



This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **AUSTRALIAN PRODUCT INFORMATION – VAXNEUVANCE® (Pneumococcal 15-valent Conjugate Vaccine [CRM<sub>197</sub> Protein], adsorbed)**

### **1 NAME OF THE MEDICINE**

VAXNEUVANCE (Pneumococcal 15-valent Conjugate Vaccine [CRM<sub>197</sub> Protein], adsorbed)

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 0.5 mL dose contains 32 micrograms of total pneumococcal purified capsular polysaccharide (2.0 micrograms each of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.0 micrograms of serotype 6B) conjugated to 30 micrograms of non-toxic diphtheria CRM<sub>197</sub> protein, adsorbed on 125 micrograms of aluminium (as aluminium phosphate adjuvant).

For the full list of excipients, see Section 6.1 List of excipients.

### **3 PHARMACEUTICAL FORM**

VAXNEUVANCE is a suspension for injection available in 0.5 mL single-dose prefilled syringes.

The vaccine is an opalescent suspension.

### **4 CLINICAL PARTICULARS**

#### **4.1 THERAPEUTIC INDICATIONS**

VAXNEUVANCE is indicated for active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults and children from 6 weeks of age.

VAXNEUVANCE may not prevent disease caused by *S. pneumoniae* serotypes that are not contained in the vaccine.

The use of VAXNEUVANCE should be guided by official recommendations.

#### **4.2 DOSE AND METHOD OF ADMINISTRATION**

The vaccination schedule for VAXNEUVANCE should be based on official recommendations.

##### **Dosage (dose and interval)**

Administer a 0.5 mL dose of VAXNEUVANCE intramuscularly.

##### **Paediatrics**

###### ***Routine Vaccination Schedule for Infants and Toddlers***

###### ***3 Dose Regimen (Two Dose Primary Series Followed by a Toddler Dose)***

The vaccination regimen consists of 3 doses of VAXNEUVANCE, with the first dose given as early as 6 weeks of age, and a second dose administered 8 weeks later. The third dose should be administered at approximately 11 through 15 months of age.

###### ***4 Dose Regimen (Three Dose Primary Series Followed by a Toddler Dose)***

The vaccination regimen consists of 4 doses of VAXNEUVANCE, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth dose

should be administered at approximately 11 through 15 months of age and at least 2 months after the third dose.

**Preterm Infants**

Preterm infants (<37 weeks gestation at birth) should receive a 4-dose regimen (three dose primary series followed by a toddler dose) of VAXNEUVANCE, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth dose should be administered at approximately 11 through 15 months of age and at least 2 months after the third dose. [See Section 4.4 Special Warnings and Precautions for Use, Section 4.8 Adverse Effects (Undesirable Effects) and Section 5.1 Pharmacodynamic Properties – Clinical trials].

**Prior Vaccination with Another Pneumococcal Conjugate Vaccine**

The vaccination regimen can be completed with VAXNEUVANCE if initiated with another pneumococcal conjugate vaccine [see Section 5.1 Pharmacodynamic Properties – Clinical trials].

**Catch Up Vaccination Schedule for Children 7 Months Through 17 Years of Age**

For children 7 months through 17 years of age who are pneumococcal vaccine naïve or not fully vaccinated or completed a dosing regimen with lower valency pneumococcal conjugate vaccines, the following catch-up schedule should be considered:

**Infants 7 Through 11 months of age**

Three doses, with the first two doses given at least 4 weeks apart. The third dose is given after 12 months of age, separated from the second dose by at least 2 months.

**Children 12 Through 23 months of age**

Two doses, with an interval of 2 months between doses.

**Children and adolescents 2 Through 17 years of age**

One single dose.

If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before receiving VAXNEUVANCE.

**Adults**

One single dose.

**Special Populations**

The dosing schedule of VAXNEUVANCE in special populations should be guided by official recommendations.

**Method of administration**

For intramuscular use only. Do not inject intravascularly.

The preferred site for injection is the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

**Instruction for use**

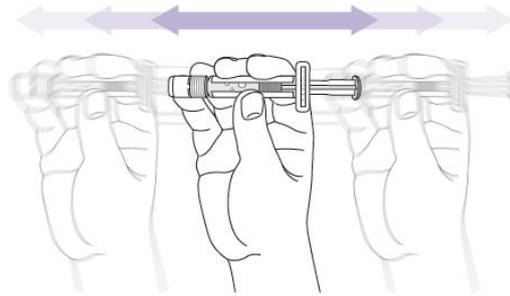
VAXNEUVANCE should not be diluted or mixed with other vaccines.

The full recommended dose of the vaccine should be used.

When VAXNEUVANCE is administered at the same time as another injectable vaccine(s), the vaccines should always be given at different injection sites [see Section 4.5 Interactions with other medicines and other forms of interactions].

VAXNEUVANCE may appear as a clear liquid with precipitate before shaking. Because this product is a suspension containing an adjuvant, hold horizontally and shake vigorously, immediately before use and prior to attaching the needle and expelling air from the syringe, to obtain an opalescent suspension in the vaccine container. Multiple attempts may be necessary to achieve complete resuspension. Do not use the

vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. This product should not be used if particulate matter is present after vigorous shaking or discoloration is found.



The prefilled syringe is for single use only and should not be used for more than one individual. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Inject the entire contents of the syringe. Exercise caution to avoid harm from an accidental needle stick.

#### **4.3 CONTRAINDICATIONS**

VAXNEUVANCE is contraindicated in individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine [See Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients].

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE [See Section 4.5 Interactions with other medicines and other forms of interactions].

The potential risk of apnoea should be considered when administering any intramuscular vaccine to infants born prematurely. As the benefit of vaccination is high in this group of infants, vaccination generally should not be withheld or delayed.

As with any vaccine, VAXNEUVANCE may not protect all vaccine recipients.

##### **Use in the elderly**

Of the 4,344 individuals aged 50 years and older who received VAXNEUVANCE, 2,470 (56.9%) were 65 years and older, and 479 (11.0%) were 75 years and older [see Section 4.8 Adverse effects (Undesirable effects) and Section 5 Pharmacological properties – Clinical Trials].

##### **Paediatric use**

The safety and effectiveness of VAXNEUVANCE in children younger than 6 weeks of age have not been established.

##### **Effects on laboratory tests**

Not applicable.

#### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

##### **Use with Other Vaccines**

##### *Infants and Children Less Than 2 Years of Age*

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 [see Section 4.8 Adverse effects (Undesirable effects) and Section 5 Pharmacological properties - Concomitant vaccination].

Concomitant administration of Vaxneuvance with meningococcal ACWY and meningococcal B vaccines has not been studied.

#### *Children and Adolescents 2 Through 17 Years of Age*

There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

#### *Adults*

VAXNEUVANCE can be administered concomitantly with inactivated influenza vaccine [see Section 4.8 Adverse effects (Undesirable effects) and Section 5 Pharmacological properties – Clinical Trials]. There are no data on the concomitant administration of VAXNEUVANCE with other vaccines.

#### **Use with Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, therapeutic proteins and targeted immunomodulators may reduce the immune responses to vaccines [see 4.4 Special warnings and precautions for use].

### **4.6 FERTILITY, PREGNANCY AND LACTATION**

#### **Effects on fertility**

VAXNEUVANCE administered to female rats at a dose approximately 200 times the adult human dose on a microgram/kg basis had no effects on mating performance, fertility or embryonic/fetal survival.

#### **Use in pregnancy - Category B1**

##### *Animal Data*

Developmental and reproductive toxicity studies have been performed in female rats at a dose approximately 200 times the adult human dose on a microgram/kg basis. In these studies, female rats received VAXNEUVANCE (32 micrograms/rat/dose) by intramuscular injection 28 days and 7 days prior to mating, on gestation day 6 and on lactation day 7. There was no evidence of embryofetal lethality or fetal malformations and variations and no adverse effects on pre-weaning development were observed. Antibodies to all 15 serotypes contained in VAXNEUVANCE were detected in offspring, attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

##### *Human Data*

There are no adequate and well-controlled studies of VAXNEUVANCE in pregnant women, and human data available from clinical trials with VAXNEUVANCE have not established the presence or absence of vaccine-associated risk during pregnancy. The decision to vaccinate a woman who is pregnant should consider the woman's risk of exposure to *S. pneumoniae*; VAXNEUVANCE should be administered only if clearly needed.

#### **Use in lactation**

It is not known whether this vaccine is excreted in human milk.

Vaccine-specific antibodies were detected in rat offspring via maternal transfer from immunised female rats [see Use in pregnancy]. Evaluation of antibody levels in animal milk was not conducted.

### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

VAXNEUVANCE has no, or negligible, influence on the ability to drive and use machines.

### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

#### **Clinical Trials Experience**

##### **Children 6 Weeks Through 17 Years of Age**

##### ***Infants and Toddlers Receiving a Routine Vaccination Schedule***

The safety of VAXNEUVANCE in healthy infants (from 6 weeks of age at first vaccination) and toddlers (11 months through 15 months of age) was assessed in 5 randomised, double-blind, active comparator-controlled clinical studies (Protocol 008, Protocol 025, Protocol 027, Protocol 029 and Protocol 031) of 7,229 participants conducted across the Americas, Europe, and Asia Pacific. In four of these studies

(Protocol 008, Protocol 027, Protocol 029 and Protocol 031), the safety of VAXNEUVANCE was evaluated when administered as a 4-dose regimen given at 2, 4, 6 and 12 through 15 months of age. A fifth study (Protocol 025) evaluated the safety of VAXNEUVANCE when administered as a 3-dose regimen given at 2, 4 and 11 through 15 months of age. All 5 studies evaluated the safety of VAXNEUVANCE when administered concomitantly with other routine paediatric vaccinations [see Section 5 Pharmacological properties – Clinical Trials]. Protocol 027 also evaluated the safety of mixed 4-dose regimens in participants who completed the regimen with VAXNEUVANCE after receiving one or more doses of Prevenar 13® [Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed]. Additionally, four of these studies evaluated safety in preterm infants (<37 weeks gestation at birth) [see Section 5 Pharmacological properties – Clinical Trials]. Across all 5 studies, 4,286 participants received a complete regimen of VAXNEUVANCE, 2,405 participants received a complete regimen of Prevenar 13 and 538 participants received a mixed regimen.

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Injection-site adverse events and systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Body temperature was solicited on Day 1 through Day 7 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14 postvaccination. The duration of the safety follow-up period following the last vaccination with VAXNEUVANCE was 1 month in Protocol 008 and 6 months in Protocol 025, Protocol 027, Protocol 029 and Protocol 031.

#### *Solicited Adverse Reactions in Infants and Toddlers Receiving a Routine Vaccination Schedule*

The percentage of infants (preterm and term) and toddlers with solicited adverse reactions that occurred within 14 days following administration of VAXNEUVANCE or Prevenar 13 based on pooled data from four studies (excluding mixed 4-dose regimens) are shown in Tables 1 and 2. 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 >7.6 cm) occurred in ≤1.3% of infants and toddlers following each dose, with the exception of irritability, which occurred in ≤5.2% of the participants.

**Table 1: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Infants Receiving a Primary Series (Protocols 025\*, 027, 029 and 031)**

Dose	Dose 1		Dose 2		Dose 3	
	VAXNEUVANCE (%) N=3,589	Prevenar 13 (%) N=2,058	VAXNEUVANCE (%) N=3,521	Prevenar 13 (%) N=1,998	VAXNEUVANCE (%) N=2,925	Prevenar 13 (%) N=1,409
<b>Local Reactions<sup>†</sup></b>						
Pain	27.1	24.1	19.8	18.0	19.1	18.8
Erythema	17.1	14.1	20.0	20.8	17.0	19.1
Swelling	13.7	11.6	11.6	10.7	9.9	9.3
Induration	12.6	13.5	12.6	15.9	11.4	13.1
<b>Systemic Reactions<sup>†</sup></b>						
Decreased Appetite	17.0	15.9	15.4	14.0	13.9	14.3
Irritability	55.1	53.2	50.7	47.3	47.0	43.7
Somnolence	40.7	41.3	27.5	27.8	22.8	24.1
Urticaria	1.1	1.5	1.4	1.6	1.6	1.8
<b>Elevated Body Temperature<sup>‡,§</sup></b>						
≥38.0°C and <39.0°C	43.4	42.0	39.3	39.6	35.7	37.4
≥39.0°C and <40.0°C	2.2	2.6	3.4	4.6	3.5	3.1
≥40.0°C	0.2	0.0	0.3	0.4	0.5	0.2

\* Full term infants in Protocol 025 received Dose 1 and Dose 2 as part of a 2-dose primary series. Preterm infants in Protocol 025 received Dose 1, Dose 2 and Dose 3 as part of a 3-dose primary series.

<sup>†</sup> Solicited on Day 1 through Day 14 postvaccination following each dose.

<sup>‡</sup> Solicited on Day 1 through Day 7 postvaccination following each dose.

<sup>§</sup> Percentages reflect the number of participants with temperature data based on a rectal equivalent temperature.

N=Number of participants vaccinated.

**Table 2: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Toddlers (Protocols 025, 027, 029 and 031)**

Dose	Toddler Dose	
	VAXNEUVANCE (%) N=3,373	Prevenar 13 (%) N=1,886
<b>Local Reactions*</b>		
Pain	21.0	18.6
Erythema	21.6	22.0
Swelling	12.6	11.6
Induration	13.1	14.8
<b>Systemic Reactions*</b>		
Decreased Appetite	19.4	17.1
Irritability	45.7	42.5
Somnolence	21.8	21.5
Urticaria	2.6	2.5
Elevated Body Temperature <sup>†,‡</sup>		
≥38.0°C and <39.0°C	34.4	35.3
≥39.0°C and <40.0°C	4.3	4.4
≥40.0°C	0.8	0.5

\* Solicited on Day 1 through Day 14 postvaccination following each dose.

† Solicited on Day 1 through Day 7 postvaccination following each dose.

‡ Percentages reflect the number of participants with temperature data based on a rectal equivalent temperature.  
N=Number of participants vaccinated.

#### *Unsolicited Adverse Reactions in Infants and Toddlers Receiving a Routine Vaccination Schedule*

Injection-site urticaria occurred in up to 0.3% of infants and toddlers following each dose of VAXNEUVANCE.

#### *Safety with Concomitant Administration in Infants and Toddlers*

The safety profile was similar when other routine paediatric vaccines were administered concomitantly with VAXNEUVANCE or Prevenar 13 [see Section 5 Pharmacological properties – Clinical Trials].

#### *Safety of a Mixed Dose Regimen of Different Pneumococcal Conjugate Vaccines*

The safety profiles of mixed 4-dose regimens of VAXNEUVANCE and Prevenar 13 were generally comparable to those of complete 4-dose regimens of either VAXNEUVANCE or Prevenar 13 [see Section 5 Pharmacological properties – Clinical Trials].

#### *Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule*

The safety of VAXNEUVANCE in healthy infants, children and adolescents from 7 months through 17 years of age was assessed in a double-blind, active comparator-controlled clinical study (Protocol 024) in which 606 participants were randomised to receive 1 to 3 doses of VAXNEUVANCE or Prevenar 13, depending on age at enrollment. All infants and children less than 2 years of age were pneumococcal vaccine-naïve. Among children and adolescents from 2 through 17 years of age (N=352), 42.9% had a history of previous vaccination with a lower-valency pneumococcal conjugate vaccine. The safety assessment was consistent with that used in the studies evaluating a routine vaccination schedule. The duration of the safety follow-up period following the last study vaccination within each age cohort was 6 months.

#### *Solicited Adverse Reactions in Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule*

The percentage of participants with solicited adverse reactions that occurred within 14 days following administration of VAXNEUVANCE or Prevenar 13 within each age cohort are shown in Tables 3, 4 and 5. 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 >7.6 cm) occurred in ≤1.6% of infants and children 7 months through 23 months of age following each dose, and ≤4.5% of children and adolescents 2 through 17 years of age.

**Table 3: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Infants Receiving a Catch-Up Vaccination Schedule (Protocol 024)**

Age	7 Months Through 11 Months of Age					
Dose	Dose 1		Dose 2		Dose 3	
	VAXNEUVANCE (%) N=64	Prevenar 13 (%) N=64	VAXNEUVANCE (%) N=63	Prevenar 13 (%) N=64	VAXNEUVANCE (%) N=63	Prevenar 13 (%) N=64
<b>Local Reactions*</b>						
Pain	7.8	6.3	14.3	1.6	7.9	1.6
Erythema	20.3	31.3	12.7	14.1	11.1	9.4
Swelling	9.4	14.1	14.3	6.3	12.7	6.3
Induration	14.1	7.8	6.3	9.4	7.9	7.8
<b>Systemic Reactions*</b>						
Decreased Appetite	6.3	12.5	9.5	7.8	4.8	4.7
Irritability	21.9	26.6	17.5	18.8	14.3	14.1
Somnolence	12.5	12.5	7.9	7.8	11.1	1.6
Urticaria	1.6	0.0	0.0	1.6	0.0	3.1
Elevated Body Temperature <sup>†,‡</sup>						
≥38.0°C and <39.0°C	46.9	39.1	44.4	46.9	50.8	39.1
≥39.0°C and <40.0°C	3.1	4.7	7.9	3.1	1.6	1.6
≥40.0°C	1.6	1.6	1.6	0.0	3.2	0.0

\* Solicited on Day 1 through Day 14 postvaccination following each dose.

† Solicited on Day 1 through Day 7 postvaccination following each dose.

‡ Percentages reflect the number of participants with temperature data based on rectal equivalent temperature.

N=Number of participants vaccinated.

**Table 4: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Toddlers Receiving a Catch-Up Vaccination Schedule (Protocol 024)**

Age	12 Months Through 23 Months of Age			
Dose	Dose 1		Dose 2	
	VAXNEUVANCE (%) N=62	Prevenar 13 (%) N=64	VAXNEUVANCE (%) N=62	Prevenar 13 (%) N=64
<b>Local Reactions*</b>				
Pain	17.7	12.5	24.2	14.1
Erythema	11.3	15.6	11.3	9.4
Swelling	11.3	9.4	6.5	3.1
Induration	6.5	9.4	4.8	3.1
<b>Systemic Reactions*</b>				
Decreased Appetite	16.1	14.1	9.7	9.4
Irritability	29.0	14.1	16.1	14.1
Somnolence	21.0	12.5	16.1	4.7
Elevated Body Temperature <sup>†,‡</sup>				
≥38.0°C and <39.0°C	32.3	35.9	29.0	26.6
≥39.0°C and <40.0°C	8.1	6.3	3.2	3.1
≥40.0°C	1.6	0.0	1.6	0.0

\* For all participants, reactions were solicited on Day 1 through Day 14 postvaccination following each dose.

† Solicited on Day 1 through Day 7 postvaccination following each dose.

‡ Percentages reflect the number of participants with temperature data based on equivalent rectal temperature.

N=Number of participants vaccinated.

**Table 5: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 14 Days Postvaccination in Children and Adolescents Receiving a Catch-Up Vaccination Schedule (Protocol 024)**

Age Dose	2 Years Through 17 Years of Age	
	Dose 1	
	VAXNEUVANCE (%) N=177	Prevenar 13 (%) N=175
<b>Local Reactions*</b>		
Pain	54.8	56.6
Erythema	19.2	21.1
Swelling	20.9	24.0
Induration	6.8	14.9
<b>Systemic Reactions*†</b>		
Decreased Appetite	2.3	2.9
Irritability	2.8	4.0
Somnolence	2.8	2.9
Urticaria	1.1	1.1
Fatigue	15.8	17.1
Headache	11.9	13.7
Myalgia	23.7	16.6
Elevated Body Temperature‡§		
≥38.0°C and <39.0°C	4.0	4.6
≥39.0°C and <40.0°C	1.7	0.0
≥40.0°C	0.0	0.0

\* For all participants, reactions were solicited on Day 1 through Day 14 postvaccination following each dose.

† Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to 17 years of age. For participants <3 years of age (VAXNEUVANCE N=32, Prevenar 13 N=28), decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to 17 years of age, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.

‡ Solicited on Day 1 through Day 7 postvaccination following each dose.

§ Percentages reflect the number of participants with temperature data based on equivalent oral temperature.

N=Number of participants vaccinated.

### Adults 18 Years of Age and Older

The safety of VAXNEUVANCE in healthy and immunocompetent adults was assessed in 6 randomised, double-blind clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across the Americas, Europe and Asia Pacific, which included 7,136 adults ranging in age from 18 to 98 years. Each study enrolled adults with stable underlying medical conditions and/or risk factors that are known to increase the risk of pneumococcal disease.

VAXNEUVANCE was administered to 5,478 adults; 1,134 were 18 to 49 years of age, 1,874 were 50 to 64 years of age, and 2,470 were 65 years of age and older. Of those who received VAXNEUVANCE, 5,101 adults were pneumococcal vaccine-naïve and 377 adults were previously vaccinated with PNEUMOVAX 23® [pneumococcal vaccine polyvalent] at least 1 year prior to enrollment.

The safety of VAXNEUVANCE in pneumococcal vaccine-naïve adults 50 years of age and older was evaluated in 3 active comparator-controlled clinical studies (Protocol 016, Protocol 019 and Protocol 020) in which 3,032 participants received VAXNEUVANCE and 1,154 participants received Prevenar 13 (PCV13). A descriptive study (Protocol 017) evaluated the safety of VAXNEUVANCE in pneumococcal vaccine-naïve adults 18 to 49 years of age.

The safety of VAXNEUVANCE in adults 65 years of age and older who were previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) was evaluated in an additional descriptive study (Protocol 007).

The safety of concomitant administration of VAXNEUVANCE with seasonal inactivated influenza vaccine was evaluated in 1,196 adults 50 years of age and older, including those with or without a history of prior vaccination with PNEUMOVAX 23 (Protocol 021).

Safety was evaluated using a Vaccination Report Card for up to 14 days postvaccination. Oral body temperature and injection-site adverse events were solicited on Day 1 through Day 5 postvaccination. Systemic adverse events were solicited on Day 1 through Day 14 postvaccination. Unsolicited adverse events were reported on Day 1 through Day 14 postvaccination. The duration of the safety follow-up period postvaccination with VAXNEUVANCE was 1 month in Protocol 007, 6 months in Protocol 019, Protocol 020, Protocol 017 and Protocol 021 and 12 months in Protocol 016.

### Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Prevenar 13 in 5 studies are shown in Tables 6-7. All solicited adverse reactions occurred in ≥5% of participants with VAXNEUVANCE; older adults reported fewer solicited adverse reactions than younger adults, regardless of vaccination group. 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 >10 cm) occurred in ≤1.5% of adults.

**Table 6: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 5 or 14 Days Postvaccination in Pneumococcal Vaccine-Naïve Adults**

Age in Years	Protocol 019		Protocol 020 ≥50		Protocol 016		Protocol 017 18-49	
	VAXNEUVANC E (%) N=602	PCV1 3 (%) N=600	VAXNEUVANC E (%) N=2103	PCV1 3 (%) N=230	VAXNEUVANC E (%) N=327	PCV1 3 (%) N=324	VAXNEUVANC E (%) N=1134	PCV1 3 (%) N=378
<b>Local Reactions*</b>								
Pain	54.0	42.3	66.8	52.2	55.0	41.4	75.8	68.8
Erythema	9.0	11.3	10.9	9.6	9.8	5.6	15.1	14.0
Swelling	12.5	11.2	15.4	14.3	16.2	11.4	21.7	22.2
<b>Systemic Reactions†</b>								
Fatigue	17.4	17.3	21.5	22.2	23.5	13.9	34.3	36.8
Headache	11.6	13.0	18.9	18.7	14.1	12.7	26.5	24.9
Myalgia	15.4	12.0	26.9	21.7	17.7	11.1	28.8	26.5
Arthralgia	5.3	5.5	7.7	5.7	6.4	5.2	12.7	11.6
<b>Elevated Body Temperature*‡</b>								
≥38.0°C and <39.0°C	0.3	1.3	0.7	0.4	0.6	0.6	1.3	0.3
≥39.0°C	0.2	0.0	0.0	0.0	0.6	0.6	0.2	0.0

\* Solicited on Day 1 through Day 5 postvaccination

† Solicited on Day 1 through Day 14 postvaccination

‡ Percentages are based on the number of participants with temperature data

N=Number of participants vaccinated

**Table 7: Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 5 or 14 Days Postvaccination in Adults with Previous Pneumococcal Vaccination**

Age in Years	Protocol 007 ≥65	
	VAXNEUVANCE (%) N=127	PCV13 (%) N=126
<b>Local Reactions*</b>		
Pain	55.1	44.4
Erythema	7.9	7.1
Swelling	14.2	6.3
<b>Systemic Reactions†</b>		
Fatigue	18.1	19.0
Headache	13.4	15.9
Myalgia	15.7	11.1
Arthralgia	5.5	8.7
<b>Elevated Body Temperature*‡</b>		
≥38.0°C and <39.0°C	1.6	0.0
≥39.0°C	0.0	0.0

\* Solicited on Day 1 through Day 5 postvaccination

† Solicited on Day 1 through Day 14 postvaccination

‡ Percentages are based on the number of participants with temperature data

N=Number of participants vaccinated

### Unsolicited Adverse Reactions

Injection-site pruritus occurred in 1.0% to 2.8% of pneumococcal vaccine-naïve adults vaccinated with VAXNEUVANCE.

## **Additional Information in Special Populations**

### ***Populations at Increased Risk for Pneumococcal Disease***

#### *Infants Born Prematurely*

The safety of VAXNEUVANCE was evaluated in preterm infants (<37 weeks gestation at birth) enrolled within 4 clinical studies (Protocol 025, Protocol 027, Protocol 029 and Protocol 031) in which these participants received 4 doses of VAXNEUVANCE. The safety profile in preterm infants was generally consistent with the safety profile observed in the overall healthy infant population in these studies (including preterm and term infants).

#### *Children with Sickle Cell Disease*

In children with sickle cell disease (Protocol 023), the safety profile of VAXNEUVANCE was generally consistent with its safety profile in healthy children.

#### *Individuals Living with HIV*

##### Children Living with HIV

In children living with HIV (Protocol 030), the safety profile of VAXNEUVANCE was generally consistent with its safety profile in healthy children.

##### Adults Living with HIV

In adults living with HIV (Protocol 018), the safety profile of VAXNEUVANCE was generally consistent with its safety profile in immunocompetent pneumococcal vaccine-naïve adults.

#### *Individuals with Haematopoietic Stem Cell Transplant*

Safety was assessed in 131 adults and 8 children  $\geq 3$  years of age who had received an allogeneic haematopoietic stem cell transplant (allo-HSCT) 3 to 6 months prior to enrolment, 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.

#### *Adults with Chronic Conditions and Other Risk Factors*

In adults 18 to 49 years of age with 1 risk factor or 2 or more risk factors for pneumococcal disease (Protocol 017), the safety profile of VAXNEUVANCE was generally consistent with its safety profile in the overall study population.

### **Safety with Concomitant Influenza Vaccine Administration**

The safety profile of VAXNEUVANCE when administered concomitantly with inactivated influenza vaccine was generally consistent with the safety profile of VAXNEUVANCE.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

## **4.9 OVERDOSE**

There are no data with regard to overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### **Mechanism of action**

VAXNEUVANCE contains serotype-specific pneumococcal capsular polysaccharides each of which is conjugated to a carrier protein (CRM<sub>197</sub>), and elicits antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. VAXNEUVANCE is also expected to elicit a T-cell dependent immune response. Carrier protein-specific helper T-cells support specificity, functionality and maturation of serotype-specific B cells.

Immune responses following natural exposure to *S. pneumoniae* or following pneumococcal vaccination can be determined through the measurements of opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses. OPA represents functional antibodies capable of opsonising pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing and are considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Serotype-specific immune responses (OPA and IgG) for the 15 serotypes contained in VAXNEUVANCE were measured using a validated multiplexed opsonophagocytic assay (MOPA) and a validated pneumococcal electrochemiluminescence (Pn ECL) assay, bridged to the WHO reference enzyme linked immunosorbent assay (ELISA). In children, a serotype-specific IgG antibody level corresponding to  $\geq 0.35$  mcg/mL using the WHO ELISA has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines.

#### **Burden of Disease**

Pneumococcal disease is associated with significant morbidity and mortality in both children and adults worldwide. Although all age groups may be affected by pneumococcal disease, the highest rates of disease occur in young children <5 years of age and adults  $\geq 65$  years of age. Furthermore, the incidence of invasive pneumococcal disease (IPD) in Aboriginal and Torres Straits Islanders (ATSI) adults is approximately 3 times higher than non-ATSI adults. Among children, the incidence of IPD and mortality associated with IPD is highest among infants <1 year of age. Mortality rates are elevated in older adults, adults with comorbid conditions (e.g., diabetes mellitus, chronic lung disease, chronic liver disease), and especially in immunocompromised individuals (e.g., HIV infection, cancer, transplant, immunosuppressive therapies). Adults with 2 or more comorbid conditions may have a risk of pneumococcal disease that is comparable to that of immunocompromised individuals.

Clinical syndromes include both IPD (i.e. sepsis, meningitis, and bacteraemic pneumonia) and noninvasive disease (e.g., non-bacteraemic pneumonia and acute otitis media). Bacteraemic pneumococcal pneumonia represents approximately 80-90% of IPD cases in adults. Community acquired pneumonia (CAP) remains one of the most important causes of death from infection in many countries, with *S. pneumoniae* being one of the most commonly identified bacterial pathogens. Acute otitis media, a middle ear infection frequently caused by *S. pneumoniae*, is one of the most common infectious diseases of childhood and is a major cause of morbidity and antibiotic usage.

#### **Clinical trials**

##### **Clinical Trials Experience in Children 6 Weeks Through 17 Years of Age**

Six double-blind, clinical studies (Protocol 008, Protocol 024, Protocol 025, Protocol 026, Protocol 027, and Protocol 029) conducted across the Americas, Europe and Asia Pacific evaluated the immunogenicity of VAXNEUVANCE in healthy infants, children and adolescents. In each study, immunogenicity was assessed by serotype-specific immunoglobulin G (IgG) response rates (the proportion of participants meeting the serotype-specific IgG threshold value of  $\geq 0.35$  mcg/mL) and IgG geometric mean concentrations (GMCs) at 30 days following the primary series and/or following the toddler dose. In a subset of participants, opsonophagocytic activity (OPA) geometric mean titers (GMTs) were also measured at 30 days following the primary series and/or following the toddler dose.

##### ***Infants and Toddlers Receiving a Routine Vaccination Schedule***

###### **3-Dose Regimen**

In a pivotal, double-blind, active comparator-controlled study (Protocol 025), 1,184 participants were randomised to receive VAXNEUVANCE or Prevenar 13 as a 3-dose regimen. The primary series was

administered to infants at 2 and 4 months of age and the toddler dose was administered at 11 through 15 months of age. Participants also received other paediatric vaccines concomitantly, including Rotarix [rotavirus vaccine, live] with the infant primary series and INFANRIX hexa [diphtheria, tetanus, pertussis (acellular), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed)] with all 3 doses in the complete regimen [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions].

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, serotype-specific IgG response rates and IgG GMCs were generally comparable for the 13 shared serotypes and higher for the 2 unique serotypes (22F and 33F) in VAXNEUVANCE recipients, compared to Prevenar 13 recipients. At 30 days following the toddler dose, VAXNEUVANCE is non-inferior to Prevenar 13 for the 13 shared serotypes and superior for the 2 unique serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of  $\geq 0.35$  mcg/mL (response rate) (Table 8). Serotype-specific IgG GMCs are non-inferior to Prevenar 13 for the 13 shared serotypes and superior to Prevenar 13 for the 2 unique serotypes at 30 days following the toddler dose (Table 9).

**Table 8: Proportions of Participants with IgG Response Rates  $\geq 0.35$  mcg/mL in Toddlers Administered a 3-Dose Regimen (Protocol 025)**

Pneumococcal Serotype	VAXNEUVANCE (N=588)	Prevenar 13 (N=591)	Percentage Point Difference* (VAXNEUVANCE - Prevenar 13) (95% CI)*
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	
13 Shared Serotypes <sup>†</sup>			
1	96.7 (521/539)	99.4 (534/537)	-2.8 (-4.7, -1.3)
3	92.0 (496/539)	83.8 (450/537)	8.2 (4.4, 12.2)
4	95.7 (516/539)	97.9 (524/535)	-2.2 (-4.5, -0.1)
5	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
6A	98.5 (531/539)	98.9 (529/535)	-0.4 (-1.9, 1.1)
6B	97.4 (525/539)	99.1 (530/535)	-1.7 (-3.5, -0.1)
7F	99.8 (538/539)	99.8 (535/536)	0.0 (-0.9, 0.9)
9V	98.9 (533/539)	100.0 (537/537)	-1.1 (-2.4, -0.4)
14	99.8 (538/539)	100.0 (537/537)	-0.2 (-1.0, 0.5)
18C	98.9 (533/539)	99.3 (532/536)	-0.4 (-1.8, 0.9)
19A	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
19F	99.6 (537/539)	100.0 (537/537)	-0.4 (-1.3, 0.3)
23F	96.8 (521/538)	97.4 (521/535)	-0.5 (-2.7, 1.5)
2 Serotypes Unique to VAXNEUVANCE <sup>‡</sup>			
22F	99.6 (537/539)	5.8 (31/535)	93.8 (91.5, 95.6)
33F	99.1 (534/539)	4.2 (22/530)	94.9 (92.7, 96.5)

\* Estimated difference and CI are based on the Miettinen & Nurminen method.

<sup>†</sup> A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevenar 13) being  $> -10$  percentage points.

<sup>‡</sup> A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevenar 13) being  $> 10$  percentage points.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.

CI=confidence interval; IgG=immunoglobulin G.

**Table 9: Serotype-Specific IgG GMCs in Toddlers Administered a 3-Dose Regimen (Protocol 025)**

Pneumococcal Serotype	VAXNEUVANCE (N=588)		Prevenar 13 (N=591)		GMC Ratio* (VAXNEUVANCE/Prevenar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	539	1.29	537	2.08	0.62 (0.57, 0.68)
3	539	0.84	537	0.66	1.28 (1.17, 1.39)
4	539	1.29	535	1.73	0.75 (0.68, 0.82)
5	539	1.97	535	3.06	0.64 (0.59, 0.70)
6A	539	3.10	535	4.57	0.68 (0.61, 0.76)
6B	539	4.17	535	4.37	0.95 (0.85, 1.07)
7F	539	3.09	536	3.93	0.79 (0.72, 0.85)
9V	539	2.14	537	2.99	0.72 (0.66, 0.78)
14	539	5.26	537	7.04	0.75 (0.67, 0.83)
18C	539	1.94	536	2.22	0.88 (0.80, 0.95)
19A	539	4.68	535	5.65	0.83 (0.75, 0.91)
19F	539	4.09	537	4.63	0.88 (0.80, 0.97)
23F	538	1.52	535	1.75	0.87 (0.79, 0.97)
2 Serotypes Unique to VAXNEUVANCE‡					
22F	539	5.98	535	0.08	71.79 (65.16, 79.10)
33F	539	3.41	530	0.07	46.58 (42.19, 51.42)

\* GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilizing 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 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevenar 13) being >0.5.

‡ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevenar 13) being >2.0.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis. CI=confidence interval; GMC=geometric mean concentration (mcg/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 to Prevenar 13 for the 13 shared serotypes. OPA GMTs for both 22F and 33F were higher in VAXNEUVANCE recipients compared to Prevenar 13 recipients.

In another double-blind, active comparator-controlled study (Protocol 026), 1,191 participants were randomised to receive VAXNEUVANCE or Prevenar 13 as a 3-dose regimen. The primary series was administered to infants at 3 and 5 months of age followed by the toddler dose at 12 months of age. Participants also received other paediatric vaccines concomitantly, including VAXELIS (Diphtheria, tetanus, pertussis [acellular, component], hepatitis B, poliovirus [inactivated], and Haemophilus type b conjugate vaccine) with all 3 doses, and M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) and VARIVAX (Varicella Virus Vaccine Live) with the toddler dose [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions].

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 Prevenar 13 for the 13 shared serotypes (the lower bound of the 2-sided 95% CI for the difference in the serotype-specific IgG response rates [VAXNEUVANCE - Prevenar 13] was greater than -10 percentage points). VAXNEUVANCE is superior to Prevenar 13 for the 2 unique serotypes, 22F and 33F (the lower bound of the 2-sided 95% CI for the difference in the serotype-specific IgG response rates [VAXNEUVANCE - Prevenar 13] was greater than 10 percentage points). Similarly, VAXNEUVANCE is non-inferior to Prevenar 13 for the 13 shared serotypes (the lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio [VAXNEUVANCE/Prevenar 13] was greater than 0.5). VAXNEUVANCE is superior to Prevenar 13 for the 2 unique serotypes (the lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio [VAXNEUVANCE/Prevenar 13] was greater than 2.0).

Additionally, VAXNEUVANCE elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the toddler dose, that are generally comparable to Prevenar 13 for the 13 shared serotypes and higher for the two unique serotypes (22F and 33F).

#### 4-Dose Regimen

In a double-blind, active comparator-controlled study (Protocol 008), 1,051 participants were randomised in a 1:1:1 ratio to receive one of two lots of VAXNEUVANCE or Prevenar 13 as a 4-dose regimen. The primary series was administered to infants at 2, 4 and 6 months of age and the toddler dose was administered at 12 through 15 months of age. VAXNEUVANCE met non-inferiority criteria (the lower bound of the 2-sided 95% CI of the differences in the response rates [VAXNEUVANCE - Prevenar 13] was greater than -15 percentage points) for the 13 shared serotypes as assessed by the serotype-specific IgG response rates at 30 days after the primary series. Serotype-specific IgG GMCs at 30 days following the primary series and 30 days following the toddler dose were generally comparable across both lots of VAXNEUVANCE and Prevenar 13 for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes (22F and 33F).

In a pivotal, double-blind, active comparator-controlled study (Protocol 029), 1,720 participants were randomised to receive VAXNEUVANCE or Prevenar 13 as a 4-dose regimen. The primary series was administered to infants at 2, 4, and 6 months of age and the toddler dose was administered at 12 through 15 months of age. Participants also received other paediatric vaccines concomitantly, including H-B VAX II (Hepatitis B Vaccine [Recombinant]), RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) and Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] Vaccine in the infant primary series. HIBERIX (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), M-M-R II (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 [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions].

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 non-inferior to Prevenar 13 for the 13 shared serotypes, as assessed by IgG response rates. VAXNEUVANCE is non-inferior for the 2 unique 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 Prevenar 13 (the lowest response rate for any of the shared serotypes, excluding serotype 3) (Table 10).

**Table 10: Proportions of Participants with IgG Response Rates  $\geq 0.35$  mcg/mL in Infants Administered a 3-Dose Primary Series (Protocol 029)**

Pneumococcal Serotype	VAXNEUVANCE (N=858)	Prevenar 13 (N=856)	Percentage Point Difference* (VAXNEUVANCE – Prevenar 13) (95% CI)*
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	
13 Shared Serotypes <sup>†</sup>			
1	95.7 (672/702)	99.1 (659/665)	-3.4 (-5.2, -1.8)
3	94.7 (662/699)	79.2 (524/662)	15.6 (12.1, 19.2)
4	96.4 (674/699)	98.6 (654/663)	-2.2 (-4.0, -0.6)
5	95.3 (669/702)	97.4 (647/664)	-2.1 (-4.2, -0.2)
6A	93.7 (658/702)	98.6 (654/663)	-4.9 (-7.1, -3.0)
6B	88.6 (619/699)	92.0 (609/662)	-3.4 (-6.6, -0.3)
7F	99.0 (694/701)	99.8 (664/665)	-0.8 (-1.9, -0.1)
9V	97.1 (680/700)	98.2 (649/661)	-1.0 (-2.8, 0.6)
14	97.9 (685/700)	97.9 (647/661)	-0.0 (-1.6, 1.6)
18C	97.4 (682/700)	98.3 (651/662)	-0.9 (-2.6, 0.7)
19A	97.9 (687/702)	99.7 (663/665)	-1.8 (-3.2, -0.8)
19F	99.0 (693/700)	100.0 (663/663)	-1.0 (-2.1, -0.4)
23F	91.5 (639/698)	91.8 (607/661)	-0.3 (-3.2, 2.7)
2 Serotypes Unique to VAXNEUVANCE			
22F	98.6 (691/701)	‡	6.7 (4.6, 9.2)
33F	87.3 (613/702)	‡	-4.5 (-7.8, -1.3)

\* Estimated difference and CI are based on the Miettinen & Nurminen method.

<sup>†</sup> A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the difference in percentages (VAXNEUVANCE – Prevenar 13) being  $> -10$  percentage points.

<sup>‡</sup> A conclusion of non-inferiority of VAXNEUVANCE to Prevenar 13 is based on the comparison of the response rate for the 2 additional serotypes to the lowest responding Prevenar 13 serotype (serotype 23F), excluding serotype 3.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.

CI=confidence interval; IgG=immunoglobulin G.

At 30 days following the primary series, serotype-specific IgG GMCs are non-inferior to Prevenar 13 for 12 of the 13 shared serotypes. The IgG response to serotype 6A narrowly missed the prespecified non-inferiority criteria by a small margin (the lower bound of the 2-sided 95% CI for the GMC ratio [VAXNEUVANCE/Prevenar 13] being 0.48 versus  $> 0.5$ ). VAXNEUVANCE is non-inferior to Prevenar 13 for the 2 unique serotypes, as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F in recipients of VAXNEUVANCE compared with the IgG GMC for serotype 4 in recipients of Prevenar 13 (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) (Table 11).

**Table 11: Serotype-Specific IgG GMCs in Infants Administered a 3-Dose Primary Series (Protocol 029)**

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevenar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevenar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	702	1.21	665	1.89	0.64 (0.59, 0.69)
3	699	1.08	662	0.62	1.73 (1.61, 1.87)
4	699	1.29	663	1.35	0.95 (0.88, 1.03)
5	702	1.63	664	2.25	0.72 (0.66, 0.80)
6A	702	1.55	663	2.95	0.52 (0.48, 0.58)
6B	699	1.60	662	1.97	0.81 (0.71, 0.93)
7F	701	2.48	665	3.23	0.77 (0.71, 0.83)
9V	700	1.73	661	1.89	0.91 (0.84, 1.00)
14	700	4.78	661	6.80	0.70 (0.63, 0.78)
18C	700	1.53	662	2.00	0.76 (0.70, 0.83)
19A	702	1.63	665	2.29	0.71 (0.65, 0.77)
19F	700	2.01	663	2.72	0.74 (0.69, 0.79)
23F	698	1.31	661	1.47	0.89 (0.80, 0.99)
2 Serotypes Unique to VAXNEUVANCE					
22F	701	4.91	‡	‡	3.64 (3.33, 3.98)
33F	702	1.67	‡	‡	1.24 (1.10, 1.39)

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

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevenar 13) being >0.5.

‡ A conclusion of non-inferiority of VAXNEUVANCE to Prevenar 13 is based on the comparison of the GMC for the 2 additional serotypes to the lowest responding Prevenar 13 serotype (serotype 4), excluding serotype 3.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis. CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G.

At 30 days following the toddler dose, serotype-specific IgG GMCs for VAXNEUVANCE are non-inferior to Prevenar 13 for all 13 shared serotypes and for the 2 unique serotypes as assessed by the IgG GMCs for serotypes 22F and 33F in VAXNEUVANCE recipients compared with the IgG GMC for serotype 4 in Prevenar 13 recipients (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) (Table 12).

**Table 12: Serotype-Specific IgG GMCs in Toddlers Administered a 4-Dose Regimen (Protocol 029)**

Pneumococcal Serotype	VAXNEUVANCE (N=858)		Prevenar 13 (N=856)		GMC Ratio* (VAXNEUVANCE/Prevenar 13) (95% CI)*
	n	GMC	n	GMC	
13 Shared Serotypes†					
1	715	1.35	685	2.03	0.66 (0.62, 0.72)
3	712	0.96	686	0.71	1.35 (1.25, 1.46)
4	713	1.23	682	1.60	0.77 (0.71, 0.84)
5	713	2.49	682	3.95	0.63 (0.58, 0.69)
6A	713	3.70	682	6.21	0.60 (0.54, 0.65)
6B	712	4.76	682	6.43	0.74 (0.67, 0.81)
7F	714	3.42	686	4.85	0.70 (0.65, 0.77)
9V	716	2.40	686	3.29	0.73 (0.67, 0.80)
14	716	5.61	685	6.95	0.81 (0.73, 0.89)
18C	713	2.62	684	3.08	0.85 (0.78, 0.93)
19A	715	4.10	685	5.53	0.74 (0.68, 0.80)
19F	715	3.55	685	4.47	0.79 (0.74, 0.86)
23F	713	2.04	683	3.32	0.61 (0.56, 0.68)
2 Serotypes Unique to VAXNEUVANCE					
22F	714	7.52	‡	‡	4.69 (4.30, 5.11)
33F	714	4.15	‡	‡	2.59 (2.36, 2.83)

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

† A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (VAXNEUVANCE/Prevenar 13) being >0.5.

‡ A conclusion of non-inferiority of VAXNEUVANCE to Prevenar 13 is based on the comparison of the GMC for the 2 additional serotypes to the lowest responding Prevenar 13 serotype (serotype 4), excluding serotype 3.

N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis. CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G.

Additionally, IgG response rates and IgG GMCs at 30 days following the primary series and IgG GMCs at 30 days following the toddler dose were statistically significantly greater for VAXNEUVANCE compared to Prevenar 13 for serotype 3 and the 2 unique serotypes (22F, 33F).

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 to Prevenar 13 for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

#### *Infants and Toddlers 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 Prevenar 13. In the three other vaccination groups, the vaccination series was initiated with Prevenar 13 and changed to VAXNEUVANCE at Dose 2, Dose 3 or Dose 4. Participants also received other paediatric vaccines concomitantly, including RECOMBIVAX HB (Hepatitis B Vaccine [Recombinant]) and RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions]. Serotype-specific IgG GMCs at 30 days following the toddler dose were generally comparable for participants administered mixed regimens of VAXNEUVANCE and Prevenar 13 and for participants administered a complete dosing regimen of Prevenar 13 for the 13 shared serotypes, as assessed by IgG GMC ratios.

#### *Infants, Children and Adolescents Receiving a Catch-Up Vaccination Schedule*

In a double-blind, active comparator-controlled, descriptive study (Protocol 024), 606 participants were randomised to receive 1 to 3 doses of VAXNEUVANCE or Prevenar 13, depending on age at enrollment. Children who were either pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower-valency pneumococcal conjugate vaccines were randomised into three different age cohorts (7 through 11 months of age, 12 through 23 months of age and 2 through 17 years of age), to receive 3, 2 or 1 dose of VAXNEUVANCE or Prevenar 13 respectively, according to an age-appropriate schedule [see Section 4.2 Dose and Method of Administration]. VAXNEUVANCE elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days following the last dose of vaccine within each

age cohort, for all 15 serotypes contained in the vaccine. Catch-up vaccination with VAXNEUVANCE elicited immune responses in children 7 months through 17 years of age that are comparable to Prevenar 13 for the shared serotypes and higher than Prevenar 13 for the unique 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 unique serotypes.

#### **Clinical trials Experience in Adults 18 Years of Age and Older**

Six double-blind, clinical studies (Protocol 007, Protocol 016, Protocol 017, Protocol 019, Protocol 020 and Protocol 021) conducted across 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. The clinical studies 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 behavioral risk factors (e.g., smoking, increased alcohol use) that are known to increase the risk of pneumococcal disease.

In each study, immunogenicity was assessed by serotype-specific opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses at 30 days postvaccination. Study endpoints included OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs). The pivotal study (Protocol 19) was designed to show non-inferiority of the OPA GMTs compared to Prevenar 13 for the 13 shared serotypes (in common between VAXNEUVANCE and Prevenar 13) and superiority for the 2 serotypes unique to VAXNEUVANCE (22F and 33F) and for shared serotype 3. Superiority assessment was based on the between-group comparisons of OPA GMTs and proportions of participants with a  $\geq 4$ -fold rise in serotype-specific OPA titers from prevaccination to 30 days postvaccination.

#### *Clinical Trials Conducted in Pneumococcal Vaccine-Naïve Adults*

In the pivotal, double-blind, active comparator-controlled study (Protocol 019), 1,205 pneumococcal vaccine-naïve adults aged 50 years or older were randomised to receive either VAXNEUVANCE or Prevenar 13. The study demonstrated that VAXNEUVANCE is non-inferior to Prevenar 13 for the 13 shared serotypes and superior for the 2 unique serotypes and for shared serotype 3. Table 13 summarises the OPA GMTs at 30 days postvaccination. Serotype-specific IgG GMCs were generally consistent with the results observed for the OPA GMTs.

**Table 13: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age (Protocol 019)**

Pneumococcal Serotype	VAXNEUVANCE (N = 602)		Prevenar 13 (N = 600)		GMT Ratio* (VAXNEUVANCE/Prevenar 13) (95% CI)*
	n	GMT*	n	GMT*	
<b>13 Shared Serotypes†</b>					
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)
<b>2 Serotypes Unique to VAXNEUVANCE§</b>					
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/Prevenar 13) 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/Prevenar 13) being > 1.2.

§ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE/Prevenar 13) 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 titer (1/dil);

OPA=opsonophagocytic activity

In a double-blind, lot consistency study (Protocol 020), 2,340 pneumococcal vaccine-naïve adults 50 years of age and older were randomised in a 3:3:3:1 ratio to receive 1 of 3 lots of VAXNEUVANCE or Prevenar 13. The study demonstrated that all 3 lots are equivalent as the lower and upper limits of the 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes. Immune responses following vaccination with VAXNEUVANCE were comparable to Prevenar 13 for the shared serotypes.

In a double-blind, descriptive study (Protocol 017), 1,515 immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease were randomised 3:1 to receive either VAXNEUVANCE or Prevenar 13, followed by PNEUMOVAX 23 six months later. VAXNEUVANCE elicited immune responses to all 15 serotypes as assessed by OPA GMTs (Table 14) and IgG GMCs. OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes. Following vaccination with PNEUMOVAX 23, OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for all 15 serotypes in VAXNEUVANCE.

Immune responses in adults with no risk factors (n=285; 25.2%) who received VAXNEUVANCE were generally consistent with those observed in the overall study population.

**Table 14: Serotype-Specific OPA GMTs 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)			Prevenar 13 (N = 379)		
	n	Observed GMT	95% CI*	n	Observed GMT	95% CI*
<b>13 Shared Serotypes</b>						
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)
<b>2 Serotypes Unique to VAXNEUVANCE</b>						
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 titer (1/dil); OPA=opsonophagocytic activity.

#### *Sequential Administration of Pneumococcal Vaccines in Adults*

In a double-blind, active, comparator-controlled study (Protocol 016), 652 pneumococcal vaccine-naïve adults 50 years of age and older were randomised to receive either VAXNEUVANCE or Prevenar 13, followed by PNEUMOVAX 23 one year later. Following vaccination with PNEUMOVAX 23, 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. Immune responses at 30 days and 12 months postvaccination were comparable between the two vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

The sequential administration of VAXNEUVANCE followed by PNEUMOVAX 23 was evaluated with an interval of 2 months in immunocompromised individuals (Protocol 018) and an interval of 6 months in immunocompetent individuals with or without risk factors for pneumococcal disease (Protocol 017) [See Clinical immunogenicity in special populations].

#### *Clinical Trials Conducted in Adults with Prior Pneumococcal Vaccination*

In a double-blind, descriptive study (Protocol 007), 253 adults 65 years of age and older who were previously vaccinated with PNEUMOVAX 23 at least 1 year prior to study entry were randomised to receive either VAXNEUVANCE or Prevenar 13. IgG GMCs and OPA GMTs were generally comparable between the vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the 2 unique serotypes.

#### *Clinical Immunogenicity in Special Populations*

##### *Populations at Increased Risk for Pneumococcal Disease*

##### *Infants Born Prematurely*

The immunogenicity of VAXNEUVANCE was evaluated in preterm infants (27 to <37 weeks gestation at birth) enrolled within 4 double-blind, active comparator controlled studies (Protocol 025, Protocol 027 [groups receiving a complete 4 dose regimen of either VAXNEUVANCE or Prevenar 13, Protocol 029 and Protocol 031). In these studies, 354 participants were randomised to receive VAXNEUVANCE or Prevenar 13 as a 4 dose regimen with the first dose administered at 2 months of age,

followed by 2 additional doses at least 4 weeks apart and a fourth dose at 11 through 15 months of age. Serotype-specific IgG and OPA responses at 30 days following the primary series, prior to the toddler dose and at 30 days following the toddler dose were generally comparable between vaccination groups for the 13 shared serotypes and higher in VAXNEUVANCE for the two unique serotypes (22F and 33F). The immune responses in preterm infants receiving 4 doses of VAXNEUVANCE were generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants). The effectiveness of VAXNEUVANCE in infants born prematurely has not been established.

#### *Children with Sickle Cell Disease*

In a double blind, descriptive study (Protocol 023), 104 children 5 to 17 years of age with sickle cell disease were randomised 2:1 to receive a single dose of either VAXNEUVANCE or Prevenar 13. 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 unique serotypes (22F and 33F). The effectiveness of VAXNEUVANCE in children with sickle cell disease has not been established.

#### *Individuals Living with HIV*

##### Children Living with HIV

In a double blind, descriptive study (Protocol 030), 407 children 6 to 17 years of age living with HIV, with CD4+ T cell count  $\geq 200$  cells per microliter and plasma HIV RNA value  $< 50,000$  copies/mL were randomised to receive a single dose of either VAXNEUVANCE or Prevenar 13, followed by PNEUMOVAX 23 two 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 unique serotypes (22F and 33F). After sequential administration with PNEUMOVAX 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. The effectiveness of VAXNEUVANCE in children living with HIV has not been established.

##### Adults Living with HIV

In a double-blind, descriptive study (Protocol 018), 302 pneumococcal vaccine-naïve adults  $\geq 18$  years of age living with HIV with CD4+ T-cell count  $\geq 50$  cells per microliter and plasma HIV ribonucleic acid (RNA)  $< 50,000$  copies/mL were randomised to receive either VAXNEUVANCE or Prevenar 13, followed by PNEUMOVAX 23 two months later. VAXNEUVANCE elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination. After sequential administration with PNEUMOVAX 23, OPA GMTs and IgG GMCs were generally comparable between the two vaccination groups for all 15 serotypes.

#### *Individuals with Hematopoietic Stem Cell Transplant*

In a double-blind, descriptive study (Protocol 022), the immunogenicity of VAXNEUVANCE was evaluated in children ( $\geq 3$  years of age) and adults who received an allo-HSCT 3 to 6 months prior to enrollment. All participants had a history of stable engraftment and none had uncontrolled graft-versus-host disease. In this study, 277 participants were randomised to receive 3 doses of VAXNEUVANCE or Prevenar 13, administered one month apart. Twelve months after allo-HSCT, participants without chronic graft-versus-host disease (cGVHD) received a single dose of PNEUMOVAX 23 and those with cGVHD received a fourth dose of either VAXNEUVANCE or Prevenar 13. 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 unique serotypes (22F and 33F). Similarly, in participants who received either VAXNEUVANCE or Prevenar 13 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 unique serotypes (22F and 33F). In participants who received PNEUMOVAX 23 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. The effectiveness of VAXNEUVANCE in recipients of allo-HSCT has not been established.

### *Adults with Chronic Conditions and Other Risk Factors*

In the double-blind, descriptive study (Protocol 017), the immunogenicity of VAXNEUVANCE was evaluated in a subset of immunocompetent adults 18 to 49 years of age with one or more of the following risk factors for pneumococcal disease: 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. Of those who received VAXNEUVANCE, 54.7% (n=620) had 1 risk factor and 20.1% (n=228) had 2 or more risk factors. In both of these risk factor subgroups, VAXNEUVANCE elicited immune responses to all 15 serotypes contained in the vaccine as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination, which were generally consistent with those observed in the overall study population. Sequential administration of VAXNEUVANCE followed by 6 months later by PNEUMOVAX 23 was also immunogenic for all 15 serotypes contained in the vaccine.

### *Concomitant Vaccination*

#### Infants and Toddlers

The immunogenicity of routine infant vaccines administered concomitantly with VAXNEUVANCE was evaluated within 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 026, Protocol 029 and Protocol 027). In Protocol 025, approximately 1,200 participants received Rotarix concomitantly with the infant primary series and INFANRIX hexa concomitantly with the infant primary series and toddler dose of VAXNEUVANCE or Prevenar 13. Immune responses to Rotarix administered concomitantly with VAXNEUVANCE met non-inferiority criteria, as assessed by anti-rotavirus immunoglobulin A GMTs at 30 days following completion of the primary series. Similarly, immune responses to INFANRIX hexa administered concomitantly with VAXNEUVANCE met non-inferiority criteria, as assessed by the antigen-specific response rate to each antigen in INFANRIX hexa at 30 days following the toddler dose.

In Protocol 026, approximately 1,100 participants received VAXELIS administered concomitantly with all 3 doses of VAXNEUVANCE or Prevenar 13. At 30 days following the toddler dose, immune responses to the vaccine specific antigens for VAXELIS met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

In Protocol 029, approximately 1,700 participants received Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine administered concomitantly with the infant primary series of VAXNEUVANCE or Prevenar 13. Approximately 1,500 participants received VAQTA, HIBERIX, M-M-R II and VARIVAX, administered concomitantly with the toddler dose of VAXNEUVANCE or Prevenar 13. At 30 days following completion of the primary series, immune responses to the antigens contained in Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine met non-inferiority criteria when administered concomitantly with VAXNEUVANCE. At 30 days following the toddler dose, immune responses to vaccine-specific antigens for VAQTA, HIBERIX, M-M-R II and VARIVAX met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

In Protocol 027, approximately 900 participants received H-B VAX II and RotaTeq concomitantly with VAXNEUVANCE or Prevenar 13 in the infant primary series. At 30 days following the primary series, immune responses to vaccine-specific antigens for H-B VAX II and RotaTeq met non-inferiority criteria when administered concomitantly with VAXNEUVANCE.

These studies support the concomitant administration of VAXNEUVANCE with any of the following vaccine antigens: diphtheria, tetanus, pertussis, poliomyelitis (serotypes 1, 2 and 3), hepatitis A, hepatitis B, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella and rotavirus vaccine, either as monovalent or combination vaccines.

Concomitant administration of VAXNEUVANCE with meningococcal ACWY and meningococcal B vaccines has not been studied.

#### Adults

In a double-blind, randomised study (Protocol 021), 1,200 adults 50 years of age and older, with or without a history of prior PNEUMOVAX 23 vaccination, were randomised to receive VAXNEUVANCE concomitantly or nonconcomitantly with seasonal inactivated quadrivalent influenza vaccine (QIV). One vaccination group

received VAXNEUVANCE and QIV concomitantly, followed by placebo 30 days later. A second vaccination group received QIV and placebo concomitantly, followed by VAXNEUVANCE 30 days later.

VAXNEUVANCE administered concomitantly with QIV is non-inferior to VAXNEUVANCE administered nonconcomitantly with QIV (based on a 2-fold non-inferiority margin), as assessed by pneumococcal OPA GMTs at 30 days postvaccination with VAXNEUVANCE for all 15 serotypes contained in the vaccine. OPA GMTs were slightly lower for some serotypes when VAXNEUVANCE was administered concomitantly with QIV compared to VAXNEUVANCE administered alone. QIV administered concomitantly with VAXNEUVANCE is non-inferior to QIV administered nonconcomitantly (based on a 2-fold non-inferiority margin) as assessed by influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV for all 4 influenza strains.

## **5.2 PHARMACOKINETIC PROPERTIES**

Not applicable.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

VAXNEUVANCE has not been evaluated for the potential to cause genotoxicity.

### **Carcinogenicity**

VAXNEUVANCE has not been evaluated for the potential to cause carcinogenicity.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Histidine  
Polysorbate 20  
Sodium chloride  
Water for injections

For adjuvant, see Section 2 Qualitative and quantitative composition.

The product does not contain antimicrobial preservative.

### **6.2 INCOMPATIBILITIES**

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

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store refrigerated at 2°C to 8°C.  
Do not freeze.  
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**

VAXNEUVANCE is presented as a suspension in 0.5 mL single-dose pre-filled syringes (Type I glass) in packs of 1 and 10.

The tip cap and plunger stopper of the pre-filled syringe are not made with natural rubber latex.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Not applicable.

### CAS number

Not applicable.

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited  
Level 1, Building A, 26 Talavera Road  
Macquarie Park NSW 2113  
<http://www.msd-australia.com.au>  
Tel (+61) 02 8988 8000

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### Summary table of changes

Section changed	Summary of new information
4.2	Update to clarify instructions for use on product resuspension.
N/A	Editorial updates are made throughout the document Update to copyright statement.

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