingredients are:**

- Pneumococcal polysaccharide serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated to Non-Typeable *Haemophilus influenzae* (NTHi) protein D
- Pneumococcal polysaccharide serotype 18C conjugated to tetanus toxoid carrier protein
- Pneumococcal polysaccharide serotype 19F conjugated to diphtheria toxoid carrier protein

**What the important nonmedicinal ingredients are:**

SYNFLORIX™ contains the following nonmedicinal ingredients: aluminum phosphate, sodium chloride, water for injections.

**What dosage forms it comes in:**

SYNFLORIX™ is presented as a suspension for injection.

**WARNINGS AND PRECAUTIONS**

SYNFLORIX™ should not be given if your child has previously had any allergic reaction to SYNFLORIX™, or any ingredient contained in SYNFLORIX™. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

**Take special care with SYNFLORIX™**

Before your child is vaccinated, make sure your doctor knows if any of the following apply to your child:

- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- has a bleeding problem or bruise easily.
- has breathing difficulties, please contact your doctor. This may be more common in the first three days following vaccination if your child is born prematurely (before or at 28 weeks of pregnancy).

**INTERACTIONS WITH THIS MEDICATION**

Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

SYNFLORIX™ may not work as well if your child is taking medicines that reduce the effectiveness of their immune system to fight infection.

SYNFLORIX™ can be given at the same time as other childhood vaccines. A different injection site will be used for each type of vaccine.

**PROPER USE OF THIS MEDICATION****Usual dose:**

Usually, your child will receive a total of three injections with an interval of at least one month between each one. The first injection can be given from the age of 6 weeks onwards. If additional injections (boosters) are necessary, the doctor will tell you.

SYNFLORIX™ is always injected into a muscle, usually in the thigh or upper arm.

You will be informed when your child should come back for their next injection.

**Missed dose:**

If your child misses a scheduled injection, it is important that you make another appointment.

Make sure your child finishes the complete vaccination course.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SYNFLORIX™ can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with SYNFLORIX™ were as follows:

Very common (these may occur in 1 in 10 doses or more of the vaccine):

- Pain, redness and swelling at the injection site
- Fever (38°C or higher)
- Drowsiness
- Irritability
- Loss of appetite

Common (these may occur in up to 1 in 10 doses of the vaccine):

- Hardness at the injection site

Uncommon (these may occur in up to 1 in 100 doses of the vaccine):

- Blood clot, bleeding and small lump at the injection site
- Diarrhoea, vomiting
- Unusual crying
- Temporarily stopping breathing (apnoea) if your child is born prematurely (before or at 28 weeks of pregnancy)

Rare (these may occur in up to 1 in 1,000 doses of the vaccine):

- Rash, hives, allergic reactions such as skin rash or allergies
- Fits without temperature or due to high temperature (fever)

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.

### HOW TO STORE IT

- 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).
- Do not freeze.
- Store in the original package in order to protect from light.

- Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

### REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine, you may notify the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

E-mail: caefi@phac-aspc.gc.ca

By regular mail:

Vaccine Safety Section

Public Health Agency of Canada

130 Colonnade Road

A/L 6502A

Tunney's Pasture

Ottawa, Ontario

K1A 0K9

**NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.**

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.gsk.ca> or can be obtained by contacting the sponsor,

GlaxoSmithKline Inc.  
7333 Mississauga Road  
Mississauga, Ontario  
L5N 6L4  
1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: May 5, 2009

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