ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vaxneuvance suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Pneumococcal polysaccharide serotype 1[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 3[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 4[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 5[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 6A[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 6B[1,2]	4.0 micrograms
Pneumococcal polysaccharide serotype 7F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 9V[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 14[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 18C[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 19A[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 19F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 22F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 23F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 33F[1,2]	2.0 micrograms

[1]Conjugated to CRM_{197} carrier protein. CRM_{197} is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.
[2]Adsorbed on aluminium phosphate adjuvant.

1 dose (0.5 mL) contains 125 micrograms aluminium (Al^{3+}) and approximately 30 micrograms CRM_{197} carrier protein.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (injection).
The vaccine is an opalescent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to less than 18 years of age.

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.

See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of Vaxneuvance should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Routine vaccination schedule in infants and children aged 6 weeks to less than 2 years	
Two-dose primary series followed by a booster dose	The recommended immunisation regimen consists of 3 doses of Vaxneuvance, each of 0.5 mL. The first dose is given as early as 6 weeks of age, with a second dose administered 8 weeks later. The third (booster) dose is recommended between 11 through 15 months of age.
Three-dose primary series followed by a booster dose	An immunisation regimen consisting of 4 doses of Vaxneuvance, each of 0.5 mL, may be given. This primary series consists of 3 doses, with the first dose given as early as 6 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth (booster) dose is recommended between 11 through 15 months of age and at least 2 months after the third dose.
Preterm infants (<37 weeks gestation at birth)	The recommended immunisation regimen consists of a three-dose primary series of Vaxneuvance followed by a fourth (booster) dose, each of 0.5 mL, as per three-dose primary series followed by a booster dose posology (see sections 4.4 and 5.1).
Prior vaccination with another pneumococcal conjugate vaccine	Infants and children who have begun immunisation with another pneumococcal conjugate vaccine may switch to Vaxneuvance at any point in the schedule (see section 5.1).
Catch-up vaccination schedule for children 7 months to less than 18 years of age	
Unvaccinated infants 7 to less than 12 months of age	3 doses, each of 0.5 mL, with the first two doses given at least 4 weeks apart. A third (booster) dose is recommended after 12 months of age, separated from the second dose by at least 2 months.
Unvaccinated children 12 months to less than 2 years of age	2 doses, each of 0.5 mL, with an interval of 2 months between doses.
Unvaccinated or not fully vaccinated children and adolescents 2 to less than 18 years of age	1 dose (0.5 mL). If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before administering Vaxneuvance.
Vaccination schedule for individuals 18 years of age and older	
Individuals 18 years of age and older	1 dose (0.5 mL). The need for revaccination with a subsequent dose of Vaxneuvance has not been established.

Special populations
One or more doses of Vaxneuvance may be given to individuals who have one or more underlying conditions predisposing them to an increased risk of pneumococcal disease (such as individuals with

sickle cell disease or living with human immunodeficiency virus (HIV) infection or recipients of haematopoietic stem cell transplant (HSCT) or immunocompetent individuals 18 to 49 years of age with risk factors for pneumococcal disease; see section 5.1).

Method of administration

The vaccine should be administered by intramuscular injection. The preferred site is the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children and adults.

No data are available for administration via the intradermal route.

For instructions on the handling of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, or to any diphtheria toxoid-containing vaccine.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precaution related to route of administration

Vaxneuvance must not be administered intravascularly.

Anaphylaxis

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.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution to individuals receiving anticoagulant therapy, or to those with thrombocytopenia or any coagulation disorder such as haemophilia. Bleeding or bruising may occur following an intramuscular administration in these individuals. Vaxneuvance may be given subcutaneously if the potential benefit clearly outweighs the risks (see section 5.1).

Apnoea in premature infants

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

Immunocompromised individuals

Immunocompromised individuals, whether due to the use of immuno-suppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Safety and immunogenicity data for Vaxneuvance are available for individuals with sickle cell disease or living with HIV infection or with a haematopoietic stem cell transplant (see section 5.1). Safety and immunogenicity data for Vaxneuvance are not available for individuals in other specific immunocompromised groups and vaccination should be considered on an individual basis.

Protection

As with any vaccine, vaccination with Vaxneuvance may not protect all vaccine recipients. Vaxneuvance will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine (see sections 2 and 5.1).

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Different injectable vaccines should always be administered at different injection sites.

Immunosuppressive therapies may reduce the immune responses to vaccines.

Infants and children aged 6 weeks to less than 2 years
Vaxneuvance can be given concomitantly with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, pertussis, poliomyelitis (serotypes 1, 2 and 3), hepatitis A, hepatitis B, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella and rotavirus vaccine.

Children and adolescents 2 to less than 18 years of age
There are no data on the concomitant administration of Vaxneuvance with other vaccines.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to other pneumococcal vaccines suggest that administration of antipyretics concomitantly or within the same day of vaccination may reduce the immune response after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Adults
Vaxneuvance can be administered concomitantly with seasonal quadrivalent influenza vaccine (split virion, inactivated). There are no data on the concomitant administration of Vaxneuvance with other vaccines.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There is limited experience with the use of Vaxneuvance in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3).

Administration of Vaxneuvance in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and the foetus.

Breast-feeding

It is unknown whether Vaxneuvance is excreted in human milk.

Fertility

No human data on the effect of Vaxneuvance on fertility are available. Animal studies in female rats do not indicate harmful effects (see section 5.3).

4.7 Effects on ability to drive and use machines

Vaxneuvance has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Paediatric population

Infants and children aged 6 weeks to less than 2 years

The safety of Vaxneuvance in healthy infants, including preterm infants (from 6 weeks of age at first vaccination) and children (11 through 15 months of age) was assessed as a 3 dose or 4 dose regimen in 5 clinical studies with a total of 7,229 participants.

All 5 studies evaluated the safety of Vaxneuvance when administered concomitantly with other routine paediatric vaccines. In these studies, 4,286 participants received a complete regimen of Vaxneuvance, 2,405 participants received a complete regimen of the 13-valent pneumococcal conjugate vaccine (PCV) and 538 participants received Vaxneuvance when used to complete a regimen initiated with the 13-valent PCV (mixed dose regimen).

The most frequent adverse reactions were pyrexia ≥38 °C (75.2%), irritability (74.5%), somnolence (55.0%), injection-site pain (44.4%), injection-site erythema (41.7%), decreased appetite (38.2%), injection-site induration (28.3%) and injection-site swelling (28.2%) based on results in 3,589 participants (Table 1), excluding participants who received a mixed dose regimen. The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤3 days). Severe reactions (defined as being extremely distressed or unable to do usual activities or size of injection site reaction >7.6 cm) occurred in ≤3.5% of infants and children following any dose, with the exception of irritability which occurred in 11.4% of participants.

Children and adolescents 2 to less than 18 years of age

The safety of Vaxneuvance in healthy children and adolescents was assessed in a study that included 352 participants 2 to less than 18 years of age, of whom 177 received a single dose of Vaxneuvance. In this age cohort, 42.9% of all participants had a history of previous vaccination with a lower valency pneumococcal conjugate vaccine.

The most frequent adverse reactions were injection-site pain (54.8%), myalgia (23.7%), injection-site swelling (20.9%), injection-site erythema (19.2%), fatigue (15.8%), headache (11.9%), injection-site induration (6.8%), and pyrexia ≥38 °C (5.6%) (Table 1). The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤3 days); severe reactions

(defined as being extremely distressed or unable to do usual activities or size of injection site reaction >7.6 cm) occurred in ≤4.5% of children and adolescents.

Adults 18 years of age and older

The safety of Vaxneuvance in healthy and immunocompetent adults was assessed in 6 clinical studies in 7,136 adults ≥18 years of age. An additional clinical study assessed 302 adults ≥18 years of age living with HIV. Vaxneuvance was administered to 5,630 adults; 1,241 were 18 to 49 years of age, 1,911 were 50 to 64 years of age, and 2,478 were 65 years of age and older. Of those who received Vaxneuvance, 1,134 were immunocompetent adults 18 to 49 years of age who had no (n=285), 1 (n=620) or ≥ 2 (n=229) risk factors for pneumococcal disease and 152 were adults ≥18 years of age living with HIV. In addition, 5,253 adults were pneumococcal vaccine-naïve and 377 adults were previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPV23) at least 1 year prior to enrollment.

The most frequently reported adverse reactions following vaccination with Vaxneuvance were solicited. In the pooled analysis of the 7 studies, the most frequent adverse reactions were injection-site pain (64.6%), fatigue (23.4%), myalgia (20.7%), headache (17.3%), injection-site swelling (16.1%), injection-site erythema (11.3%) and arthralgia (7.9%) (Table 1). The majority of solicited adverse reactions were mild (based on intensity or size) and of short duration (≤3 days); severe reactions (defined as an event that prevents normal daily activity or size of injection site reaction >10 cm) occurred in ≤1.5% of adults across the clinical program.

Older adults reported fewer adverse reactions than younger adults.

Tabulated list of adverse reactions

In clinical studies of adults, local and systemic adverse reactions were solicited daily after vaccination for 5 and 14 days, respectively and in infants, children and adolescents up to 14 days after vaccination. In all populations, unsolicited adverse reactions were reported for 14 days after vaccination.

Adverse reactions reported for all age groups are listed in this section per system organ class, in decreasing order of frequency and seriousness. The frequency is defined as follows:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

System Organ Class	Adverse Reactions	Frequency		
		Infants/Children/Adolescents		Adults
		6W to <2Y	2 to <18Y[§]	
Metabolism and nutrition disorders	Decreased appetite	Very common	Common	-
Psychiatric disorders	Irritability	Very common	Common	-
Immune system disorders	Hypersensitivity reaction including tongue oedema, flushing, and throat tightness	-	-	Rare
Nervous system disorders	Somnolence	Very common	Common	-
	Headache	-	Very common	Very common
	Dizziness	-	-	Uncommon[†]
Skin and subcutaneous tissue disorders	Urticaria	Common	Common	Rare
	Rash	Common	Not known [‡]	Uncommon
Gastrointestinal disorders	Nausea	-	Common	Uncommon[†]
	Vomiting	Common	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	-	Very common	Very common
	Arthralgia	-	-	Common*
General disorders and administration site conditions	Pyrexia[ɻ]	Very common	Common	Uncommon[†]
	≥39°C	Very common	-	-
	≥40 °C	Common	-	-
	Injection-site pain	Very common	Very common	Very common
	Injection-site erythema	Very common	Very common	Very common
	Injection-site swelling	Very common	Very common	Very common
	Injection-site induration	Very common	Common	-
	Injection-site urticaria	Uncommon	-	-
	Fatigue	-	Very common	Very common
	Injection-site pruritus	-	-	Common
	Injection-site warmth	-	-	Uncommon
	Injection-site bruising/haematoma	Common	Common	Uncommon
	Chills	-	-	Uncommon[†]

[§]Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to less than 18 years of age. For participants <3 years of age (Vaxneuvance N=32, 13-valent PCV N=28), decreased appetite, irritability, somnolence and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to less than 18 years of age, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.

[†]common in adults 18 to 49 years of age

[‡]In clinical trials, no events were observed following Vaxneuvance in healthy children and adolescents and two events were observed in special populations (sickle cell disease and HIV).

*very common in adults 18 to 49 years of age

[ɻ]defined as temperature ≥38 °C

Additional information for other dosing regimens, vaccination schedules and special populations

Mixed dose regimen of different pneumococcal conjugate vaccines

The safety profiles of mixed 4-dose regimens of Vaxneuvance and the 13-valent PCV in healthy infants and children were generally comparable to those of complete 4-dose regimens of either Vaxneuvance or the 13-valent PCV (see section 5.1).

Catch-up vaccination schedule

Safety was also assessed as a catch-up vaccination schedule in 126 healthy infants and children from 7 months to less than 2 years of age who received 2 or 3 doses of Vaxneuvance based on age at enrollment. The safety profile of the catch-up vaccination schedule was generally consistent with the safety profile of the routine vaccination schedule initiated from 6 weeks of age (see section 5.1).

Children and adolescents with sickle cell disease or living with HIV
Safety was also assessed in 69 children and adolescents 5 to less than 18 years of age with sickle cell disease and in 203 children and adolescents 6 to less than 18 years of age living with HIV, all of whom received a single dose of Vaxneuvance. The safety profile of Vaxneuvance in children with these conditions was generally consistent with the safety profile in healthy children (see section 5.1).

Children and adults receiving Haematopoietic Stem Cell Transplant
Safety was also assessed in 131 adults and 8 children ≥3 years of age who had received an allogeneic haematopoietic stem cell transplant (allo-HSCT) 3 to 6 months prior to enrollment, all of whom received between 1 and 4 doses of Vaxneuvance. The safety profile of Vaxneuvance in recipients of allo-HSCT was generally consistent with the safety profile in a healthy population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data with regard to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, pneumococcal vaccines, ATC code: J07AL02

Mechanism of action

Vaxneuvance contains 15 purified pneumococcal capsular polysaccharides from *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, with the additional serotypes 22F and 33F), each conjugated to a carrier protein (CRM_{197}). Vaxneuvance elicits a T-cell dependent immune response to induce antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

Immune responses following natural exposure to *Streptococcus pneumoniae* or following pneumococcal vaccination can be determined by measuring opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses. OPA represents functional antibodies and is considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. In children, a serotype-specific IgG antibody level corresponding to ≥0.35 µg/mL using the WHO enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines.

Clinical immunogenicity in healthy infants, children and adolescents

Immunogenicity was assessed by serotype-specific IgG response rates (the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL) and IgG geometric mean concentrations (GMCs) at 30 days following the primary series and/or following the toddler (booster) dose. In a subset of participants, OPA geometric mean titres (GMTs) were also measured at 30 days following the primary series and/or following the toddler dose.

Infants and children receiving a routine vaccination schedule

3-dose regimen (2-dose primary series + 1 toddler dose)
In the double-blind, active comparator-controlled study (Protocol 025), 1,184 participants were randomised to receive Vaxneuvance or the 13-valent PCV in a 3-dose regimen. The first two doses were administered to infants at 2 and 4 months of age (primary series) and the third dose was administered to children at 11 through 15 months of age (toddler dose). Participants also received other paediatric vaccines concomitantly, including Rotavirus vaccine (live) with the infant primary series and Diphtheria, Tetanus, Pertussis (acellular), Hepatitis B (rDNA), Poliomyelitis (inactivated), *Haemophilus influenzae* type b conjugate vaccine (adsorbed) with all 3 doses in the complete regimen.

Vaxneuvance elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs, for all 15 serotypes contained in the vaccine. At 30 days following the two-dose primary series, serotype-specific IgG response rates and GMCs were generally comparable for the 13 shared serotypes and higher for the 2 additional serotypes (22F and 33F) in Vaxneuvance recipients, compared to the 13-valent PCV recipients. At 30 days following the toddler dose, Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes and superior for the 2 additional serotypes, as assessed by IgG response rate and IgG GMCs (Table 2).

Table 2: Serotype-specific IgG response rates and IgG GMCs at 30 days following the 2-dose primary series (3-dose regimen, Protocol 025)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=497)	13-valent PCV (n=468-469)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=497)	13-valent PCV (n=468-469)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	95.6	97.4	-1.9 (-4.3, 0.5)	1.30	1.60	0.81 (0.74, 0.89)
3	93.2	66.1	27.1 (22.3, 31.9)	0.87	0.45	1.91 (1.75, 2.08)
4	93.8	96.8	-3.0 (-5.9, -0.4)	1.40	1.25	1.12 (1.01, 1.24)
5	84.1	88.1	-4.0 (-8.3, 0.4)	0.88	1.03	0.86 (0.76, 0.97)
6A	72.6	92.3	-19.7 (-24.3, -15.1)	0.64	1.39	0.46 (0.40, 0.53)
6B	57.7	50.2	7.5 (1.2, 13.8)	0.43	0.33	1.31 (1.11, 1.56)
7F	97.8	98.9	-1.1 (-3.0, 0.5)	2.03	2.42	0.84 (0.76, 0.92)
9V	88.3	95.3	-7.0 (-10.5, -3.6)	1.23	1.39	0.88 (0.78, 0.99)
14	96.8	97.2	-0.4 (-2.7, 1.8)	3.81	4.88	0.78 (0.68, 0.90)
18C	92.2	92.5	-0.4 (-3.8, 3.0)	1.16	1.30	0.89 (0.80, 0.99)
19A	96.2	97.2	-1.1 (-3.4, 1.3)	1.68	2.09	0.81 (0.72, 0.90)
19F	98.8	99.4	-0.6 (-2.0, 0.8)	2.63	3.35	0.79 (0.71, 0.87)
23F	77.9	70.1	7.8 (2.3, 13.3)	0.75	0.58	1.30 (1.14, 1.50)
2 Additional Serotypes in Vaxneuvance‡						
22F	95.6	5.3	90.2 (87.1, 92.6)	2.74	0.05	57.67 (50.95, 65.28)
33F	48.1	3.0	45.1 (40.4, 49.7)	0.30	0.05	6.11 (5.32, 7.02)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

‡ A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI being > 10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 2.0 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Table 3: Serotype-specific IgG response rates and IgG GMCs at 30 days following the toddler dose (3-dose regimen, Protocol 025)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=510-511)	13-valent PCV (n=504-510)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=510-511)	13-valent PCV (n=504-510)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	96.5	99.4	-2.9 (-5.0, -1.3)	1.28	2.05	0.62 (0.57, 0.68)
3	91.8	83.7	8.1 (4.1, 12.1)	0.84	0.66	1.29 (1.18, 1.41)
4	95.7	97.8	-2.1 (-4.5, 0.0)	1.29	1.74	0.74 (0.67, 0.82)
5	99.0	100.0	-1.0 (-2.3, -0.2)	1.98	3.01	0.66 (0.60, 0.72)
6A	98.4	98.8	-0.4 (-2.0, 1.2)	3.09	4.53	0.68 (0.61, 0.76)
6B	97.3	99.0	-1.8 (-3.7, -0.1)	4.15	4.33	0.96 (0.85, 1.08)
7F	99.8	99.8	0.0 (-0.9, 0.9)	3.08	3.89	0.79 (0.73, 0.86)
9V	98.8	100.0	-1.2 (-2.5, -0.4)	2.14	2.97	0.72 (0.66, 0.78)
14	99.8	100.0	-0.2 (-1.1, 0.6)	5.22	6.90	0.76 (0.68, 0.84)
18C	98.8	99.2	-0.4 (-1.8, 1.0)	1.93	2.18	0.89 (0.81, 0.97)
19A	99.0	100.0	-1.0 (-2.3, -0.2)	4.65	5.61	0.83 (0.75, 0.92)
19F	99.6	100.0	-0.4 (-1.4, 0.4)	4.06	4.59	0.89 (0.81, 0.97)
23F	96.9	97.2	-0.4 (-2.6, 1.8)	1.52	1.69	0.90 (0.81, 1.00)
2 Additional Serotypes in Vaxneuvance‡						
22F	99.6	5.9	93.7 (91.2, 95.5)	5.97	0.08	71.76 (64.88, 79.38)
33F	99.0	4.4	94.7 (92.3, 96.3)	3.38	0.07	46.38 (41.85, 51.40)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.
** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.
† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).
‡ A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI being > 10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 2.0 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).
n=Number of participants randomised, vaccinated and contributing to the analysis.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Additionally, Vaxneuvance elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the toddler dose, that are generally comparable but slightly lower for the 13 serotypes shared with 13-valent PCV. The clinical relevance of this slightly lower response is unknown. OPA GMTs for both 22F and 33F were higher in Vaxneuvance recipients compared to the 13-valent PCV recipients.

In another double-blind, active comparator-controlled study (Protocol 026), 1,191 participants were randomised to receive Vaxneuvance or the 13-valent PCV as a 3-dose regimen given concomitantly with other paediatric vaccines including Vaxelis with all three doses and M-M-RvaxPro and Varivax with the toddler dose. The primary series was administered to infants at 3 and 5 months of age followed by the toddler dose at 12 months of age.

Vaxneuvance elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs, for all 15 serotypes contained in the vaccine. At 30 days following the toddler dose, Vaxneuvance is non-inferior to the 13-valent PCV for the 13 shared serotypes and superior for the 2 additional serotypes, 22F and 33F, as assessed by IgG response rates. Similarly, Vaxneuvance is non-inferior to the 13-valent PCV for the 13 shared serotypes and superior to the 13-valent PCV for the 2 additional serotypes, as assessed by IgG GMCs. Following the toddler dose, Vaxneuvance

generates functional antibodies (OPA GMTs) for all 15 serotypes that are generally comparable with the 13-valent PCV.

4-dose regimen (3-dose primary series + 1 toddler dose)
A 4-dose regimen was evaluated in healthy infants in one phase 2 and three phase 3 studies. The primary series were administered to infants at 2, 4, and 6 months of age and the toddler dose was administered to children at 12 through 15 months of age.

In a double-blind, active comparator-controlled study (Protocol 029), 1,720 participants were randomised to receive Vaxneuvance or the 13-valent PCV. Participants also received other paediatric vaccines concomitantly, including HBVaxPro (Hepatitis B Vaccine [Recombinant]), RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) and Diphtheria, Tetanus Toxoids, Acellular Pertussis Adsorbed, Poliomyelitis (inactivated), *Haemophilus* b Conjugate (Tetanus Toxoid Conjugate) Vaccine in the infant series. *Haemophilus* b Conjugate Vaccine (Tetanus Toxoid Conjugate), M-M-RvaxPro (Measles, Mumps, and Rubella Virus Vaccine Live), Varivax (Varicella Virus Vaccine Live) and Vaqta (Hepatitis A Vaccine, Inactivated) were administered concomitantly with the toddler dose of Vaxneuvance.

Vaxneuvance elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs for all 15 serotypes contained in the vaccine. At 30 days following the primary series, Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes, as assessed by IgG response rates (Table 4). Vaxneuvance is noninferior for the 2 additional serotypes, as assessed by the IgG response rates for serotypes 22F and 33F in recipients of Vaxneuvance compared with the response rate for serotype 23F in recipients of the 13-valent PCV (the lowest response rate for any of the shared serotypes, excluding serotype 3), with percentage point differences of 6.7% (95% CI: 4.6, 9.2) and -4.5% (95% CI: -7.8, -1.3), respectively.

At 30 days following the primary series, serotype-specific IgG GMCs are noninferior to the 13-valent PCV for 12 of the 13 shared serotypes. The IgG response to serotype 6A narrowly missed the prespecified noninferiority criteria by a small margin (0.48 versus >0.5) (Table 4). Vaxneuvance is noninferior to the 13-valent PCV for the 2 additional serotypes, as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F in recipients of Vaxneuvance compared with the IgG GMCs for serotype 4 in recipients of the 13-valent PCV (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 3.64 and 1.24, respectively.

Additionally, Vaxneuvance induces immune responses to shared serotype 3 and the 2 additional serotypes, which were substantially higher compared to the immune response induced by the 13-valent PCV as assessed by IgG response rates and IgG GMCs at 30 days following the primary series (Table 4).

Table 4: Serotype-specific IgG response rates and IgG GMCs at 30 days following the 3-dose primary series (4-dose regimen, Protocol 029)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=698-702)	13-valent PCV (n=660-665)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=698-702)	13-valent PCV (n=660-665)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	95.7	99.1	-3.4 (-5.2, -1.8)	1.21	1.89	0.64 (0.59, 0.69)
3	94.7	79.2	15.6 (12.1, 19.2)	1.08	0.62	1.73 (1.61, 1.87)
4	96.4	98.6	-2.2 (-4.0, -0.6)	1.29	1.35	0.95 (0.88, 1.03)
5	95.3	97.4	-2.1 (-4.2, -0.2)	1.63	2.25	0.72 (0.66, 0.80)
6A	93.7	98.6	-4.9 (-7.1, -3.0)	1.55	2.95	0.52 (0.48, 0.58)
6B	88.6	92.0	-3.4 (-6.6, -0.3)	1.60	1.97	0.81 (0.71, 0.93)
7F	99.0	99.8	-0.8 (-1.9, -0.1)	2.48	3.23	0.77 (0.71, 0.83)
9V	97.1	98.2	-1.0 (-2.8, 0.6)	1.73	1.89	0.91 (0.84, 1.00)
14	97.9	97.9	-0.0 (-1.6, 1.6)	4.78	6.80	0.70 (0.63, 0.78)
18C	97.4	98.3	-0.9 (-2.6, 0.7)	1.53	2.00	0.76 (0.70, 0.83)
19A	97.9	99.7	-1.8 (-3.2, -0.8)	1.63	2.29	0.71 (0.65, 0.77)
19F	99.0	100.0	-1.0 (-2.1, -0.4)	2.01	2.72	0.74 (0.69, 0.79)
23F	91.5	91.8	-0.3 (-3.2, 2.7)	1.31	1.47	0.89 (0.80, 0.99)
2 Additional Serotypes in Vaxneuvance						
22F	98.6	3.5	95.1 (93.1, 96.5)	4.91	0.05	92.03 (83.47, 101.47)
33F	87.3	2.1	85.2 (82.3, 87.7)	1.67	0.06	29.50 (26.16, 33.26)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

At 30 days following the toddler dose, serotype-specific IgG GMCs for Vaxneuvance are noninferior to the 13-valent PCV for all 13 shared serotypes and for the 2 additional serotypes as assessed by the IgG GMCs for serotypes 22F and 33F in Vaxneuvance recipients compared with the IgG GMC for serotype 4 in the 13-valent PCV recipients (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 4.69 and 2.59, respectively (Table 5).

Vaxneuvance induces immune responses to shared serotype 3 and the 2 additional serotypes, which were substantially higher compared to the immune response induced by the 13-valent PCV, as assessed by IgG response rates and IgG GMCs at 30 days following the toddler dose (Table 5).

Table 5: Serotype-specific IgG response rates and IgG GMCs at 30 days following the toddler dose (4-dose regimen, Protocol 029)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=712-716)	13-valent PCV (n=677-686)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=712-716)	13-valent PCV (n=677-686)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	96.6	99.4	-2.8 (-4.4, -1.4)	1.35	2.03	0.66 (0.62, 0.72)
3	94.0	86.9	7.1 (4.0, 10.2)	0.96	0.71	1.35 (1.25, 1.46)
4	95.1	97.5	-2.4 (-4.5, -0.4)	1.23	1.60	0.77 (0.71, 0.84)
5	99.2	99.9	-0.7 (-1.7, 0.1)	2.49	3.95	0.63 (0.58, 0.69)
6A	98.7	99.3	-0.5 (-1.7, 0.6)	3.70	6.21	0.60 (0.54, 0.65)
6B	98.7	99.3	-0.5 (-1.7, 0.6)	4.76	6.43	0.74 (0.67, 0.81)
7F	99.6	99.9	-0.3 (-1.1, 0.4)	3.42	4.85	0.70 (0.65, 0.77)
9V	99.4	99.7	-0.3 (-1.2, 0.6)	2.40	3.29	0.73 (0.67, 0.80)
14	99.3	99.6	-0.3 (-1.2, 0.7)	5.61	6.95	0.81 (0.73, 0.89)
18C	99.7	99.6	0.2 (-0.6, 1.0)	2.62	3.08	0.85 (0.78, 0.93)
19A	99.9	99.9	0.0 (-0.7, 0.7)	4.10	5.53	0.74 (0.68, 0.80)
19F	99.7	99.7	0.0 (-0.8, 0.8)	3.55	4.47	0.79 (0.74, 0.86)
23F	98.6	99.0	-0.4 (-1.7, 0.9)	2.04	3.32	0.61 (0.56, 0.68)
2 Additional Serotypes in Vaxneuvance						
22F	99.6	7.2	92.4 (90.1, 94.2)	7.52	0.11	68.80 (63.10, 75.02)
33F	98.9	6.2	92.7 (90.4, 94.4)	4.15	0.09	44.91 (41.04, 49.14)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.
** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.
† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).
n=Number of participants randomised, vaccinated and contributing to the analysis.
CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Vaxneuvance elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the primary series and following the toddler dose, that are generally comparable but slightly lower for the 13 serotypes shared with 13-valent PCV. The clinical relevance of this slightly lower response is unknown. OPA GMTs for both 22F and 33F were higher in Vaxneuvance recipients compared to the 13-valent PCV recipients.

Infants and children receiving a mixed dose regimen of different pneumococcal conjugate vaccines
In a double-blind, active comparator-controlled, descriptive study (Protocol 027), 900 participants were randomised in a 1:1:1:1:1 ratio to one of five vaccination groups to receive a complete or mixed dosing regimen of pneumococcal conjugate vaccines. In two vaccination groups, participants received a 4-dose regimen of either Vaxneuvance or the 13-valent PCV. In the three other vaccination groups, the vaccination series were initiated with the 13-valent PCV and changed to Vaxneuvance at Dose 2, Dose 3 or Dose 4. Participants also received other paediatric vaccines concomitantly, including HBVaxPro (Hepatitis B Vaccine [Recombinant]) and RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent). Serotype-specific IgG GMCs at 30 days following the toddler dose were generally comparable for participants administered mixed regimens of Vaxneuvance and the 13-valent PCV and for participants administered a complete dosing regimen of the 13-valent PCV for the 13 shared serotypes, as assessed by IgG GMC ratios.
Higher antibodies to serotypes 22F and 33F were only observed when at least one dose of Vaxneuvance was administered during primary infant series and at the toddler age.

Immunogenicity in preterm infants
The immune responses (serotype-specific IgG and OPA) in preterm infants receiving 4 doses of pneumococcal conjugate vaccine in 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 027, Protocol 029 and Protocol 031), were generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants).

Infants, children and adolescents receiving a catch-up vaccination schedule
In a double-blind, active comparator-controlled, descriptive study (Protocol 024), 606 children who were either pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower valency pneumococcal conjugate vaccines were randomised to receive 1 to 3 doses of Vaxneuvance or the 13-valent PCV in three different age cohorts (7 through 11 months, 12 through 23 months and 24 months to less than 18 years of age), according to an age-appropriate schedule. Catch-up vaccination with Vaxneuvance elicited immune responses in children 7 months to less than 18 years of age that are comparable to the 13-valent PCV for the shared serotypes and higher than the 13-valent PCV for the additional serotypes 22F and 33F. Within each age cohort, serotype-specific IgG GMCs at 30 days following the last dose of vaccine were generally comparable between the vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the 2 additional serotypes.

Immune responses after subcutaneous administration in infants and children
In a double-blind, active comparator-controlled, descriptive study (Protocol 033), 694 healthy Japanese infants from 2 to 6 months of age were randomised to receive either Vaxneuvance or the 13-valent PCV as a 4-dose regimen via a subcutaneous route of administration. The first dose was given at 2 to 6 months of age and second and third dose were given at an interval of ≥27 days from the prior dose. The fourth dose was administered at 12 to 15 months of age. Vaxneuvance elicited serotype-specific immune responses (IgG and OPA) in healthy infants and toddlers that were generally comparable to the 13-valent PCV for the shared serotypes and higher in Vaxneuvance for the 2 additional serotypes.

Clinical immunogenicity in immunocompetent adults ≥18 years of age

Five clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, and Protocol 021) conducted in the Americas, Europe and Asia Pacific evaluated the immunogenicity of Vaxneuvance in healthy and immunocompetent adults across different age groups including individuals with or without previous pneumococcal vaccination. Each clinical study included adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or behavioural risk factors (e.g., current tobacco use, increased alcohol consumption) that are known to increase the risk of pneumococcal disease.

In each study, immunogenicity was assessed by serotype-specific OPA and IgG responses at 30 days postvaccination. Study endpoints included OPA geometric mean titres (GMTs) and IgG geometric mean concentrations (GMCs). The pivotal study (Protocol 019) aimed to show noninferiority of the OPA GMTs for 12 of 13 serotypes that Vaxneuvance shares with the 13-valent pneumococcal polysaccharide conjugate vaccine, noninferiority and superiority for the shared serotype 3, and superiority for serotypes 22F and 33F, additional to Vaxneuvance. Superiority assessment of Vaxneuvance to the 13-valent pneumococcal polysaccharide conjugate vaccine was based on the between-group comparisons of OPA GMTs and the proportions of participants with a ≥4-fold rise in serotype-specific OPA titres from prevaccination to 30 days postvaccination.

Pneumococcal vaccine-naïve adults

In the pivotal, double-blind, active comparator-controlled study (Protocol 019), 1,205 immunocompetent pneumococcal vaccine-naïve subjects ≥50 years of age were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine. The median age of participants was 66 years (range: 50 to 92 years), with approximately 69% over 65 years of age,

and approximately 12% over 75 years of age. 57.3% were female and 87% reported history of at least one underlying medical condition.

The study demonstrated that Vaxneuvance is noninferior to the 13-valent pneumococcal polysaccharide conjugate vaccine for the 13 shared serotypes and superior for the 2 additional serotypes and for the shared serotype 3. Table 6 summarises the OPA GMTs at 30 days postvaccination. IgG GMCs were generally consistent with the results observed for the OPA GMTs.

Table 6: Serotype-specific OPA GMTs at 30 days Postvaccination in Pneumococcal Vaccine-Naïve Adults ≥50 Years of age (Protocol 019)

Pneumococcal Serotype	Vaxneuvance (N = 602)		13-valent PCV (N = 600)		GMT Ratio* (Vaxneuvance/13-valent PCV) (95% CI)*
	n	GMT*	n	GMT*	
13 Shared Serotypes[†]					
1	598	256.3	598	322.6	0.79 (0.66, 0.96)
3[‡]	598	216.2	598	135.1	1.60 (1.38, 1.85)
4	598	1125.6	598	1661.6	0.68 (0.57, 0.80)
5	598	447.3	598	563.5	0.79 (0.64, 0.98)
6A	596	5407.2	598	5424.5	1.00 (0.84, 1.19)
6B	598	4011.7	598	3258.2	1.23 (1.02, 1.48)
7F	597	4617.3	598	5880.6	0.79 (0.68, 0.90)
9V	598	1817.3	597	2232.9	0.81 (0.70, 0.94)
14	598	1999.3	598	2656.7	0.75 (0.64, 0.89)
18C	598	2757.7	598	2583.7	1.07 (0.91, 1.26)
19A	598	3194.3	598	3979.8	0.80 (0.70, 0.93)
19F	598	1695.1	598	1917.8	0.88 (0.76, 1.02)
23F	598	2045.4	598	1740.4	1.18 (0.96, 1.44)
2 Serotypes Additional to Vaxneuvance[§]					
22F	594	2375.2	586	74.6	31.83 (25.35, 39.97)
33F	598	7994.7	597	1124.9	7.11 (6.07, 8.32)

*GMTs, GMT ratio, and 95% CI are estimated from a cLDA model.

[†]A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being >0.5.

[‡]A conclusion of superiority for serotype 3 is based on the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being >1.2.

[§]A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being >2.0.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis.

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titre (1/dil); OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine.

In a double-blind, descriptive study (Protocol 017), 1,515 immunocompetent subjects 18 to 49 years of age with or without risk factors for pneumococcal disease were randomised 3:1 and received Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine, followed by PPV23 6 months later. Risk factors for pneumococcal disease included the following: diabetes mellitus, chronic heart disease including heart failure, chronic liver disease with compensated cirrhosis, chronic lung disease including persistent asthma and chronic obstructive pulmonary disease (COPD), current tobacco use, and increased alcohol consumption. Overall, of those who received Vaxneuvance, 285 (25.2%) had no risk factor, 620 (54.7%) had 1 risk factor, and 228 (20.1%) had 2 or more risk factors.

Vaxneuvance elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs (Table 7) and IgG GMCs. OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in the Vaxneuvance group

for the 2 additional serotypes. Following vaccination with PPV23, OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for all 15 serotypes.

In a subgroup analysis based on the number of reported risk factors, Vaxneuvance elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination in adults with no, 1, or 2 or more risk factors. The results in each subgroup were generally consistent with those observed in the overall study population. Sequential administration of Vaxneuvance followed 6 months later by PPV23 was also immunogenic for all 15 serotypes contained in Vaxneuvance.

Table 7: Serotype-specific OPA GMTs at 30 days Postvaccination in Pneumococcal Vaccine-Naïve Adults 18-49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Protocol 017)

Pneumococcal Serotype	Vaxneuvance (N = 1,133)			13-valent PCV (N = 379)		
	n	Observed GMT	95% CI*	n	Observed GMT	95% CI*
13 Shared Serotypes						
1	1019	268.6	(243.7, 296.0)	341	267.2	(220.4, 323.9)
3	1004	199.3	(184.6, 215.2)	340	150.6	(130.6, 173.8)
4	1016	1416.0	(1308.9, 1531.8)	342	2576.1	(2278.0, 2913.2)
5	1018	564.8	(512.7, 622.2)	343	731.1	(613.6, 871.0)
6A	1006	12928.8	(11923.4, 14019.0)	335	11282.4	(9718.8, 13097.5)
6B	1014	10336.9	(9649.4, 11073.4)	342	6995.7	(6024.7, 8123.2)
7F	1019	5756.4	(5410.4, 6124.6)	342	7588.9	(6775.3, 8500.2)
9V	1015	3355.1	(3135.4, 3590.1)	343	3983.7	(3557.8, 4460.7)
14	1016	5228.9	(4847.6, 5640.2)	343	5889.8	(5218.2, 6647.8)
18C	1014	5709.0	(5331.1, 6113.6)	343	3063.2	(2699.8, 3475.5)
19A	1015	5369.9	(5017.7, 5746.8)	343	5888.0	(5228.2, 6631.0)
19F	1018	3266.3	(3064.4, 3481.4)	343	3272.7	(2948.2, 3632.9)
23F	1016	4853.5	(4469.8, 5270.2)	340	3887.3	(3335.8, 4530.0)
2 Serotypes Additional to Vaxneuvance						
22F	1005	3926.5	(3645.9, 4228.7)	320	291.6	(221.8, 383.6)
33F	1014	11627.8	(10824.6, 12490.7)	338	2180.6	(1828.7, 2600.2)

*The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis.
CI=confidence interval; GMT=geometric mean titre (1/dil); OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine.

Sequential administration of pneumococcal vaccines in adults

The sequential administration of Vaxneuvance followed by PPV23 was assessed in Protocol 016, Protocol 017 (see section 5.1, *Pneumococcal vaccine-naïve adults*), and Protocol 018 (see section 5.1, *Adults living with HIV*).

In a double-blind, active comparator-controlled study (Protocol 016), 652 pneumococcal vaccine-naïve subjects ≥50 years of age were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine, followed by PPV23 one year later.

Following vaccination with PPV23, OPA GMTs and IgG GMCs were comparable between the two vaccination groups for all 15 serotypes in Vaxneuvance.

Immune responses elicited by Vaxneuvance persisted up to 12 months postvaccination as assessed by OPA GMTs and IgG GMCs. Serotype-specific OPA GMTs declined over time, as they were lower at Month 12 than Day 30, but remained above baseline levels for all the serotypes contained in either Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine. OPA GMTs and IgG

GMCs were generally comparable between the intervention groups at Month 12 for the 13 shared serotypes and higher for the 2 additional serotypes among recipients of Vaxneuvance.

Adults with prior pneumococcal vaccination

In a double-blind, descriptive study (Protocol 007), 253 subjects ≥65 years of age who were previously vaccinated with PPV23 at least one year prior to study entry were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine.

IgG GMCs and OPA GMTs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in the Vaxneuvance group for the 2 additional serotypes.

In a clinical study, in which another PCV was administered ≤1 year after PPV23, reduced immune responses were observed for the common serotypes compared to immune responses observed when PCV was given either alone or before PPV23. The clinical significance of this is unknown.

Clinical immunogenicity in special populations

Children living with HIV
In a double-blind, descriptive study (Protocol 030), Vaxneuvance was evaluated in 203 children 6 to less than 18 years of age living with HIV. Of these children, 17 (8.4%) had a CD4+ T-cell count <500 cells/µL and plasma HIV RNA value <50,000 copies/mL. In this study, 407 participants were randomised to receive a single dose of either Vaxneuvance or the 13-valent PCV, followed by PPV 23 2 months later. Vaxneuvance was immunogenic as assessed by serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination for all 15 serotypes contained in Vaxneuvance. Serotype-specific IgG GMCs and OPA GMTs were generally comparable for the 13 shared serotypes and higher for the 2 additional serotypes (22F and 33F). After sequential administration with PPV 23, IgG GMCs and OPA GMTs were generally comparable at 30 days postvaccination between the two vaccination groups for all 15 serotypes contained in Vaxneuvance.

Adults living with HIV
In a double-blind, descriptive study (Protocol 018), 302 pneumococcal vaccine-naïve subjects ≥ 18 years of age living with HIV with CD4+ T-cell count ≥50 cells/µL and plasma HIV ribonucleic acid (RNA) <50,000 copies/mL were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine, followed by PPV23 2 months later. The majority of participants had a CD4+ T-cell count ≥200 cells/µL; 4 (1.3%) had a CD4+ T-cell count ≥50 to <200 cells/µL, 152 (50.3%) had a CD4+ T-cell count ≥200 to <500 cells/µL, and 146 (48.3%) had a CD4+ T-cell count ≥500 cells/µL.

Vaxneuvance elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination. Immune responses seen in the HIV-infected participants were consistently lower compared to healthy participants but comparable for both vaccination groups, except for serotype 4. OPA GMT and IgG GMC for serotype 4 were lower for Vaxneuvance. After sequential administration with PPV23, OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for all 15 serotypes.

Children with Sickle Cell Disease
In a double-blind, descriptive study (Protocol 023), Vaxneuvance was evaluated in children 5 to less than 18 years of age with sickle cell disease. In this study, participants enrolled may have received routine pneumococcal vaccines during the first two years of life but had not received pneumococcal vaccines in the 3 years prior to study entry. A total of 104 participants were randomised 2:1 to receive a single dose of either Vaxneuvance or the 13-valent PCV. Vaxneuvance was immunogenic as assessed by serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination for all 15 serotypes contained in Vaxneuvance. Serotype-specific IgG GMCs and OPA GMTs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the two additional serotypes 22F and 33F.

Children and adults receiving Haematopoietic Stem Cell Transplant
In a double-blind, descriptive study (Protocol 022), Vaxneuvance was evaluated in adults and children ≥3 years of age who had received an allogeneic haematopoietic stem cell transplant (allo-HSCT) 3 to 6 months prior to enrollment. In this study, 277 participants were randomised to receive 3 doses of Vaxneuvance or the 13-valent PCV, administered one month apart. Twelve months after allo-HSCT, participants without chronic graft-versus-host disease (cGvHD) received a single dose of PPV23 and those with cGvHD received a fourth dose of either Vaxneuvance or the 13-valent PCV. Vaxneuvance was immunogenic in recipients of allo-HSCT, as assessed by IgG GMCs and OPA GMTs at 30 days following the third dose of Vaxneuvance for all 15 serotypes contained in the vaccine. Serotype-specific IgG GMCs and OPA GMTs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the two additional serotypes (22F and 33F). Similarly, in participants who received either Vaxneuvance or the 13-valent PCV twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the two additional serotypes (22F and 33F). In participants who received PPV23 twelve months after allo-HSCT, IgG GMCs and OPA GMTs at 30 days following vaccination were generally comparable between the two vaccination groups for all 15 serotypes contained in Vaxneuvance.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical study data revealed no hazard for humans based on conventional studies of repeated dose toxicity and toxicity to reproduction and development.

Vaxneuvance administered to female rats had no effects on mating performance, fertility, embryonic/foetal development, or development of the offspring.

Vaxneuvance administered to pregnant female rats resulted in detectable antibodies to all 15 serotypes in offspring. This was attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (NaCl)
L-histidine
Polysorbate 20
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

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

In the event of temporary temperature excursions, stability data indicate that Vaxneuvance is stable at temperatures up to 25 °C for 48 hours.

6.5 Nature and contents of container

0.5 mL suspension in pre-filled syringe (Type I glass) with a plunger stopper (latex-free bromobutyl rubber) and a tip cap (latex-free styrene-butadiene rubber).

Pack sizes of 1 or 10 pre-filled syringes, either without needles, with 1 separate needle, or with 2 separate needles.
Multipacks containing 50 (5 packs of 10) pre-filled syringes without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- The vaccine should be used as supplied.
- Immediately prior to use, hold the pre-filled syringe horizontally and shake vigorously to obtain an opalescent suspension. Do not use the vaccine if it cannot be resuspended.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Attach a needle with Luer lock connection by twisting in a clockwise direction until the needle fits securely on the syringe.
- Inject immediately using the intramuscular (IM) route, preferably in the anterolateral aspect of the thigh in infants or in the deltoid area of the upper arm in children and adults.
- Exercise care to avoid harm from an accidental needle stick.

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1591/001
EU/1/21/1591/002
EU/1/21/1591/003
EU/1/21/1591/004
EU/1/21/1591/005
EU/1/21/1591/006
EU/1/21/1591/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 December 2021

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

MSD International GmbH
Brinny, Innishannon
County Cork
Ireland

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Study V114-032: To evaluate the efficacy of V114 in preventing vaccine-type (VT) pneumococcal Acute Otitis Media (AOM) in children.	Final Study Report due by 2Q2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Vaxneuvance suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 mL) contains 2 µg of pneumococcal polysaccharide of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F and 4 µg for serotype 6B conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate adjuvant. One dose contains 125 µg Al^{3+}.

3. LIST OF EXCIPIENTS

Excipients: NaCl, L-histidine, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 pre-filled syringe (0.5 mL) without needle
10 pre-filled syringes (0.5 mL) without needle
1 pre-filled syringe (0.5 mL) + 1 separate needle
10 pre-filled syringes (0.5 mL) + 10 separate needles
1 pre-filled syringe (0.5 mL) + 2 separate needles
10 pre-filled syringes (0.5 mL) + 20 separate needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake vigorously immediately before use.
Read the package leaflet before use.
Intramuscular use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1591/001 - pack of 1 without needle
EU/1/21/1591/002 - pack of 10 without needle
EU/1/21/1591/003 - pack of 1 + 1 separate needle
EU/1/21/1591/004 - pack of 10 + 10 separate needles
EU/1/21/1591/005 - pack of 1 + 2 separate needles
EU/1/21/1591/006 - pack of 10 + 20 separate needles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON WITHOUT BLUE BOX – Multipack

1. NAME OF THE MEDICINAL PRODUCT

Vaxneuvance suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 mL) contains 2 µg of pneumococcal polysaccharide of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F and 4 µg for serotype 6B conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate adjuvant. One dose contains 125 µg Al^{3+}.

3. LIST OF EXCIPIENTS

Excipients: NaCl, L-histidine, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 pre-filled syringes (0.5 mL) without needles. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake vigorously immediately before use.
Read the package leaflet before use.
Intramuscular use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1591/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON WITH BLUE BOX – Multipack

1. NAME OF THE MEDICINAL PRODUCT

Vaxneuvance suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose (0.5 mL) contains 2 µg of pneumococcal polysaccharide of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F and 4 µg for serotype 6B conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate adjuvant. One dose contains 125 µg Al^{3+}.

3. LIST OF EXCIPIENTS

Excipients: NaCl, L-histidine, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
Multipack: 50 (5 packs of 10) pre-filled syringes (0.5 mL) without needles.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake vigorously immediately before use.
Read the package leaflet before use.
Intramuscular use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1591/007 50 pre-filled syringes without needles (5 packs of 10)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL – Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vaxneuvance
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)
IM Injection

2. METHOD OF ADMINISTRATION

Shake vigorously before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

MSD

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Vaxneuvance suspension for injection in pre-filled syringe
Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you or your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child is vaccinated because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vaxneuvance is and what it is used for

Vaxneuvance is a pneumococcal vaccine given to:
- **children from 6 weeks to less than 18 years of age** to help protect against diseases such as lung infection (pneumonia), inflammation of the coverings of the brain and spinal cord (meningitis), a severe infection in the blood (bacteraemia) and ear infections (acute otitis media),
- **individuals 18 years of age and older** to help protect against diseases such as lung infection (pneumonia), inflammation of the coverings of the brain and spinal cord (meningitis) and a severe infection in the blood (bacteraemia), caused by 15 types of bacteria called *Streptococcus pneumoniae* or pneumococcus.

2. What you need to know before you or your child receives Vaxneuvance

Do not receive Vaxneuvance if:
- you or your child is allergic to the active substances or to any of the ingredients of this vaccine (listed in section 6), or to any vaccine that contains diphtheria toxoid.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you or your child receives Vaxneuvance if:
- the immune system is weak (which means the body is less able to fight off infections) or if you or your child is taking certain medicines that may make the immune system weak (for example, immunosuppressants or steroids).
- you or your child has a high fever or severe infection. In these cases, the vaccination may have to be postponed until you or your child has recovered. However, a mild fever or infection (for example having a cold) itself is not a reason to delay vaccination.
- you or your child has any bleeding problems, bruises easily, or is taking medicines to prevent blood clots.

If your child is an infant, also tell your doctor if your child was born prematurely (too early).

As with any vaccine, Vaxneuvance may not fully protect all persons who are vaccinated.

Other medicines/vaccines and Vaxneuvance
Your child can be given Vaxneuvance at the same time as other routine childhood vaccines.

In adults, Vaxneuvance can be given at the same time as the flu (inactivated influenza) vaccine.

Tell your doctor, pharmacist, or nurse if:
- you or your child is taking, has recently taken, or might take any prescription medicines (for example, immunosuppressants or steroids which may make the immune system weak) or any medicines obtained without a prescription.
- you or your child has recently received or plan to receive any other vaccine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before you receive this vaccine.

Driving and using machines
Vaxneuvance has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4 “Possible side effects” may temporarily affect the ability to drive or use machines.

Vaxneuvance contains sodium
This medicine contains less than 1 mmol sodium (23 milligrams) per dose, that is to say essentially ‘sodium-free’.

3. How Vaxneuvance is given

Tell your doctor, pharmacist, or nurse if you or your child has been given a pneumococcal vaccine before.
Your doctor or nurse will give the vaccine into your arm muscle or into your child's arm or leg muscle.

Infants and children aged 6 weeks to less than 2 years
Your child should receive an initial course of 2 injections of the vaccine followed by a booster dose.
- The first injection may be given as early as 6 weeks of age.
- A second injection is administered 2 months later.
- A third injection (booster) will be given between 11 through 15 months of age.

You will be told when your child should come back for each injection.

According to official recommendations in your country, an alternative schedule of 3 injections followed by a booster dose may be used by your healthcare provider. Please speak to your doctor, pharmacist, or nurse for more information.

Premature infants (born earlier than 37 weeks of pregnancy)
Your child should receive an initial course of 3 injections of the vaccine followed by a booster dose.
- The first injection may be given as early as 6 weeks of age.
- The second and third injections are given thereafter with an interval of 4 to 8 weeks between doses.
- A fourth injection (booster) will be given between 11 through 15 months of age.

Infants, children and adolescents starting the vaccination at 7 months of age or older
Infants 7 to less than 12 months of age should receive a total of 3 injections. The first two injections will be given at least 1 month apart. The third injection (booster) will be given after 12 months of age and at least 2 months after the second injection.
Children 12 months to less than 2 years of age should receive a total of 2 injections. The two injections will be given at least 2 months apart.
Children and adolescents 2 to less than 18 years of age should receive 1 injection.

Adults
Adults should receive 1 injection.

Special populations
One or more injections of Vaxneuvance may be given to individuals who have one or more underlying conditions that increase their risk for pneumococcal disease (such as individuals with sickle cell disease or living with human immunodeficiency virus [HIV] or recipients of a stem cell transplant).

If you have any further questions on the use of Vaxneuvance, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all vaccines, Vaxneuvance can cause side effects, although not everybody gets them.

Get medical care right away if you or your child has symptoms of an allergic reaction, which may include:
- Wheezing or trouble breathing
- Swelling of the face, lips, or tongue
- Hives
- Rash

The following side effects can be seen after the use of Vaxneuvance in infants, children and adolescents:

Very common (may affect more than 1 in 10 people):
- Fever (temperature of 38 °C or higher in those 6 weeks to less than 2 years of age)
- Irritability (in those 6 weeks to less than 2 years of age)
- Drowsiness (in those 6 weeks to less than 2 years of age)
- Pain, redness or swelling at the injection site
- Decreased appetite (in those 6 weeks to less than 2 years of age)
- Hardness at the injection site (in those 6 weeks to less than 2 years of age)
- Muscle aches (in those 2 to less than 18 years of age)
- Feeling tired (in those 2 to less than 18 years of age)
- Headache (in those 2 to less than 18 years of age)

Common (may affect up to 1 in 10 people):
- Hardness at the injection site (in those 2 to less than 18 years of age)
- Hives
- Fever (temperature of 38 °C or higher in those 2 to less than 18 years of age)
- Vomiting (in those 6 weeks to less than 2 years of age)
- Rash (in those 6 weeks to less than 2 years of age)
- Irritability (in those 2 to less than 18 years of age)
- Drowsiness (in those 2 to less than 18 years of age)
- Decreased appetite (in those 2 to less than 18 years of age)
- Bruising at the injection site
- Nausea (in those 2 to less than 18 years of age)

Uncommon (may affect up to 1 in 100 people):
- Vomiting (in those 2 to less than 18 years of age)

Not known (cannot be estimated from the available data):
- Rash (in those 2 to less than 18 years of age)

The following side effects can be seen after the use of Vaxneuvance in adults:

Very common (may affect more than 1 in 10 people):
- Pain, swelling, or redness at the injection site
- Feeling tired
- Muscle aches
- Headaches
- Joint pain (in those 18 to 49 years of age)

Common (may affect up to 1 in 10 people):
- Joint pain (in those 50 years of age and older)
- Nausea (in those 18 to 49 years of age)
- Fever (in those 18 to 49 years of age)
- Itchiness at the injection site
- Dizziness (in those 18 to 49 years of age)
- Chills (in those 18 to 49 years of age)

Uncommon (may affect up to 1 in 100 people):
- Fever (in those 50 years of age and older)
- Warmth at the injection site
- Bruising at the injection site
- Dizziness (in those 50 years of age and older)
- Nausea (in those 50 years of age and older)
- Vomiting
- Chills (in those 50 years of age and older)
- Rash

Rare (may affect up to 1 in 1,000 people):
- Allergic reaction such as hives, tongue swelling, flushing, and throat tightness

These side effects are generally mild and last a short time.

Reporting of side effects
If you or your child gets any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vaxneuvance

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton and syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

Vaxneuvance should be administered as soon as possible after being removed from the refrigerator. However, in circumstances where Vaxneuvance is temporarily held outside of refrigeration, the vaccine is stable at temperatures up to 25 °C for 48 hours.

6. Contents of the pack and other information

What Vaxneuvance contains
The active substances are:
- bacterial sugars from pneumococcus types 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F (2.0 micrograms of each type);
- bacterial sugar from pneumococcus type 6B (4.0 micrograms).

Each bacterial sugar is linked to a carrier protein (CRM_{197}). The bacterial sugars and the carrier protein are not alive and do not cause disease.

One dose (0.5 mL) contains approximately 30 micrograms carrier protein, adsorbed on aluminium phosphate (125 micrograms aluminium [Al^{3+}]). Aluminium phosphate is included in the vaccine as an adjuvant. Adjuvants are included to improve the immune responses of vaccines.

The other ingredients are sodium chloride (NaCl), L-histidine, polysorbate 20, and water for injections.

What Vaxneuvance looks like and contents of the pack
Vaxneuvance is an opalescent suspension for injection, provided in a single-dose, pre-filled syringe (0.5 mL). Vaxneuvance is available in pack sizes of 1 or 10, either without needles, with 1 separate needle, or with 2 separate needles.
Vaxneuvance is also available in multipacks comprising 5 cartons, each containing 10 pre-filled syringes without needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

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

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: **http://www.ema.europa.eu.**

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The following information is intended for healthcare professionals only:

Vaxneuvance must not be injected intravascularly.

- Immediately prior to use, hold the pre-filled syringe horizontally and shake vigorously to obtain an opalescent suspension. Do not use the vaccine if it cannot be resuspended.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Attach a needle with Luer lock connection by twisting in a clockwise direction until the needle fits securely on the syringe.
- Inject immediately using the intramuscular (IM) route, preferably in the anterolateral aspect of the thigh in infants or in the deltoid area of the upper arm in children and adults.
- Exercise care to avoid harm from an accidental needle stick.

No data are available for administration via the intradermal route.

Vaxneuvance must not be mixed with any other vaccines in the same syringe.

Vaxneuvance can be given concomitantly with other routine childhood vaccines.
Vaxneuvance can be administered concomitantly with seasonal quadrivalent influenza vaccine (split virion, inactivated) in adults.
Different injectable vaccines should always be administered at different injection sites.

Store in a refrigerator (2 °C– 8 °C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

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

In the event of temporary temperature excursions, stability data indicate that Vaxneuvance is stable at temperatures up to 25 °C for 48 hours.

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