

## PRODUCT MONOGRAPH

### **SYNFLORIX<sup>®</sup>**

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

Suspension for injection

Active immunizing agent

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# SYNFLORIX<sup>®</sup>

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

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Suspension for injection 1 dose (0.5 mL) contains: Pneumococcal polysaccharide serotype 1 <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 4 <sup>1</sup> 3 µg Pneumococcal polysaccharide serotype 5 <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 6B <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 7F <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 9V <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 14 <sup>1</sup> 1 µg Pneumococcal polysaccharide serotype 18C <sup>2</sup> 3 µg Pneumococcal polysaccharide serotype 19F <sup>3</sup> 3 µg Pneumococcal polysaccharide serotype 23F <sup>1</sup> 1 µg	aluminum phosphate, sodium chloride, water for injections.  <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

<sup>1</sup> conjugated to protein D (derived from Non-Typeable *Haemophilus influenzae*) carrier protein

<sup>2</sup> conjugated to tetanus toxoid carrier protein

<sup>3</sup> conjugated to diphtheria toxoid carrier protein

### DESCRIPTION

SYNFLORIX<sup>®</sup> [(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<sup>®</sup> is indicated for active immunization of infants and children from 6 weeks up to 5 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of SYNFLORIX<sup>®</sup>.

SYNFLORIX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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 48-72 hours 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. Also see DOSAGE AND ADMINISTRATION and Part II, CLINICAL TRIALS.

SYNFLORIX<sup>®</sup> is indicated and intended for use in children up to 5 years of age (see INDICATIONS AND CLINICAL USE). For appropriate usage of SYNFLORIX<sup>®</sup> across age groups, children below 5 years of age should receive the appropriate-for-age SYNFLORIX<sup>®</sup> vaccination series (see DOSAGE AND ADMINISTRATION).

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

### **Hematologic**

As for other vaccines administered intramuscularly, SYNFLORIX<sup>®</sup> 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.

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

## **Special Populations**

**Pregnant Women:** As SYNFLORIX<sup>®</sup> 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<sup>®</sup> 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 21,000 doses of SYNFLORIX<sup>®</sup> to 7000 healthy children and 137 healthy premature infants as primary vaccination. Five thousand and eight hundred infants and 116 premature infants received a booster dose of SYNFLORIX<sup>®</sup> in the second year of life. Safety was also assessed in 400 children from 2 to 5 years of age. In all trials, SYNFLORIX<sup>®</sup> was administered concurrently with the recommended childhood vaccines.

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

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

The most common adverse reactions observed after primary vaccination were redness at the injection site and irritability which occurred after 37.1% and 50.8% of all doses respectively. Following booster vaccination, these adverse reactions occurred at 50.3% and 52.3% respectively. The majority of these reactions were of mild to moderate severity and were not long lasting.

Adverse reactions reported (for all age groups) are listed according to the following frequency (see Table 1).

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

<b>Frequency</b>	<b>Adverse Reactions</b>
Very common ( $\geq 1/10$ )	drowsiness, appetite loss, pain, redness, swelling at the injection site, fever $\geq 38^{\circ}\text{C}$ rectally (age 2 to 5 years)*, irritability
Common ( $\geq 1/100$ to $< 1/10$ )	injection site induration, fever $> 39^{\circ}\text{C}$ rectally (age $< 2$ years),
Uncommon ( $\geq 1/1,000$ to $< 1/100$ )	diarrhoea, vomiting, injection site haematoma, haemorrhage and nodule, apnoea (see section “Warnings and Precautions” in very premature infants [ $\leq 28$ weeks of gestation]), headache (age 2 to 5 years)*, nausea (age 2 to 5 years)*, injection site reactions like pruritus, fever $> 40^{\circ}\text{C}$ rectally (age $< 2$ years), fever $> 39^{\circ}\text{C}$ rectally (age 2 to 5 years), diffuse swelling of the injected limb, sometimes involving the adjacent joint*
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), crying abnormal
Very rare $< 1/10000$	angioedema

\* reported following booster vaccination of primary series and/or catch-up vaccination

Following booster vaccination, children  $> 12$  months of age are more likely to experience injection site reactions such as rash (uncommon) and crying abnormal (uncommon) compared to the rates observed in infants during the primary series with SYNFLORIX<sup>®</sup>.

The incidence of solicited local and general adverse events reported within 4 days after each vaccination dose of SYNFLORIX<sup>®</sup> was within the same range as after vaccination with the 7-valent PCV vaccine (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 the 7-valent PCV vaccine in primary study 10PN-PD-DIT-001 and subsequent booster study 10PN-PD-DIT-007**

	Dose 1		Dose 2		Dose 3		Dose 4	
	SYNFLORIX®	7-valent PCV vaccine						
<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 ≥ 38°C	36.7	30.1	35.3	39.6	25.6	31.4	33.3	36.3
Fever > 39°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 the 7-valent PCV vaccine+ DTPa-HBV-IPV/Hib at 2, 3 and 4 months of age  
 Study 10PN-PD-DIT-007 = 1 dose of SYNFLORIX® or the 7-valent PCV vaccine+ DTPa-HBV-IPV/Hib at 12 to 18 months of age

The most common adverse reactions after primary vaccination of premature and healthy full-term children were irritability (36.1%), redness (28.3%) and pain (27.3%) in premature children and irritability (40.0%), redness (48.2%) and swelling (43.5%) in the healthy full-term children. Following booster vaccination of premature and healthy full-term children, the most common adverse reactions observed were pain (42.0% and 54.9%, respectively) and irritability (32.1% and 40.2%, respectively) in both premature and healthy children.

**Table 3** The overall per dose incidence of local adverse events within 4 days (day 0-3) following the primary vaccination course of SYNFLORIX® co-administered with DTPa-HBV-IPV/Hib vaccine in preterm infants (Study10PN-PD-DIT-015) and after a booster dose of SYNFLORIX® co-administered with DTPa-IPV/Hib at 16-18 months of age (Study10PN-PD-DIT-016)

Study 10PN-PD-DIT-015						
Local Symptom	Premature (N = 399) (%†)			Full-Term (N = 425) (%†)		
	Total‡	SYNFLORIX®	DTPa-HBV-IPV/Hib	Total	SYNFLORIX®	DTPa-HBV-IPV/Hib
Pain	27.3	24.1	21.8	32.7	28.7	28.8
Redness	28.3	24.1	21.1	48.2	41.9	39.9
Swelling	21.1	16.0	14.8	43.5	36.5	36.3

Study 10PN-PD-DIT-016						
Local Symptom	Premature (N = 112) (%†)			Full-Term (N = 122) (%†)		
	Total	SYNFLORIX®	DTPa-IPV/Hib	Total	SYNFLORIX®	DTPa-IPV/Hib
Pain	42.0	37.5	33.9	54.9	48.4	46.7
Redness	31.3	27.7	23.2	53.3	50.8	45.1
Swelling	24.1	21.4	17.0	45.1	40.2	36.9

Premature – infants born after a gestation period of 27-36 weeks

Full-Term – infants born after a gestation period of more than 36 weeks

N – number of documented doses

†Percentage of doses followed by at least one type of symptom

‡Total represents percentage of doses with at least one local symptom whatever the number of injections

During the primary vaccination course, the overall per dose incidence of fever with rectal temperature > 39.0°C was 1.0% in the pooled Premature group and 2.1% in the Full-term group. Following booster vaccination, fever > 39°C was reported in 7.1% of subjects in the pooled Premature group and in 4.9% in the Full-term group.

### 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 ≥ 11 months of age, following booster or catch-up vaccination. Eight (out of 2202) 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 two to three days of vaccination, and all resolved within three to four days.

### Serious Adverse Events (SAE)

Six out of 4,431 subjects (0.1%) receiving primary vaccination with SYNFLORIX® and two out of 1,072 7-valent PCV 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 7-valent PCV vaccinees reported an SAE that was assessed by the investigator as causally related to vaccination.

## **Deaths**

In primary vaccination studies, three (out of 4,431) SYNFLORIX<sup>®</sup> 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), one case of brain neoplasm, and one case of choking due to aspiration. One out of 1,072 7-valent PCV 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.

## **Post-Marketing Adverse Drug Reactions**

The following events have been spontaneously reported during post-approval use of SYNFLORIX<sup>®</sup>. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

### Nervous system disorders:

Rare: hypotonic-hyporesponsive episode

### Immune system disorder

Very rare: anaphylaxis

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

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

SYNFLORIX<sup>®</sup> 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), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate) and rotavirus vaccine. Different injectable vaccines should always be given at different injection 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%). In addition one month after co-administration with a meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay (OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). There was no impact of co-administration on the other nine pneumococcal

serotypes. Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed. The clinical relevance of the above observations is unknown.

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<sup>®</sup>.

It is recommended that subjects who receive a first dose of SYNFLORIX<sup>®</sup> complete the full vaccination course with SYNFLORIX<sup>®</sup>.

#### **Recommended Dose and Dosage Adjustment**

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

##### ***Three-dose primary series***

The recommended immunization series to ensure optimal protection consists of four doses, each of 0.5 mL.

**Table 4 Vaccine Schedule for Infants from 6 weeks to 6 months of age**

Dose	Dose 1*	Dose 2**	Dose 3**	Dose 4^
Age at Dose	2 months	4 months	6 months	12 - 15 months

\* First dose may be given as early as 6 weeks of age.

\*\*An interval of at least 1 month between doses is recommended. 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 primary dose.

See Part II, CLINICAL TRIALS.

***Two-dose primary series***

Alternatively, when SYNFLORIX<sup>®</sup> is given as part of a routine infant immunization programme, a series consisting of three doses, each of 0.5 mL may be given.

**Table 5 Vaccine Schedule for Infants from 2 to 6 months of age**

Dose	Dose 1	Dose 2*	Dose 3^
Age at Dose	2 months	4 months	11-12 months

\*An interval of 2 months between doses is recommended.

^ A booster dose is recommended at least 6 months after the last primary dose.

Note: it is possible that the 2-dose primary schedule, outside of a routine infant schedule, may not provide optimal protection, especially in infants with high risk of pneumococcal disease.

See Part II, CLINICAL TRIALS.

**Premature infants born between 27 to 36 weeks of gestation:**

The primary vaccination schedule consists of three doses of 0.5 mL with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses (see Part II, CLINICAL TRIALS).

A booster dose is recommended at least 6 months after the last priming dose (see Part II, CLINICAL TRIALS).

**Previously unvaccinated older infants and children:**

For children who are beyond the age of routine infant vaccination schedule, the following catch-up schedule applies:

**Table 6 SYNFLORIX<sup>®</sup> Schedule for Previously Unvaccinated Children ≥ 7 Months through 5 Years of Age**

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3 <sup>a</sup>
12-23 months of age	2 <sup>b*</sup>
≥ 24 months through 5 years of age (prior to the 6 <sup>th</sup> birthday)	2 <sup>b</sup>

<sup>a</sup>2 doses at least 1 month between doses; third dose is recommended after the 1 year birthday, separated by the second dose by at least 2 months.

<sup>b</sup>2 doses at least 2 months apart.

\*The immune response elicited after two doses of SYNFLORIX<sup>®</sup> 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<sup>®</sup> 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**

No cases of overdose have been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **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 7-valent PCV 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 when the vaccine has been stored outside the refrigerator for up to 72 hours at temperatures between 8°C and 25°C. These data are not recommendations for storage.

### **Multidose vials**

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.

## **SPECIAL HANDLING INSTRUCTIONS**

In the absence of compatibility studies, SYNFLORIX<sup>®</sup> must not be mixed with other medicinal products.

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

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

The vaccine should be well shaken before use.

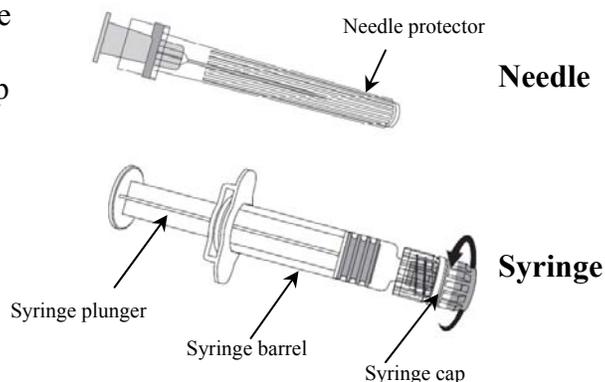
Any unused product or waste material should be disposed of in accordance with local requirements.

### **Use of Pre-Filled Syringes**

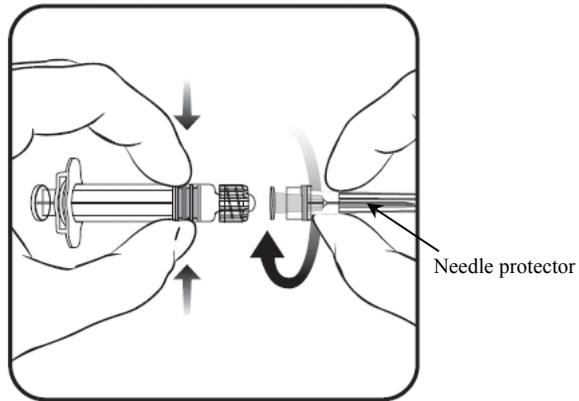
To attach the needle to the syringe, refer to the drawing below.

Note: However the syringe provided with SYNFLORIX<sup>®</sup> might be slightly different (without screw thread) than the syringe described in the drawing. In that case the needle should be attached without screwing.

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see drawing).



3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Form

SYNFLORIX<sup>®</sup> 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 aluminum 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<sup>®</sup> 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.

### **Vials**

SYNFLORIX<sup>®</sup> 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 7 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 <sup>®</sup> = 1235 7-valent PCV vaccine = 415
10PN-PD-DIT-002*	Multi-centre, open, randomized	2 and 4 months or 2, 3 and 4 months of age	SYNFLORIX <sup>®</sup> = 351
10PN-PD-DIT-003	Single centre, single-blind, randomized, controlled	2, 3 and 4 months of age	SYNFLORIX <sup>®</sup> = 70 7-valent PCV vaccine = 64
10PN-PD-DIT-005	Single centre, observer-blind, randomized, controlled	2, 4 and 6 months of age	SYNFLORIX <sup>®</sup> = 119 Hepatitis A vaccine = 121
10PN-PD-DIT-010	Single centre, open, randomized, controlled	3, 4 and 5 months of age	SYNFLORIX <sup>®</sup> = 459
10PN-PD-DIT-011	Multi-centre, open, randomized, controlled	2, 4, and 6 months of age	SYNFLORIX <sup>®</sup> = 1158 7-valent PCV vaccine = 390
10PN-PD-DIT-013 <sup>§</sup>	Single-centre, open, controlled	3, 4 and 5 months of age	SYNFLORIX <sup>®</sup> = 150
		24 months-5 years of age	SYNFLORIX <sup>®</sup> = 150
10-PN-PD-DIT-015 <sup>◇</sup>	Multi-centre, open, randomized, controlled	2, 4 and 6 months of age	SYNFLORIX <sup>®</sup> = 286 <sup>◇</sup> Preterm I group = 50 Preterm II group = 87 Full term group = 149
10PN-PD-DIT-046**	Multi-centre, open, controlled, long-term study	36-46 months of age and 38-48 months of age	SYNFLORIX <sup>®</sup> = 62
<b>Booster studies</b>			
10PN-PD-DIT-002 <sup>¶</sup>	Multi-centre, open, randomized	11 months of age	SYNFLORIX <sup>®</sup> = 345
10PN-PD-DIT-007	Multi-centre, single-blind, partially randomized, controlled	12-18 months of age	SYNFLORIX <sup>®</sup> = 1020 7-valent PCV vaccine = 92
10PN-PD-DIT-022	Single centre, open, randomized, controlled	12-16 months of age	SYNFLORIX <sup>®</sup> = 324
10-PN-PD-DIT-016 <sup>Ω</sup>	Multi-centre, open, controlled	16-18 months of age	SYNFLORIX <sup>®</sup> = 245 <sup>Ω</sup> Preterm I group = 44 Preterm II group = 72 Full term group = 129
<b>Post-Booster studies</b>			
10PN-PD-DIT-046 <sup>Δ</sup> (Follow-up of Study 10PN-PD-DIT-002)	Multi-centre, open, controlled, long-term, follow-up study	36-46 months of age	SYNFLORIX <sup>®</sup> = 110

<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 and 24 months-5 years 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.
- \*\***Study 10PN-PD-DIT-046 evaluated the long-term immunogenicity and safety in children from study 10PN-PD-DIT-002. It also evaluated the immunogenicity and safety of a 2-dose catch-up vaccination in the 4<sup>th</sup> year of age in children who had not received any pneumococcal vaccine.
- <sup>Δ</sup> Study 10PN-PD-DIT-046 evaluated the immunological memory after an additional dose of SYNFLORIX™ at 36-46 months of age in children previously vaccinated in Study 10PN-PD-DIT-002 by a 2-dose or 3-dose primary course within the first 6 months and booster vaccination at 11-12 months of age.
- <sup>◇</sup> Study 10PN-PD-DIT-015 evaluated primary vaccination in premature infants versus full term born infants less than 6 months of age. The study included three parallel groups as follows: Preterm group I (very premature infants born after a gestation period of 27-30 weeks, Preterm group II (mild premature infants born after a gestation period of 31-36 weeks) and Full term group (infants born after a gestation period of more than 36 weeks).
- <sup>Ω</sup> Study 10PN-PD-DIT-016 is the booster study of 10-PN-DIT-015 and included the same three parallel groups as study 10PN-PD-DIT-015.

### ***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 (7-valent PCV vaccine). These immunological data are presented below. In line with WHO recommendations, no clinical study has evaluated the efficacy of SYNFLORIX® 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 7-valent PCV vaccine 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 7-valent PCV vaccine 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 7-valent PCV vaccine 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 (7-valent PCV vaccine 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 8, 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 7-valent PCV vaccine). 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 7-valent PCV vaccine response against the 7 common serotypes (95.8%).

**Table 8 Study 10PN-PD-DIT-001: Non-inferiority analysis using ELISA**

Antibody	SYNFLORIX®		7-valent PCV vaccine		Difference in %≥ 0.2µg/ml (7-valent PCV vaccine minus SYNFLORIX®)		
	N	%	N	%	%	96.5%CI	
Anti-4	1106	97.1	373	100	<b>2.89</b>	1.71	4.16
Anti-6B	1100	65.9	372	79.0	<b>13.12</b>	7.53	18.28
Anti-9V	1103	98.1	374	99.5	<b>1.37</b>	-0.28	2.56
Anti-14	1100	99.5	374	99.5	<b>-0.08</b>	-1.66	0.71
Anti-18C	1102	96.0	374	98.9	<b>2.92</b>	0.88	4.57
Anti-19F	1104	95.4	375	99.2	<b>3.83</b>	1.87	5.50
Anti-23F	1102	81.4	374	94.1	<b>12.72</b>	8.89	16.13

Table 9 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® or 7-valent PCV vaccine in the pivotal non-inferiority study (10PN-PD-DIT-001) and its booster phase (10PN-PD-DIT-007).

Post-primary GMCs elicited by SYNFLORIX® against the seven serotypes in common were lower than those elicited by 7-valent PCV vaccine. However, antibody persistence 8 to 12 months after the last primary dose was similar or higher in SYNFLORIX® vaccinees compared to 7-valent PCV vaccine vaccinees for all serotypes, except serotype 14. After the booster dose, the GMCs elicited by SYNFLORIX® remained lower for most serotypes in common with 7-valent PCV vaccine (see Table 9), however the percentages of subjects reaching the 0.2 µg/mL threshold were similar for both vaccines.

In the same study, SYNFLORIX® was shown to elicit functional antibodies to all vaccine serotypes. For each of the serotypes in common, 87.7% to 100% of SYNFLORIX® vaccinees and 92.1% to 100% of 7-valent PCV vaccine 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® 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 9 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®		7-valent PCV vaccine	
		% ≥0.2µg/ml	GMC	% ≥0.2µg/ml	GMC
1	Post-primary	97.3 (96.1;98.2)	1.05 (1.00;1.10)	4.0 (2.3;6.6)	0.03 (0.03;0.03)
	Pre-booster	36.4 (31.3;41.8)	0.14 (0.13;0.16)	3.7 (0.8;10.3)	0.03 (0.03;0.04)
	Post-booster	99.4 (97.9;99.9)	1.53 (1.40;1.68)	4.9 (1.4;12.2)	0.04 (0.03;0.05)
4	Post-primary	97.1 (95.9;98.0)	1.45 (1.38;1.53)	100.0 (99.0;100.0)	2.78 (2.58;3.00)
	Pre-booster	57.3 (51.9;62.6)	0.23 (0.21;0.26)	67.9 (56.4;78.1)	0.30 (0.25;0.37)
	Post-booster	99.7 (98.4;100.0)	3.35 (3.06;3.67)	100.0 (95.9;100.0)	4.40 (3.75;5.15)
5	Post-primary	99.0 (98.2; 99.5)	1.70 (1.62;1.78)	1.9 (0.8;3.8)	0.03 (0.03;0.03)
	Pre-booster	67.2 (61.9;72.1)	0.27 (0.25;0.30)	6.0 (2.0;13.3)	0.04 (0.04;0.05)
	Post-booster	99.4 (97.9;99.9)	2.20 (2.00;2.42)	6.1 (2.0;13.7)	0.05 (0.04;0.07)
6B	Post-primary	65.9 (63.0;68.7)	0.33 (0.30;0.36)	79.0 (74.5;83.1)	0.59 (0.51;0.67)
	Pre-booster	67.0 (61.6;72.0)	0.31 (0.27;0.35)	30.7 (20.5;42.4)	0.14 (0.11;0.19)
	Post-booster	96.5 (93.9;98.2)	1.94 (1.74;2.17)	97.7 (91.9;99.7)	3.53 (2.83;4.41)
7F	Post-primary	99.5 (98.8;99.8)	1.72 (1.64;1.80)	4.5 (2.7;7.2)	0.04 (0.04;0.04)
	Pre-booster	90.6 (87.0;93.5)	0.57 (0.52;0.62)	4.7 (1.3;11.6)	0.03 (0.03;0.04)
	Post-booster	100.0 (98.9;100.0)	3.50 (3.25;3.76)	7.1 (2.6;14.7)	0.04 (0.03;0.05)
9V	Post-primary	98.1 (97.1;98.8)	1.32 (1.25;1.38)	99.5 (98.1;99.9)	2.68 (2.47;2.91)
	Pre-booster	84.6 (80.3;88.2)	0.54 (0.48;0.60)	90.9 (82.2;96.3)	0.62 (0.51;0.76)
	Post-booster	100.0 (98.9;100.0)	3.25 (2.99;3.53)	100.0 (95.9;100.0)	6.09 (5.19;7.15)
14	Post-primary	99.5 (98.9;99.9)	2.90 (2.75;3.05)	99.5 (98.1;99.9)	4.49 (4.07;4.96)
	Pre-booster	79.8 (75.1;83.9)	0.66 (0.56;0.76)	93.3 (85.1;97.8)	1.06 (0.82;1.38)
	Post-booster	99.1 (97.4;99.8)	5.56 (5.01;6.18)	100.0 (95.8;100.0)	9.29 (7.85;10.99)

Serotype	Timing	SYNFLORIX®		7-valent PCV vaccine	
		% ≥0.2µg/ml	GMC	% ≥0.2µg/ml	GMC
18C	Post-primary	96.0 (94.7;97.1)	1.66 (1.56;1.77)	98.9 (97.3;99.7)	2.46 (2.25;2.69)
	Pre-booster	70.4 (65.2;75.2)	0.30 (0.28;0.34)	72.3 (61.4;81.6)	0.32 (0.26;0.39)
	Post-booster	100.0 (98.9;100.0)	5.01 (4.60;5.46)	100.0 (95.8;100.0)	5.21 (4.44;6.11)
19F	Post-primary	95.4 (94.0;96.5)	1.84 (1.71;1.98)	99.2 (97.7;99.8)	3.42 (3.16;3.70)
	Pre-booster	78.4 (73.7;82.6)	0.53 (0.46;0.61)	44.7 (33.9;55.9)	0.23 (0.17;0.31)
	Post-booster	99.4 (97.9;99.9)	6.05 (5.46;6.71)	100.0 (95.8;100.0)	3.35 (2.83;3.97)
23F	Post-primary	81.4 (79.0;83.7)	0.53 (0.50;0.57)	94.1 (91.2;96.3)	1.34 (1.18;1.52)
	Pre-booster	60.9 (55.5;66.2)	0.27 (0.23;0.31)	55.8 (44.1;67.2)	0.24 (0.19;0.31)
	Post-booster	97.4 (95.0;98.8)	2.38 (2.13;2.66)	98.9 (93.8;100.0)	6.67 (5.38;8.26)

### Additional immunogenicity data

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

##### ***3-dose primary schedule***

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 7-valent PCV vaccine. 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 7-valent PCV vaccine 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.

**2-dose primary schedule**

In addition to the 3-dose primary schedule, the immunogenicity of SYNFLORIX<sup>®</sup> following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in two clinical studies.

In the first study (study 011), the immunogenicity two months after the second dose of SYNFLORIX<sup>®</sup> was compared with a 7-valent PCV vaccine in a post-hoc analysis. The analysis is based on a random subset of sera (about one third) from the SYNFLORIX<sup>®</sup> group and all available sera from the 7-valent PCV vaccines. Please refer to Table 10.

**Table 10 Study 011 (Post-hoc analysis): ELISA/OPA responders and ELISA GMCs/OPA GMTs to the 7 common serotypes in 7-valent PCV vaccine and SYNFLORIX<sup>®</sup> after two vaccine doses**

Serotypes		4	6B	9V	14	18C	19F	23F
	N	ELISA GMC (µg/mL)						
SYNFLORIX <sup>®</sup>	151-170	1.23	0.34	0.92	2.09	1.21	2.17	0.47
7-valent PCV Vaccine	49-166	2.02	0.16	2.24	2.63	1.79	2.10	0.49
		% ELISA ≥ 0.20 µg/mL						
SYNFLORIX <sup>®</sup>	151-170	98.2	64.1	95.2	98.8	87.1	95.9	75.3
7-valent PCV Vaccine	49-166	99.4	30.7	97.0	98.2	97.6	99.4	75.9
		OPA GMT						
SYNFLORIX <sup>®</sup>	131-151	239.1	94.2	675.4	385.9	22.4	65.8	860.4
7-valent PCV Vaccine	42-156	241.6	22.8	658.4	432.2	22.8	19.3	556.6
		% OPA ≥ 8						
SYNFLORIX <sup>®</sup>	131-151	96.6	62.8	98.6	97.3	60.6	84.1	96.6
7-valent PCV Vaccine	42-156	96.1	34.9	99.4	94.2	74.7	67.9	88.7

N = number of subjects with available results.

In the second study (10PN-PD-DIT-002), the immunogenicity was compared in an exploratory analysis between the 2+1 schedule and 3+1 schedule. Please refer to **Table 11**.

**Table 11 Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (ATP cohort for immunogenicity)**

Antibody	Group	Timing	N	≥ 0.2 µg/mL			GMC	
				n	%	95% CI	value	95% CI
ANTI-1	10Pn_2d	PII(M3)	153	149	97.4	93.4; 99.3	1.03	0.90; 1.18
		PIII(M10)	156	155	99.4	96.5; 100	1.85	1.59; 2.15
	10Pn_3d	PIII(M3)	151	149	98.7	95.3; 99.8	1.23	1.07; 1.42
		PIV(M10)	147	147	100	97.5; 100	1.88	1.62; 2.17
ANTI-4	10Pn_2d	PII(M3)	153	150	98.0	94.4; 99.6	1.37	1.21; 1.55
		PIII(M10)	155	155	100	97.6; 100	3.06	2.68; 3.49
	10Pn_3d	PIII(M3)	153	152	99.3	96.4; 100	1.71	1.47; 1.99
		PIV(M10)	147	147	100	97.5; 100	3.47	3.03; 3.98
ANTI-5	10Pn_2d	PII(M3)	152	146	96.1	91.6; 98.5	1.32	1.14; 1.52
		PIII(M10)	155	155	100	97.6; 100	2.65	2.31; 3.03
	10Pn_3d	PIII(M3)	149	149	100	97.6; 100	1.85	1.63; 2.10
		PIV(M10)	147	147	100	97.5; 100	3.21	2.81; 3.67
ANTI-6B	10Pn_2d	PII(M3)	149	83	55.7	47.3; 63.8	0.19	0.15; 0.24
		PIII(M10)	156	138	88.5	82.4; 93.0	1.12	0.88; 1.41
	10Pn_3d	PIII(M3)	149	94	63.1	54.8; 70.8	0.31	0.25; 0.38
		PIV(M10)	147	142	96.6	92.2; 98.9	1.85	1.54; 2.22
ANTI-7F	10Pn_2d	PII(M3)	153	148	96.7	92.5; 98.9	1.28	1.13; 1.46
		PIII(M10)	156	156	100	97.7; 100	2.81	2.51; 3.15
	10Pn_3d	PIII(M3)	152	151	99.3	96.4; 100	2.14	1.90; 2.40
		PIV(M10)	147	147	100	97.5; 100	3.88	3.45; 4.37
ANTI-9V	10Pn_2d	PII(M3)	152	142	93.4	88.2; 96.8	0.92	0.81; 1.05
		PIII(M10)	156	155	99.4	96.5; 100	2.95	2.59; 3.37
	10Pn_3d	PIII(M3)	153	152	99.3	96.4; 100	1.47	1.29; 1.68
		PIV(M10)	147	147	100	97.5; 100	3.97	3.49; 4.50
ANTI-14	10Pn_2d	PII(M3)	152	146	96.1	91.6; 98.5	1.72	1.45; 2.05
		PIII(M10)	156	155	99.4	96.5; 100	4.19	3.62; 4.85
	10Pn_3d	PIII(M3)	152	152	100	97.6; 100	2.57	2.22; 2.97
		PIV(M10)	147	145	98.6	95.2; 99.8	5.47	4.68; 6.40
ANTI-18C	10Pn_2d	PII(M3)	152	146	96.1	91.6; 98.5	1.26	1.06; 1.51
		PIII(M10)	156	156	100	97.7; 100	6.24	5.43; 7.18
	10Pn_3d	PIII(M3)	153	152	99.3	96.4; 100	3.42	2.87; 4.07
		PIV(M10)	147	146	99.3	96.3; 100	7.20	6.08; 8.52
ANTI-19F	10Pn_2d	PII(M3)	152	141	92.8	87.4; 96.3	2.43	1.97; 2.98
		PIII(M10)	156	150	96.2	91.8; 98.6	5.58	4.65; 6.69
	10Pn_3d	PIII(M3)	152	146	96.1	91.6; 98.5	4.43	3.60; 5.45
		PIV(M10)	147	144	98.0	94.2; 99.6	6.95	5.92; 8.17
ANTI-23F	10Pn_2d	PII(M3)	153	106	69.3	61.3; 76.5	0.38	0.30; 0.47
		PIII(M10)	154	148	96.1	91.7; 98.6	2.41	1.98; 2.94
	10Pn_3d	PIII(M3)	152	118	77.6	70.2; 84.0	0.52	0.42; 0.63
		PIV(M10)	147	141	95.9	91.3; 98.5	2.78	2.31; 3.35

10Pn\_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn\_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

GMC = geometric mean antibody concentration; N = number of subjects with available results; n/% = number/percentage of subjects with concentration within the specified range.

PII(M3) = One month after dose 2 (for the 2 primary doses group); PIII(M10) = One month after booster dose (for the 2 primary doses group); PIII(M3) = One month after dose 3 (for the 3 primary doses group); PIV(M10) = One month after booster dose (for the 3 primary doses group)

Note: The Confidence Intervals are presented for descriptive purposes and are not intended to be used to draw conclusions.

In the follow-up of the second study, (10PN-PD-DIT-046) based on a subset of the subjects originally randomized to Study 10PN-PD-DIT-002 (110/351 = 31%) 24-36 months after completion of the 2+1 schedule or the 3+1 schedule, at least 83.7% or 96.6% subjects, respectively, remained seropositive (i.e., detectable antibody > 0.05 µg/mL) to each of the vaccine pneumococcal serotypes. In this subset of subjects, a single dose of SYNFLORIX<sup>®</sup> administered during the 4<sup>th</sup> year of life, as a challenge dose, elicited higher ELISA antibody GMCs 7-10 days following vaccination in 2-dose primed subjects (ranging from 4.00 to 20.28 µg/mL) and 3-dose primed subjects (ranging from 4.72 to 30.55 µg/mL).

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

### ***Premature infants***

In studies 10PN-PD-DIT-015 and 10PN-PD-DIT-016, immunogenicity of SYNFLORIX<sup>®</sup> in very premature (born after a gestation period of 27-30 weeks) (N=42), premature (born after a gestation period of 31-36 weeks) (N=82) and full term (born after a gestation period of more than 36 weeks) (N=132) infants was evaluated descriptively following a three dose primary vaccination course at 2, 4, and 6 months of age. Immunogenicity was also evaluated in 44 very premature, 69 premature and 127 full term infants following a booster dose at 16 to 18 months of age. See immunogenicity data by ELISA in Table 12 below.

**Table 12 ELISA responders and ELISA GMCs to the 10 common serotypes one month post-primary vaccination (study 10PN-PD-DIT-015), prior to and one month after booster vaccination (study 10PN-PD-DIT-016)**

			ELISA			
			≥ 0.2 µg/mL		GMC	
Serotype	Group	Timing	%	95% CI	Value	95% CI
1	PT1	Post-primary	97.6	87.4; 99.9	0.97	0.75; 1.26
		Pre-booster	37.2	23.0; 53.3	0.15	0.11; 0.20
		Post-booster	100	91.8; 100	1.57	1.20; 2.05
	PT2	Post-primary	100	95.6; 100	1.10	0.93; 1.30
		Pre-booster	42.4	30.3; 55.2	0.14	0.11; 0.18
		Post-booster	100	94.6; 100	1.74	1.41; 2.15
	FT	Post-primary	99.2	95.8; 100	1.35	1.18; 1.55
		Pre-booster	43.8	34.8; 53.1	0.17	0.15; 0.21
		Post-booster	99.2	95.4; 100	1.98	1.66; 2.37
4	PT1	Post-primary	97.6	87.1; 99.9	1.53	1.19; 1.98
		Pre-booster	53.5	37.7; 68.8	0.25	0.18; 0.35
		Post-booster	100	91.8; 100	2.98	2.31; 3.85
	PT2	Post-primary	98.8	93.4; 100	1.88	1.61; 2.20
		Pre-booster	58.0	45.5; 69.8	0.24	0.20; 0.30
		Post-booster	100	94.6; 100	3.67	3.07; 4.39
	FT	Post-primary	100	97.2; 100	2.42	2.13; 2.74
		Pre-booster	66.7	57.6; 74.9	0.30	0.25; 0.35
		Post-booster	100	96.9; 100	4.23	3.67; 4.88

			ELISA			
Serotype	Group	Timing	≥ 0.2 µg/mL		GMC	
			%	95% CI	Value	95% CI
5	PT1	Post-primary	100	91.6; 100	1.45	1.13; 1.86
		Pre-booster	62.8	46.7; 77.0	0.24	0.18; 0.33
		Post-booster	100	91.8; 100	1.84	1.43; 2.38
	PT2	Post-primary	100	95.6; 100	1.93	1.65; 2.25
		Pre-booster	63.2	50.7; 74.6	0.27	0.21; 0.34
		Post-booster	100	94.6; 100	2.38	1.93; 2.94
	FT	Post-primary	100	97.2; 100	2.31	2.00; 2.66
		Pre-booster	84.7	77.1; 90.5	0.40	0.34; 0.48
		Post-booster	100	96.9; 100	2.58	2.20; 3.02
6B	PT1	Post-primary	92.7	80.1; 98.5	0.85	0.61; 1.19
		Pre-booster	65.1	49.1; 79.0	0.28	0.21; 0.38
		Post-booster	100	91.6; 100	2.44	1.87; 3.17
	PT2	Post-primary	95.1	88.0; 98.7	1.11	0.89; 1.37
		Pre-booster	61.2	48.5; 72.9	0.30	0.23; 0.37
		Post-booster	98.5	91.8; 100	2.46	1.97; 3.06
	FT	Post-primary	93.9	88.3; 97.3	1.18	1.00; 1.39
		Pre-booster	79.8	71.7; 86.5	0.37	0.31; 0.45
		Post-booster	100	96.9; 100	2.67	2.27; 3.13
7F	PT1	Post-primary	100	91.4; 100	1.87	1.47; 2.39
		Pre-booster	79.1	64.0; 90.0	0.42	0.31; 0.56
		Post-booster	100	91.8; 100	3.11	2.48; 3.90
	PT2	Post-primary	100	95.6; 100	2.37	2.07; 2.73
		Pre-booster	86.2	75.3; 93.5	0.46	0.37; 0.58
		Post-booster	100	94.6; 100	4.16	3.52; 4.90
	FT	Post-primary	100	97.2; 100	2.69	2.39; 3.03
		Pre-booster	93.5	87.6; 97.2	0.66	0.57; 0.77
		Post-booster	100	96.9; 100	3.93	3.45; 4.47
9V	PT1	Post-primary	97.6	87.1; 99.9	1.43	1.17; 1.74
		Pre-booster	90.7	77.9; 97.4	0.51	0.39; 0.67
		Post-booster	100	91.8; 100	2.87	2.23; 3.70
	PT2	Post-primary	100	95.6; 100	1.69	1.44; 1.99
		Pre-booster	85.5	75.0; 92.8	0.42	0.35; 0.52
		Post-booster	100	94.6; 100	3.47	2.86; 4.20
	FT	Post-primary	100	97.2; 100	2.41	2.13; 2.73
		Pre-booster	93.5	87.6; 97.2	0.59	0.51; 0.69
		Post-booster	100	96.9; 100	4.17	3.60; 4.83
14	PT1	Post-primary	100	91.4; 100	3.52	2.81; 4.42
		Pre-booster	95.3	84.2; 99.4	0.78	0.54; 1.11
		Post-booster	100	91.8; 100	4.88	3.42; 6.98
	PT2	Post-primary	100	95.6; 100	3.28	2.77; 3.89
		Pre-booster	80.9	69.5; 89.4	0.48	0.37; 0.61
		Post-booster	100	94.6; 100	5.14	4.22; 6.25
	FT	Post-primary	100	97.2; 100	3.71	3.21; 4.30
		Pre-booster	84.7	77.1; 90.5	0.68	0.55; 0.84
		Post-booster	100	96.9; 100	5.98	5.10; 7.02
18C	PT1	Post-primary	100	91.4; 100	3.28	2.51; 4.29
		Pre-booster	83.7	69.3; 93.2	0.58	0.42; 0.80
		Post-booster	100	91.8; 100	9.51	7.36; 12.29
	PT2	Post-primary	100	95.5; 100	4.86	3.92; 6.02
		Pre-booster	88.2	78.1; 94.8	0.56	0.45; 0.70
		Post-booster	100	94.6; 100	13.20	10.97; 15.89
	FT	Post-primary	98.5	94.6; 99.8	5.22	4.27; 6.38
		Pre-booster	84.8	77.3; 90.6	0.60	0.49; 0.73
		Post-booster	99.2	95.4; 100	12.38	10.21; 15.00

			ELISA			
			≥ 0.2 µg/mL		GMC	
Serotype	Group	Timing	%	95% CI	Value	95% CI
19F	PT1	Post-primary	100	91.6; 100	3.60	2.83; 4.57
		Pre-booster	88.4	74.9; 96.1	0.86	0.58; 1.30
		Post-booster	100	91.8; 100	6.83	5.24; 8.89
	PT2	Post-primary	100	95.6; 100	4.80	4.15; 5.55
		Pre-booster	97.1	89.8; 99.6	1.07	0.78; 1.46
		Post-booster	100	94.6; 100	9.78	8.19; 11.68
	FT	Post-primary	100	97.2; 100	4.56	3.95; 5.26
		Pre-booster	96.0	90.9; 98.7	1.27	1.02; 1.59
		Post-booster	100	96.9; 100	9.72	8.38; 11.29
23F	PT1	Post-primary	95.1	83.5; 99.4	1.05	0.74; 1.49
		Pre-booster	69.8	53.9; 82.8	0.27	0.20; 0.36
		Post-booster	97.6	87.4; 99.9	2.70	1.91; 3.81
	PT2	Post-primary	96.3	89.7; 99.2	1.33	1.07; 1.65
		Pre-booster	65.2	52.8; 76.3	0.30	0.24; 0.38
		Post-booster	100	94.6; 100	3.45	2.93; 4.06
	FT	Post-primary	95.4	90.3; 98.3	1.54	1.28; 1.85
		Pre-booster	80.5	72.4; 87.1	0.42	0.35; 0.51
		Post-booster	99.2	95.4; 100	3.30	2.74; 3.99

PT1 = Preterm I group (children born as preterm after a gestation period of 27-30 weeks); PT2 = Preterm II group (children born as preterm after a gestation period of 31-36 weeks); FT = Full term group (children born after a gestation period of more than 36 weeks); GMC = geometric mean antibody concentration; % = percentage of subjects with concentration within the specified range

### *Previously Unvaccinated Older Infants and Children:*

One clinical study (study 013) evaluated catch-up vaccination in children older than 7 months of age (three age groups with different schedules). In the 7-11 months group, children received 2 primary doses followed by a booster dose in the second year of life, the 12 to 23 month group received 2 doses with at least a 2 month interval and the children in the group ≥ 24 months to 5 years of age received 1 dose.

**Table 13 Antibody GMCs Against the Vaccine Pneumococcal Serotypes (One month after the final dose)**

Serotype	<6 months of age (4 <sup>th</sup> dose) N=137 (95% CI)	7 to 11 months of age (3 <sup>rd</sup> dose) N=114 (95% CI)	12 to 23 months of age (2 <sup>nd</sup> dose) N=133 (95% CI)	≥ 24 months to 5 years of age (1 dose) N=138-140 (95% CI)
1	1.84 (1.59; 2.12)	1.77 (1.55; 2.02)	1.22 (1.06; 1.40)	0.77 (0.66; 0.89)
4	2.98 (2.60; 3.42)	3.79 (3.27; 4.40)	4.21 (3.77; 4.69)	5.72 (5.00; 6.54)
5	2.21 (1.94; 2.53)	2.88 (2.48; 3.34)	1.80 (1.57; 2.06)	1.16 (0.99; 1.36)
6B	1.62 (1.35; 1.94)	1.39 (1.14; 1.69)	0.53 (0.43; 0.65)	0.38 (0.30; 0.47)
7F	3.31 (2.92; 3.74)	3.73 (3.24; 4.28)	3.62 (3.22; 4.06)	2.60 (2.25; 3.01)
9V	3.41 (2.96; 3.92)	2.13 (1.82; 2.50)	1.50 (1.30; 1.73)	1.01 (0.84; 1.22)
14	3.96 (3.39; 4.62)	5.41 (4.71; 6.22)	4.24 (3.64; 4.95)	1.36 (1.06; 1.74)
18C	5.28 (4.55; 6.12)	9.40 (8.04; 10.98)	9.20 (8.22; 10.29)	4.65 (4.06; 5.31)

Serotype	<6 months of age (4 <sup>th</sup> dose) N=137 (95% CI)	7 to 11 months of age (3 <sup>rd</sup> dose) N=114 (95% CI)	12 to 23 months of age (2 <sup>nd</sup> dose) N=133 (95% CI)	≥ 24 months to 5 years of age (1 dose) N=138-140 (95% CI)
19F	3.38 (2.81; 4.06)	5.71 (4.68; 6.97)	5.45 (4.63; 6.41)	5.26 (4.34; 6.39)
23F	2.76 (2.37; 3.21)	1.65 (1.33; 2.03)	0.88 (0.73; 1.05)	0.37 (0.30; 0.47)

N=number of subjects with available results

Note: The Confidence Intervals are presented for descriptive purposes and are not intended to be used to draw conclusions.

In study 002, children were vaccinated according to either a 3-dose (shown below in Table 14) or 2-dose primary vaccination within the first 6 months of age and a booster vaccination at 11 months of age. In study 046, a 2 dose catch-up vaccination was given to children in their 4<sup>th</sup> year of life who had not previously received any pneumococcal vaccine.

**Table 14 Antibody GMCs Against the Vaccine Pneumococcal Serotypes**

Serotype	002* 3 <sup>rd</sup> dose N=149-153	046^ Unprimed N=60
1	1.23	2.81
4	1.71	8.44
5	1.85	3.54
6B	0.31	1.11
7F	2.14	6.10
9V	1.47	2.22
14	2.57	6.48
18C	3.42	22.28
19F	4.43	17.03
23F	0.52	1.09

N=number of subjects with available results

\*One month after dose 3 (3 dose primary vaccination)

^2 doses; children unprimed in their fourth year of life

### *Hyporesponsiveness*

No evidence of hyporesponsiveness has been seen following a booster dose of SYNFLORIX<sup>®</sup> or pneumococcal polysaccharide vaccine.

There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to SYNFLORIX<sup>®</sup> 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<sup>®</sup> along with serotype 3 and contained 1µg of each polysaccharide conjugated to Protein D.

Serotype 3 was removed from the SYNFLORIX<sup>®</sup> formulation based on the absence of protection against AOM caused by this serotype (see Table 15) 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 15 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 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 <sup>^</sup>	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

<sup>^</sup> 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.

## **Protective effectiveness against IPD in a clinical trial**

In a large-scale phase III/IV, double-blind, cluster-randomized, controlled, clinical trial in Finland (FinIP), 30,528 infants less than 7 months of age at enrolment and 15,449 children aged 7 months to 18 months at enrolment were followed for invasive disease for an average of 25 and 28 months respectively and included in the analysis of effectiveness. Children were enrolled into 78 study clusters. Clusters were randomised into 4 groups according to the two infant vaccination schedules (2-dose or 3-dose primary schedule followed by a booster dose: 2+1 or 3+1 schedule) to receive either SYNFLORIX<sup>®</sup> (52 clusters) or hepatitis vaccines as control (26 clusters).

### *Effectiveness in infant cohort below 7 months of age at enrolment*

Vaccine effectiveness (VE) was demonstrated in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes when SYNFLORIX<sup>®</sup> was given to infants in either 2+1 or 3+1 schedules (see Table 16).

**Table 16** Number of vaccine serotype IPD cases and vaccine effectiveness in infants below 7 months of age at enrolment receiving at least one vaccine dose (Infant total vaccinated cohort)

Type of IPD	No. of IPD cases			VE (95% CI)	
	SYNFLORIX <sup>®</sup> 3+1 schedule (N=10,273)	SYNFLORIX <sup>®</sup> 2+1 schedule (N=10,054)	Control (HBV) <sup>(2)</sup> (N=10,201)	3+1 schedule	2+1 schedule
Vaccine serotype IPD <sup>(1)</sup>	0	1	12	100% <sup>(3)</sup> (82.8; 100)	91.8% <sup>(4)</sup> (58.3; 99.6)
Serotype 6B IPD	0	0	5	100% (54.9; 100)	100% (54.5; 100)
Serotype 14 IPD	0	0	4	100% (39.6; 100)	100% (43.3; 100)

IPD Invasive Pneumococcal Disease

VE Vaccine Effectiveness

N number of subjects per group

CI Confidence Interval

(1) Apart from serotypes 6B and 14, culture-confirmed vaccine serotype IPD cases included 7F (1 case in the SYNFLORIX<sup>®</sup> 2+1 clusters), 18C, 19F and 23F (1 case of each in the control clusters).

(2) the 2 groups of control clusters of infants were pooled

(3) p-value<0.0001

(4) p-value=0.0009

The observed VE against culture-confirmed IPD due to any serotype was 100% (95% CI, 85.6-100.0%; 0 versus 14 cases) for the 3+1 schedule, 85.8% (95% CI, 49.1-97.8%; 2 versus 14 cases) for the 2+1 schedule and 93.0% (95% CI, 74.9-98.9%; 2 versus 14 cases) regardless of the primary vaccination schedule.

### *Effectiveness following catch-up immunization*

In the catch-up cohorts, children between 7-11 months of age at first vaccine dose received SYNFLORIX<sup>®</sup> or hepatitis B according to a 2-dose primary schedule followed by a booster dose and children between 12-18 months of age at first vaccine dose received 2 doses of either SYNFLORIX<sup>®</sup> or hepatitis A.

Among the 15,449 children in the catch-up vaccinated cohorts, there were no culture-confirmed IPD cases in the SYNFLORIX<sup>®</sup> groups while 7 IPD cases were observed in the control groups (serotypes 7F and 14 in the 7-11 month cohort and serotypes 3, 4, 6B, 15C and 19F in the 12-18 month cohort).

### **Protective effectiveness against IPD in post-marketing surveillance**

In Quebec, Canada, SYNFLORIX<sup>®</sup> was introduced into the infant immunization program (2 primary doses to infants less than 6 months of age and a booster dose at 12 months) following 4.5 years of use of 7-valent PCV vaccine. Based on 1.5-years of surveillance following SYNFLORIX<sup>®</sup> introduction, with over 90% coverage in the vaccine-eligible age group, a decrease in vaccine serotype IPD incidence (largely due to changes in serotype 7F disease) was observed with no concomitant increase in non-vaccine serotype IPD incidence, leading to an overall decrease in IPD incidence in the target age group compared to the incidence reported during the preceding period.

## **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 aluminum 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<sup>®</sup> 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 Aluminum-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<sup>®</sup> 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

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**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 vaccine.

**ABOUT THIS VACCINE****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 included 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).

Fainting can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if you or your child fainted with a previous injection.

**INTERACTIONS WITH THIS VACCINE**

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 VACCINE****Usual dose:**

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

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

Usually, your child will receive 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. At least six months after the last (third) injection, your child will receive an additional injection (booster).

Alternatively, your child may receive two injections with an interval of two months between injections. The first injection can be given from the age of 2 months. At least six months after the last injection, your child will receive an additional injection (booster).

*Previously unvaccinated older infants and children*

*Infants aged 7-11 months:*

Your child will receive two injections with an interval of at least one month between injections. At least two months after the last injection and during his/her second year of life, your child will receive a third injection (booster).

*Children aged 12 months-23 months:*

Your child will receive a total of two injections with an interval of at least two months between injections. If an additional injection (booster) is necessary, the doctor will tell you.

*Children aged 24 months-5 years:*

Your child will receive a total of two injections with an interval of at least two months between injections.

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

*Infants from 6 weeks to 6 months of age born prematurely (born between 27 and 36 weeks of gestation)*

Your child will receive a total of three injections with an interval of at least one month between each one. At least six months after the last (third) injection, your child will receive an additional injection (booster).

**Overdosage:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**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<sup>®</sup> can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with SYNFLORIX<sup>®</sup> 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):

- Itching, blood clot, bleeding and small lump at the injection site
- Nausea, diarrhoea, vomiting
- Temporarily stopping breathing (apnoea)
- Headache
- Skin rash
- Swelling larger than 5 cm where the injection was given

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

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

Very rare (these may occur in up to 1 in 10,000 doses of the vaccine):

- Severe allergic reactions which can be recognised by:
  - raised and itchy rash (hives)
  - swelling, sometimes of the face or mouth (angioedema) causing difficulty in breathing – collapse

These reactions will usually occur before leaving the doctor's clinic. However, if your child gets any of these symptoms you should contact a doctor urgently.

Following booster vaccination, children > 12 months of age are more likely to experience injection site reactions such as rash (uncommon) and crying abnormal (uncommon) compared to the rates observed in infants during the primary series with SYNFLORIX<sup>®</sup>.

Other side effects have been seen with SYNFLORIX<sup>®</sup> since being introduced onto the market:

- Collapse (sudden onset of muscle floppiness), periods of unconsciousness or lack of awareness, and paleness or bluish skin discolouration
- An extreme, often life-threatening, allergic reaction (on very rare instances)

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<sup>®</sup> 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 vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.**

### **For health care professionals:**

**If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in [your province/territory](#).**

### **For the General Public:**

**Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.**

**If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at 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](mailto:caefi@phac-aspc.gc.ca)**

**At the following website:**

**<http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>**

### **By regular mail:**

**The Public Health Agency of Canada  
Vaccine Safety Section  
130 Colonnade Road  
Ottawa, Ontario  
K1A 0K9 Address Locator 6502A**

**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,

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