

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VAXNEUVANCE safely and effectively. See full prescribing information for VAXNEUVANCE.

VAXNEUVANCE™ (Pneumococcal 15-valent Conjugate Vaccine) Suspension for Intramuscular Injection
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

VAXNEUVANCE™ is a vaccine indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in adults 18 years of age and older. (1)

DOSAGE AND ADMINISTRATION

For intramuscular use only.
Administer a single 0.5 mL dose. (2.1)

DOSAGE FORMS AND STRENGTHS

Suspension for injection (0.5 mL dose), supplied as a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid. (4)

ADVERSE REACTIONS

The most commonly reported solicited adverse reactions:

- in individuals 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%) and arthralgia (12.7%). (6.1)
- in individuals 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%) and arthralgia (7.7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised:

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Dosage
 - 2.2 Administration
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Altered Immunocompetence
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS
 - 7.1 Immunosuppressive Therapies
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Lactation

- 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Individuals at Increased Risk for Pneumococcal Disease
 - 11 DESCRIPTION
 - 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 14 CLINICAL STUDIES
 - 14.1 Clinical Trials in Pneumococcal Vaccine-Naïve Adults
 - 14.2 Concomitant Vaccination
 - 16 HOW SUPPLIED/STORAGE AND HANDLING
 - 17 PATIENT COUNSELING INFORMATION
- *Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VAXNEUVANCE™ is indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in adults 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only.

2.1 Dosage

Administer a single 0.5 mL dose.

2.2 Administration

Hold the prefilled syringe horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension in the prefilled syringe. 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. Do not use if particulate matter or discoloration is observed.

3 DOSAGE FORMS AND STRENGTHS

VAXNEUVANCE is a suspension for intramuscular injection supplied in a 0.5 mL single-dose prefilled syringe.

4 CONTRAINDICATIONS

Do not administer VAXNEUVANCE to individuals with a severe allergic reaction (e.g., anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid. [See *Description (11)*.]

5 WARNINGS AND PRECAUTIONS

5.1 Altered Immunocompetence

Some individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE. [See *Drug Interactions (7.1)* and *Use in Specific Populations (8.6)*.]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly reported solicited adverse reactions in individuals 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%) and arthralgia (12.7%).

The most commonly reported solicited adverse reactions in individuals 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%) and arthralgia (7.7%).

Safety Assessment in Clinical Studies

The safety of VAXNEUVANCE was assessed in 7 randomized, double-blind clinical studies conducted in the Americas, Europe and Asia Pacific, in which 5,630 adults 18 years of age and older received VAXNEUVANCE and 1,808 adults received Prevnar 13 [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein)]. In Studies 1-3 (NCT03950622, NCT03950856, and NCT03480763), a total of 3,032 adults 50 years of age and older with no history of pneumococcal vaccination received VAXNEUVANCE and 1,154 participants received Prevnar 13. In Study 4 (NCT03547167), adults 18 through 49 years of age with no history of pneumococcal vaccination, including individuals with increased risk of developing pneumococcal disease, received VAXNEUVANCE (N=1,134) or Prevnar 13 (N=378), followed by PNEUMOVAX 23 six months later. In Study 5 (NCT02573181), adults 65 years of age

and older previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) received VAXNEUVANCE (N=127) or Prevnar 13 (N=126). In Study 6 (NCT03615482), adults 50 years of age and older received VAXNEUVANCE concomitantly with a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; QIV) (Group 1, N=600) or nonconcomitantly 30 days after QIV (Group 2, N=585). In this study population, 20.9% of individuals had a history of prior vaccination with PNEUMOVAX 23. In Study 7 (NCT03480802), HIV-infected adults 18 years of age and older received VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later.

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. Overall, the mean age of the participants was 58 years and 54.6% were female. The racial distribution was as follows: 72.3% were White, 9.9% were Asian, 8.1% were American Indian or Alaska Native, 7.4% were Black or African American, and 18.1% were of Hispanic or Latino ethnicity.

In all studies, safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. Study investigators reviewed the VRC with the participants 15 days postvaccination to ensure consistency with protocol definitions. The analyses presented in Tables 1-3 below reflect the information based on the final assessment by the study investigators. Oral body temperature and injection-site adverse reactions were solicited on Day 1 through Day 5 postvaccination. Systemic adverse reactions 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 for serious adverse events postvaccination with VAXNEUVANCE was 1 month in Study 5; 2 months in Study 7; 6 months in Studies 1, 2, 4 and 6; and 12 months in Study 3.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Prevnar 13 in 3 studies are shown in Tables 1-3. The majority of solicited adverse reactions lasted ≤ 3 days.

Table 1: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 50 Years of Age and Older (Study 2)*

| | VAXNEUVANCE (%) N=2,103 | Prevnar 13 (%) N=230 |
|---------------------------------------|------------------------------------|---------------------------------|
| Local Reactions[†] | | |
| Pain | | |
| Any | 66.8 | 52.2 |
| Grade 3 [‡] | 0.9 | 0.0 |
| Erythema | | |
| Any | 10.9 | 9.6 |
| >10 cm | 0.6 | 0.4 |
| Swelling | | |
| Any | 15.4 | 14.3 |
| >10 cm | 0.2 | 0.0 |
| Systemic Reactions[§] | | |
| Fatigue | | |
| Any | 21.5 | 22.2 |
| Grade 3 [‡] | 0.7 | 0.9 |
| Headache | | |
| Any | 18.9 | 18.7 |
| Grade 3 [‡] | 0.8 | 0.0 |
| Myalgia | | |
| Any | 26.9 | 21.7 |
| Grade 3 [‡] | 0.4 | 0.0 |
| Arthralgia | | |
| Any | 7.7 | 5.7 |
| Grade 3 [‡] | 0.2 | 0.0 |
| Fever [¶] | | |
| ≥38.0°C and <38.5°C | 0.6 | 0.4 |
| ≥38.5°C and <39.0°C | 0.1 | 0.0 |
| ≥39.0°C | 0.0 | 0.0 |

* Study 2 (NCT03950856) was a randomized (9:1), double-blind, active comparator-controlled, lot to lot consistency study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.

[†] Solicited on Day 1 through Day 5 postvaccination

[‡] Any use of narcotic pain reliever or prevents daily activity

[§] 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 2: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 18 to 49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Study 4)*

| | VAXNEUVANCE (%) N=1,134 | Prevnar 13 (%) N=378 |
|---------------------------------------|--|---------------------------------------|
| Local Reactions[†] | | |
| Pain | | |
| Any | 75.8 | 68.8 |
| Grade 3 [‡] | 1.1 | 1.6 |
| Erythema | | |
| Any | 15.1 | 14.0 |
| >10 cm | 0.5 | 0.3 |
| Swelling | | |
| Any | 21.7 | 22.2 |
| >10 cm | 0.4 | 0.5 |
| Systemic Reactions[§] | | |
| Fatigue | | |
| Any | 34.3 | 36.8 |
| Grade 3 [‡] | 1.0 | 0.8 |
| Headache | | |
| Any | 26.5 | 24.9 |
| Grade 3 [‡] | 0.8 | 0.5 |
| Myalgia | | |
| Any | 28.8 | 26.5 |
| Grade 3 [‡] | 0.3 | 0.5 |
| Arthralgia | | |
| Any | 12.7 | 11.6 |
| Grade 3 [‡] | 0.4 | 0.0 |
| Fever [¶] | | |
| ≥38.0°C and <38.5°C | 1.0 | 0.3 |
| ≥38.5°C and <39.0°C | 0.3 | 0.0 |
| ≥39.0°C | 0.2 | 0.0 |

* Study 4 (NCT03547167) was a randomized (3:1), double-blind, descriptive study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.

[†] Solicited on Day 1 through Day 5 postvaccination

[‡] Any use of narcotic pain reliever or prevents daily activity

[§] 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 3: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Adults 65 Years of Age and Older with Previous Pneumococcal Vaccination (Study 5)*

| | VAXNEUVANCE (%) N=127 | Pprevnar 13 (%) N=126 |
|---------------------------------------|----------------------------------|----------------------------------|
| Local Reactions[†] | | |
| Pain | | |
| Any | 55.1 | 44.4 |
| Grade 3 [‡] | 0.8 | 0.0 |
| Erythema | | |
| Any | 7.9 | 7.1 |
| >10 cm | 0.8 | 0.0 |
| Swelling | | |
| Any | 14.2 | 6.3 |
| >10 cm | 0.0 | 0.0 |
| Systemic Reactions[§] | | |
| Fatigue | | |
| Any | 18.1 | 19.0 |
| Grade 3 [‡] | 0.0 | 0.0 |
| Headache | | |
| Any | 13.4 | 15.9 |
| Grade 3 [‡] | 0.0 | 0.0 |
| Myalgia | | |
| Any | 15.7 | 11.1 |
| Grade 3 [‡] | 0.8 | 0.0 |
| Arthralgia | | |
| Any | 5.5 | 8.7 |
| Grade 3 [‡] | 0.0 | 0.0 |
| Fever [¶] | | |
| ≥38.0°C and <38.5°C | 1.6 | 0.0 |
| ≥38.5°C and <39.0°C | 0.0 | 0.0 |
| ≥39.0°C | 0.0 | 0.0 |

* Study 5 (NCT02573181) was a randomized, double-blind, descriptive study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days postvaccination, to ensure consistency with protocol definitions.

[†] Solicited on Day 1 through Day 5 postvaccination

[‡] Any use of narcotic pain reliever or prevents daily activity

[§] 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

Across all studies, injection-site pruritus was reported to occur in up to 2.8% of adults vaccinated with VAXNEUVANCE.

Serious Adverse Events

Across all studies, among participants 18 years of age and older who received VAXNEUVANCE (excluding those who received QIV concomitantly; N=5,030) or Pprevnar 13 (N=1,808), serious adverse events within 30 days postvaccination were reported by 0.4% of VAXNEUVANCE recipients and by 0.7% of Pprevnar 13 recipients. In a subset of these studies, among those who received VAXNEUVANCE (N=4,751) and Pprevnar 13 (N=1,532), serious adverse events within 6 months postvaccination were reported by 2.5% of VAXNEUVANCE recipients and by 2.4% of Pprevnar 13 recipients.

There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to VAXNEUVANCE.

Safety with Concomitant Influenza Vaccine Administration

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

7 DRUG INTERACTIONS

7.1 Immunosuppressive Therapies

Immunosuppressive therapies may reduce the immune response to this vaccine [see *Warnings and Precautions (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

There are no adequate and well-controlled studies of VAXNEUVANCE in pregnant women. Available data on VAXNEUVANCE administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Developmental toxicity studies have been performed in female rats administered a human dose of VAXNEUVANCE on four occasions; twice prior to mating, once during gestation and once during lactation. These studies revealed no evidence of harm to the fetus due to VAXNEUVANCE [see *Animal Data below*].

Data

Animal Data

Developmental toxicity studies have been performed in female rats. In these studies, female rats received a human dose of VAXNEUVANCE by intramuscular injection on day 28 and day 7 prior to mating, and on gestation day 6 and on lactation day 7. No vaccine related fetal malformations or variations were observed. No adverse effect on pup weight up to post-natal day 21 was noted.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of VAXNEUVANCE on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VAXNEUVANCE and any potential adverse effects on the breastfed child from VAXNEUVANCE or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety and effectiveness of VAXNEUVANCE in individuals younger than 18 years of age have not been established.

8.5 Geriatric Use

Of the 4,389 individuals aged 50 years and older who received VAXNEUVANCE, 2,478 (56.5%) were 65 years and older, and 479 (10.9%) were 75 years and older [see *Adverse Reactions (6.1) and Clinical Studies (14.1)*]. Overall, there were no clinically meaningful differences in the safety profile or immune responses observed in older individuals (65 to 74 years and 75 years of age and older) when compared to younger individuals.

8.6 Individuals at Increased Risk for Pneumococcal Disease

Adults with HIV Infection

In a double-blind, descriptive study (Study 7), the safety and immunogenicity of VAXNEUVANCE were evaluated in pneumococcal vaccine-naïve HIV-infected adults 18 years of age and older, with CD4+ T-cell count ≥ 50 cells per microliter and plasma HIV RNA value $< 50,000$ copies/mL. Participants were randomized to receive VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later [see *Adverse Reactions (6.1)*]. Anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after administration of VAXNEUVANCE, compared to pre-vaccination, for the 15 serotypes contained in VAXNEUVANCE. After sequential administration with PNEUMOVAX 23, OPA GMTs observed at 30 days after PNEUMOVAX 23 vaccination were numerically similar between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The safety profile of

VAXNEUVANCE was similar between the two vaccination groups. The effectiveness of VAXNEUVANCE in HIV-infected individuals has not been evaluated.

11 DESCRIPTION

VAXNEUVANCE (Pneumococcal 15-valent Conjugate Vaccine) is a sterile suspension of purified capsular polysaccharides from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM₁₉₇. Each pneumococcal capsular polysaccharide is activated via sodium metaperiodate oxidation and then individually conjugated to CRM₁₉₇ carrier protein via reductive amination. CRM₁₉₇ is a non-toxic variant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

Each of the fifteen serotypes is manufactured independently using the same manufacturing steps with slight variations to accommodate for differences in strains, polysaccharides and process stream properties. Each *S. pneumoniae* serotype is grown in media containing yeast extract, dextrose, salts and soy peptone. Each polysaccharide is purified by a series of chemical and physical methods. Then each polysaccharide is chemically activated and conjugated to the carrier protein CRM₁₉₇ to form each glycoconjugate. CRM₁₉₇ is isolated from cultures grown in a glycerol-based, chemically-defined, salt medium and purified by chromatography and ultrafiltration. The final vaccine is prepared by blending the fifteen glycoconjugates with aluminum phosphate adjuvant in a final buffer containing histidine, polysorbate 20 and sodium chloride.

Each 0.5 mL dose contains 2.0 mcg each of *S. pneumoniae* polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.0 mcg of polysaccharide serotype 6B, 30 mcg of CRM₁₉₇ carrier protein, 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride, and 125 mcg of aluminum as aluminum phosphate adjuvant. VAXNEUVANCE does not contain any preservatives.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. VAXNEUVANCE induces opsonophagocytic activity against the serotypes contained in the vaccine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VAXNEUVANCE has not been evaluated for carcinogenic or mutagenic potential or for impairment of male fertility in animals. VAXNEUVANCE administered to female rats had no effect on fertility [see *Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

Immune responses elicited by VAXNEUVANCE and Prevnar 13 were measured by a multiplexed opsonophagocytic antibody assay (MOPA) for the 15 pneumococcal serotypes contained in VAXNEUVANCE pre- and post- vaccination.

14.1 Clinical Trials in Pneumococcal Vaccine-Naïve Adults

Study 1

Study 1 assessed serotype-specific opsonophagocytic activity (OPA) responses for each of the 15 serotypes contained in VAXNEUVANCE at 30 days postvaccination in a double-blind, active comparator-controlled study that enrolled pneumococcal vaccine-naïve participants 50 years of age and older. Participants were randomized to receive either VAXNEUVANCE (N=604) or Prevnar 13 (N=601) at sites in USA, Canada, Spain, Taiwan, and Japan. The mean age of participants was 66 years and 57.3% were female. The racial distribution was as follows: 67.7% were White, 25.1% were Asian, 6.1% were Black or African American and 22.0% were of Hispanic or Latino ethnicity.

Table 4 summarizes the OPA geometric mean antibody titers (GMTs) at 30 days postvaccination for the 15 serotypes contained in VAXNEUVANCE. The study demonstrated that VAXNEUVANCE is noninferior

to Prevnar 13 for the 13 shared serotypes and induces statistically significantly greater OPA GMTs compared to Prevnar 13 for shared serotype 3 and for the 2 unique serotypes (22F, 33F).

Table 4: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 50 Years of Age and Older (Study 1)

| Pneumococcal Serotype | VAXNEUVANCE (N = 602) | | Prevnar 13 (N = 600) | | GMT Ratio* (VAXNEUVANCE/Prevnar 13) (95% CI)* |
|-----------------------------------|-----------------------|------|----------------------|------|---|
| | n | GMT* | n | GMT* | |
| Serotype [†] | | | | | |
| 1 | 598 | 257 | 598 | 321 | 0.80 (0.66, 0.97) |
| 3 [‡] | 598 | 215 | 598 | 133 | 1.62 (1.40, 1.87) |
| 4 | 598 | 1109 | 598 | 1633 | 0.68 (0.57, 0.80) |
| 5 | 598 | 445 | 598 | 560 | 0.79 (0.64, 0.98) |
| 6A | 596 | 5371 | 596 | 5276 | 1.02 (0.85, 1.22) |
| 6B | 598 | 3984 | 598 | 3179 | 1.25 (1.04, 1.51) |
| 7F | 596 | 4575 | 596 | 5830 | 0.78 (0.68, 0.90) |
| 9V | 598 | 1809 | 597 | 2193 | 0.83 (0.71, 0.96) |
| 14 | 598 | 1976 | 598 | 2619 | 0.75 (0.64, 0.89) |
| 18C | 598 | 2749 | 598 | 2552 | 1.08 (0.91, 1.27) |
| 19A | 598 | 3177 | 597 | 3921 | 0.81 (0.70, 0.94) |
| 19F | 598 | 1688 | 598 | 1884 | 0.90 (0.77, 1.04) |
| 23F | 598 | 2029 | 598 | 1723 | 1.18 (0.96, 1.44) |
| Additional Serotypes [§] | | | | | |
| 22F | 594 | 2381 | 585 | 73 | 32.52 (25.87, 40.88) |
| 33F | 598 | 8010 | 597 | 1114 | 7.19 (6.13, 8.43) |

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

[†] Non-inferiority for the 13 shared serotypes was met if the lower bound of the 95% CI for the GMT ratio (VAXNEUVANCE/Prevnar 13) was > 0.5.

[‡] Statistically significantly greater OPA GMT for serotype 3 was based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE/Prevnar 13) > 1.2.

[§] Statistically significantly greater OPA GMTs for serotypes 22F and 33F was based on the lower bound of the 95% CI for the estimated GMT ratio (VAXNEUVANCE/Prevnar 13) > 2.0.

N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis that had at least one pre-dose OPA measurement (VAXNEUVANCE, n=537-597; Prevnar 13, n=545-595) or post-dose OPA measurement (VAXNEUVANCE, n=568-580; Prevnar 13, n=528-574).

CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titer; OPA=opsonophagocytic activity

Study 3

In a double-blind, active comparator-controlled, descriptive study (Study 3), pneumococcal vaccine-naïve adults 50 years of age and older were randomized to receive either VAXNEUVANCE (N=327) or Prevnar 13 (N=325), followed by PNEUMOVAX 23 one year later.

Following vaccination with PNEUMOVAX 23, OPA GMTs were numerically similar between the two vaccination groups for the 15 serotypes in VAXNEUVANCE.

Study 4

In a double-blind, descriptive study (Study 4), adults 18 through 49 years of age, including individuals with increased risk of developing pneumococcal disease, were randomized to receive VAXNEUVANCE (N=1,135) or Prevnar 13 (N=380), followed by PNEUMOVAX 23 six months later [see *Adverse Reactions (6.1)*]. Among those who received VAXNEUVANCE, 620 participants had one risk factor and 228 participants had two or more risk factors for pneumococcal disease.

Table 5 presents OPA GMTs in the overall study population for each of the 15 serotypes 30 days following vaccination with VAXNEUVANCE or Prevnar 13.

Table 5: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Study 4)

| Pneumococcal Serotype | VAXNEUVANCE (N = 1,133) | | | Pprevnar 13 (N = 379) | | |
|-----------------------|----------------------------|--------------|----------------|--------------------------|--------------|---------------|
| | n | Observed GMT | 95% CI* | n | Observed GMT | 95% CI* |
| Serotype | | | | | | |
| 1 | 1004 | 267 | (242, 295) | 337 | 267 | (220, 324) |
| 3 | 990 | 198 | (184, 214) | 336 | 150 | (129, 173) |
| 4 | 1001 | 1401 | (1294, 1517) | 338 | 2568 | (2268, 2908) |
| 5 | 1003 | 560 | (508, 618) | 339 | 731 | (613, 873) |
| 6A | 994 | 12763 | (11772, 13838) | 333 | 11313 | (9739, 13141) |
| 6B | 999 | 10164 | (9486, 10891) | 338 | 6958 | (5987, 8086) |
| 7F | 1004 | 5725 | (5382, 6090) | 338 | 7583 | (6762, 8503) |
| 9V | 1000 | 3353 | (3132, 3590) | 339 | 3969 | (3541, 4449) |
| 14 | 1001 | 5245 | (4860, 5660) | 339 | 5863 | (5191, 6623) |
| 18C | 999 | 5695 | (5314, 6103) | 339 | 3050 | (2685, 3465) |
| 19A | 1001 | 5335 | (4985, 5710) | 339 | 5884 | (5221, 6632) |
| 19F | 1003 | 3253 | (3051, 3468) | 339 | 3272 | (2949, 3631) |
| 23F | 1001 | 4828 | (4443, 5247) | 337 | 3876 | (3323, 4521) |
| Additional Serotypes | | | | | | |
| 22F | 991 | 3939 | (3654, 4246) | 317 | 291 | (221, 383) |
| 33F | 999 | 11734 | (10917, 12612) | 334 | 2181 | (1826, 2606) |

* 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 randomized and vaccinated; n=Number of participants contributing to the analysis. CI=confidence interval; GMT=geometric mean titer; OPA=opsonophagocytic activity.

Following vaccination with PNEUMOVAX 23, the OPA GMTs for the 15 serotypes in VAXNEUVANCE were numerically similar among subjects who had received VAXNEUVANCE or Pprevnar 13 for the first vaccination.

14.2 Concomitant Vaccination

In a double-blind, randomized study (Study 6), adults 50 years of age and older were randomized to receive VAXNEUVANCE concomitantly administered with a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; QIV) (Group 1, N=600) or VAXNEUVANCE 30 days after receiving QIV (Group 2, N=600) [see *Adverse Reactions* (6)]. Pneumococcal vaccine serotype OPA GMTs were evaluated 30 days after VAXNEUVANCE and influenza vaccine strain hemagglutinin inhibition assay (HAI) GMTs were evaluated 30 days after QIV. The noninferiority criteria for the comparisons of GMTs [lower limit of the 2-sided 95% confidence interval (CI) of the GMT ratio (Group 1/Group 2) >0.5] were met for the 15 pneumococcal serotypes in VAXNEUVANCE and for the 4 influenza vaccine strains tested.

16 HOW SUPPLIED/STORAGE AND HANDLING

VAXNEUVANCE is supplied as follows:

Carton of one 0.5 mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4329-02

Carton of ten 0.5 mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4329-03

Store refrigerated at 2°C to 8°C (36°F to 46°F).

Do not freeze. Protect from light.

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Discuss the following with the patient:

- Provide the required vaccine information to the patient.
- Inform the patient of the benefits and risks associated with vaccination.

- Inform the patient that vaccination with VAXNEUVANCE may not protect all vaccine recipients.
- Instruct the patient to report any serious adverse reactions to their healthcare provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967, or report online at www.vaers.hhs.gov.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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