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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAPVAXIVE safely and effectively. See full prescribing information for CAPVAXIVE.

CAPVAXIVE™ (Pneumococcal 21-valent Conjugate Vaccine) Injection, for intramuscular use
Initial U.S. Approval: 2024

---------- INDICATIONS AND USAGE ----------

CAPVAXIVE™ is a vaccine indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older. (1)
- active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older. (1)

The indication for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

---------- DOSAGE AND ADMINISTRATION ----------

For intramuscular use.

- Administer a single 0.5 mL dose. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

CAPVAXIVE is an injection. A single dose is 0.5 mL. (3)

---------- CONTRAINDICATIONS ----------

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

---------- ADVERSE REACTIONS ----------

The most commonly reported (>10%) solicited adverse reactions:

- in individuals 18 through 49 years of age were: injection-site pain (73.1%), fatigue (36.0%), headache (27.5%), myalgia (16.4%), injection-site erythema (13.8%), and injection-site swelling (13.3%). (6.1)
- in individuals 50 years of age and older were: injection-site pain (41.2%), fatigue (19.7%), and headache (11.0%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC 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: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CAPVAXIVE™ is indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.
- active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

The indication for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA) *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

For intramuscular use.

2.1 Dosage

Administer a single 0.5 mL dose.

2.2 Administration

CAPVAXIVE is a colorless, clear to opalescent solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed. Administer intramuscularly.

3 DOSAGE FORMS AND STRENGTHS

CAPVAXIVE is an injection. A single dose is 0.5 mL.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of CAPVAXIVE.

5.2 Altered Immunocompetence

Individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to CAPVAXIVE.

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 vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most commonly reported (>10%) solicited adverse reactions in individuals 18 through 49 years of age who received CAPVAXIVE were: injection-site pain (73.1%), fatigue (36.0%), headache (27.5%), myalgia (16.4%), injection-site erythema (13.8%), and injection-site swelling (13.3%).

The most commonly reported (>10%) solicited adverse reactions in individuals 50 years of age and older who received CAPVAXIVE were: injection-site pain (41.2%), fatigue (19.7%), and headache (11.0%).

Safety Assessment in Clinical Studies

The safety of CAPVAXIVE was assessed in four clinical studies (Studies 1-4) conducted across the Americas, Europe, and Asia Pacific, which included individuals ranging in age from 18 to 97 years. Across all 4 studies, 4,556 individuals received CAPVAXIVE and 2,021 individuals received an active comparator vaccine. Safety was monitored using an electronic Vaccination Report Card for 30 days postvaccination. Injection-site adverse reactions, systemic adverse reactions, and body temperature were solicited Day 1 through Day 5 postvaccination. Unsolicited adverse events were reported Day 1 through Day 30 postvaccination. Serious adverse events (SAEs) were reported through 6 months postvaccination in all studies.

Demographics of Individuals in Clinical Studies

Across all studies, the mean age of the individuals who were randomized and vaccinated was 53.5 years, and 57.2% were female. The racial distribution was as follows: 76.0% were White, 10.2% were Black or African American, 9.9% were Asian, and 0.5% were American Indian or Alaska Native; 20.6% were of Hispanic or Latino ethnicity. Approximately 34% of vaccinated individuals had one or more prespecified chronic medical conditions known to increase the risk of pneumococcal disease (i.e., diabetes, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma, smoking, alcoholism).

Pneumococcal Vaccine-Naïve Individuals 18 years of Age and Older

In a double-blind study, Study 1 (NCT05425732), individuals 18 years of age and older who had not previously received a pneumococcal vaccine were enrolled and randomized to receive a single dose of CAPVAXIVE or Prevnar 20. The percentage of individuals 18 through 49 years of age and 50 years of age and older who reported solicited adverse reactions that occurred within 5 days postvaccination of CAPVAXIVE or Prevnar 20 is shown in Table 1. Solicited adverse reactions following administration of CAPVAXIVE lasted a median of 2 days with 81.3% of reactions lasting ≤3 days for individuals 18 through 49 years of age and a median of 1 day with 86.5% of reactions lasting ≤3 days for individuals 50 years of age and older.

Table 1: Individuals With Solicited Local and Systemic Adverse Reactions Within 5 Days Postvaccination in Pneumococcal Vaccine-Naïve Individuals 18 through 49 Years of Age and 50 Years of Age and Older – Study 1

		18 through 49 Years of Age		50 Years of Age and older	
		CAPVAXIVE n (%)	Prevnar 20 n (%)	CAPVAXIVE n (%)	Prevnar 20 n (%)
Individuals in population*		200	100	1177	1175
Local adverse reactions†	**Severity**				
Pain	Any	143 (71.5)	74 (74.0)	464 (39.4)	607 (51.7)
	Mild	95 (47.5)	49 (49.0)	361 (30.7)	504 (42.9)
	Moderate	46 (23.0)	25 (25.0)	102 (8.7)	102 (8.7)
	Severe	2 (1.0)	0	1 (0.1)	1 (0.1)
Erythema	Any	31 (15.5)	13 (13.0)	64 (5.4) ‡	74 (6.3) ‡
	Mild (≤5.0 cm)	23 (11.5)	10 (10.0)	51 (4.3)	59 (5.0)
	Moderate (>5.0 to ≤10.0 cm)	7 (3.5)	3 (3.0)	10 (0.8)	12 (1.0)
	Severe (>10.0 cm)	1 (0.5)	0	2 (0.2)	2 (0.2)
Swelling	Any	28 (14.0)	14 (14.0)	71 (6.0)	98 (8.3)
	Mild (≤5.0 cm)	20 (10.0)	9 (9.0)	53 (4.5)	79 (6.7)
	Moderate (>5.0 to ≤10.0 cm)	7 (3.5)	5 (5.0)	15 (1.3)	17 (1.4)
	Severe (>10.0 cm)	1 (0.5)	0	3 (0.3)	2 (0.2)
Systemic adverse reactions†	**Severity**				
Fatigue	Any	81 (40.5)	34 (34.0)	237 (20.1)	230 (19.6)
	Mild	50 (25.0)	21 (21.0)	167 (14.2)	153 (13.0)
	Moderate	29 (14.5)	11 (11.0)	70 (5.9)	72 (6.1)
	Severe	2 (1.0)	2 (2.0)	0	5 (0.4)
Headache	Any	59 (29.5)	24 (24.0)	135 (11.5)	152 (12.9)
	Mild	44 (22.0)	17 (17.0)	102 (8.7)	106 (9.0)
	Moderate	14 (7.0)	7 (7.0)	33 (2.8)	45 (3.8)
	Severe	1 (0.5)	0	0	1 (0.1)
Myalgia	Any	33 (16.5)	14 (14.0)	70 (5.9)	79 (6.7)
	Mild	15 (7.5)	9 (9.0)	40 (3.4)	42 (3.6)
	Moderate	15 (7.5)	4 (4.0)	30 (2.5)	36 (3.1)
	Severe	3 (1.5)	1 (1.0)	0	1 (0.1)
Pyrexia §	≥38.0°C (100.4°F)	7 (3.5)	1 (1.0)	15 (1.3)	15 (1.3)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	3 (1.5)	0	7 (0.6)	7 (0.6)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (1.0)	0	6 (0.5)	5 (0.4)
	≥39.0°C (102.2°F)	2 (1.0)	1 (1.0)	2 (0.2)	3 (0.3)

* Every individual is counted a single time for each applicable row and column.

† Injection-site erythema, injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

‡ Includes one individual with an event of missing / unknown intensity.

§ Pyrexia was defined as temperature ≥38.0°C (100.4°F) solicited from Day 1 through Day 5 postvaccination. Percentages are based on the number of individuals with temperature data: 18 through 49 years of age: CAPVAXIVE, n=199, Prevnar 20, n=100. 50 years of age and older: CAPVAXIVE, n=1169, Prevnar 20, n=1170.

Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

In Study 2 (NCT05464420), individuals 18 through 49 years of age who had not previously received a pneumococcal vaccine were enrolled and randomized to receive a single dose of CAPVAXIVE or PNEUMOVAX 23. The percentage of individuals 18 through 49 years of age with solicited adverse reactions that occurred within 5 days postvaccination of CAPVAXIVE or PNEUMOVAX 23 is shown in Table 2.

Table 2: Individuals with Solicited Local and Systemic Adverse Reactions Within 5 Days Postvaccination in Pneumococcal Vaccine-Naïve Individuals 18 through 49 Years of Age – Study 2

		CAPVAXIVE n (%)	PNEUMOVAX 23 n (%)
Individuals in population*		1,616	541
Local adverse reactions†	**Severity**		
Pain	Any	1,184 (73.3)	328 (60.6)
	Mild	759 (47.0)	234 (43.3)
	Moderate	395 (24.4)	86 (15.9)
	Severe	30 (1.9)	8 (1.5)
Erythema	Any	219 (13.6)	41 (7.6)
	Mild (≤5.0 cm)	143 (8.8)	30 (5.5)
	Moderate (>5.0 to ≤10.0 cm)	57 (3.5)	8 (1.5)
	Severe (>10.0 cm)	19 (1.2)	3 (0.6)
Swelling	Any	213 (13.2)	41 (7.6)
	Mild (≤5.0 cm)	148 (9.2)	29 (5.4)
	Moderate (>5.0 to ≤10.0 cm)	55 (3.4)	10 (1.8)
	Severe (>10.0 cm)	10 (0.6)	2 (0.4)
Systemic adverse reactions†	**Severity**		
Fatigue	Any	573 (35.5)	184 (34.0)
	Mild	338 (20.9)	119 (22.0)
	Moderate	201 (12.4)	60 (11.1)
	Severe	34 (2.1)	5 (0.9)
Headache	Any	440 (27.2)	116 (21.4)
	Mild	275 (17.0)	70 (12.9)
	Moderate	151 (9.3)	43 (7.9)
	Severe	14 (0.9)	3 (0.6)
Myalgia	Any	264 (16.3)	47 (8.7)
	Mild	146 (9.0)	33 (6.1)
	Moderate	103 (6.4)	12 (2.2)
	Severe	15 (0.9)	2 (0.4)
Pyrexia‡	≥38.0°C (100.4°F)	48 (3.0)	12 (2.2)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	31 (1.9)	4 (0.7)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	11 (0.7)	2 (0.4)
	≥39.0°C (102.2°F)	6 (0.4)	6 (1.1)

* Every individual is counted a single time for each applicable row and column.

† Injection-site erythema, injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

‡ Pyrexia was defined as temperature ≥38.0°C (100.4°F) solicited from Day 1 through Day 5 postvaccination. Percentages are based on the number of individuals with temperature data: CAPVAXIVE, n=1,606; PNEUMOVAX 23, n=541.
Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

Individuals 50 Years of Age and Older Who Previously Received Pneumococcal Vaccines

Study 3 (NCT05420961) enrolled individuals 50 years of age and older who had previously received a pneumococcal vaccine at least 1 year prior to enrollment. Participants were enrolled into 1 of 3 cohorts based on their pneumococcal vaccination history (cohort 1: PNEUMOVAX 23, cohort 2: Prevnar 13, or cohort 3: PNEUMOVAX 23 followed by or preceded by Prevnar 13, PNEUMOVAX 23 preceded by VAXNEUVANCE, or VAXNEUVANCE alone). Participants in cohort 1 were randomized to receive CAPVAXIVE or VAXNEUVANCE, participants in cohort 2 were randomized to receive CAPVAXIVE or PNEUMOVAX 23, and participants in cohort 3 received CAPVAXIVE. The percentage of individuals with solicited adverse reactions that occurred within 5 days postvaccination of CAPVAXIVE or active comparator is shown in Table 3.

Table 3: Individuals with Solicited Local and Systemic Adverse Reactions Within 5 Days Postvaccination in Individuals 50 Years of Age and Older with Prior Pneumococcal Vaccination – Study 3

		Cohort 1*		Cohort 2†		Cohort 3‡
		CAPVAXIVE n (%)	VAXNEUVANCE n (%)	CAPVAXIVE n (%)	PNEUMOVAX 23 n (%)	CAPVAXIVE n (%)
Individuals in population§		230	117	174	85	105
Local adverse reactions¶	**Severity**					
Pain	Any	82 (35.7)	51 (43.6)	72 (41.4)	40 (47.1)	46 (43.8)
	Mild	65 (28.3)	43 (36.8)	52 (29.9)	30 (35.3)	37 (35.2)
	Moderate	16 (7.0)	8 (6.8)	20 (11.5)	10 (11.8)	9 (8.6)
	Severe	1 (0.4)	0	0	0	0
Erythema	Any	17 (7.4)	9 (7.7)	13 (7.5)	8 (9.4)	8 (7.6)
	Mild (≤5.0 cm)	10 (4.3)	6 (5.1)	5 (2.9)	2 (2.4)	4 (3.8)
	Moderate (>5.0 to ≤10.0 cm)	5 (2.2)	2 (1.7)	6 (3.4)	6 (7.1)	3 (2.9)
	Severe (>10.0 cm)	2 (0.9)	1 (0.9)	2 (1.1)	0	1 (1.0)
Swelling	Any	19 (8.3)	10 (8.5)	8 (4.6)	14 (16.5)	11 (10.5)
	Mild (≤5.0 cm)	15 (6.5)	9 (7.7)	6 (3.4)	7 (8.2)	6 (5.7)
	Moderate (>5.0 to ≤10.0 cm)	4 (1.7)	1 (0.9)	2 (1.1)	7 (8.2)	4 (3.8)
	Severe (>10.0 cm)	0	0	0	0	1 (1.0)
Systemic adverse reactions¶	**Severity**					
Fatigue	Any	33 (14.3)	20 (17.1)	33 (19.0)	11 (12.9)	23 (21.9)
	Mild	25 (10.9)	11 (9.4)	24 (13.8)	6 (7.1)	19 (18.1)
	Moderate	8 (3.5)	9 (7.7)	8 (4.6)	5 (5.9)	4 (3.8)
	Severe	0	0	1 (0.6)	0	0
Headache	Any	16 (7.0)	11 (9.4)	18 (10.3)	10 (11.8)	9 (8.6)
	Mild	10 (4.3)	9 (7.7)	10 (5.7)	7 (8.2)	9 (8.6)
	Moderate	5 (2.2)	2 (1.7)	8 (4.6)	3 (3.5)	0
	Severe	1 (0.4)	0	0	0	0
Myalgia	Any	17 (7.4)	3 (2.6)	17 (9.8)	8 (9.4)	9 (8.6)
	Mild	9 (3.9)	2 (1.7)	7 (4.0)	4 (4.7)	7 (6.7)
	Moderate	8 (3.5)	1 (0.9)	9 (5.2)	4 (4.7)	2 (1.9)
	Severe	0	0	1 (0.6)	0	0
Pyrexia#	≥38.0°C (100.4°F)	4 (1.7)	3 (2.6)	5 (2.9)	1 (1.2)	0
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	2 (0.9)	0	1 (0.6)	0	0
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (0.9)	2 (1.7)	2 (1.1)	1 (1.2)	0
	≥39.0°C (102.2°F)	0	1 (0.9)	2 (1.1)	0	0

* Cohort 1 prior vaccination with PNEUMOVAX 23

† Cohort 2 prior vaccination with Prevnar 13

‡ Cohort 3 prior vaccination with Prevnar 13+PNEUMOVAX 23 (n=45), or VAXNEUVANCE+PNEUMOVAX 23 (n=5), or PNEUMOVAX 23+Prevnar 13 (n=54), or VAXNEUVANCE (n=1) or Prevnar 20 (n=0)

§ Every individual is counted a single time for each applicable row and for each column.

¶ Injection-site erythema, injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

Pyrexia was defined as temperature ≥38.0°C (100.4°F) solicited from Day 1 through Day 5 postvaccination.

Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

Safety with Concomitant Influenza Vaccine Administration

In Study 4 (NCT05526716), individuals 50 years of age and older with or without a history of prior pneumococcal vaccination were enrolled and randomized to receive either CAPVAXIVE and quadrivalent influenza vaccine [Fluzone Quadrivalent, (QIV)] concomitantly followed by placebo 30 days later (concomitant group), or QIV and placebo concomitantly followed by CAPVAXIVE 30 days later (sequential group).

In Study 4, the rates and severity of solicited systemic adverse reactions and solicited local adverse reactions at the CAPVAXIVE injection site were similar when CAPVAXIVE was administered with or without inactivated QIV.

Serious Adverse Events

Across studies 1-4, the proportion of individuals reporting 1 or more SAEs within 1-month postvaccination was 0.3% in individuals vaccinated with CAPVAXIVE (n=14) and 0.3% in individuals vaccinated with an active comparator (n=7). The proportion of individuals reporting 1 or more SAEs within 6 months postvaccination was 1.4% in individuals vaccinated with CAPVAXIVE (n=56) and 2.0% in individuals vaccinated with an active comparator (n=40). There were no notable patterns or imbalances between vaccine groups for SAEs. Two individuals who received CAPVAXIVE had SAEs considered related to vaccination. One individual experienced an acute allergic reaction of bronchospasm (Grade 3, required medical intervention) which occurred within 30 minutes postvaccination; one individual experienced injection-site cellulitis (Grade 4, required hospitalization) on Day 6 postvaccination.

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 CAPVAXIVE in pregnant individuals. Data on CAPVAXIVE administered to pregnant individuals are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered 0.25 mL of a conjugated polysaccharide vaccine formulation on four occasions: twice prior to mating, once during gestation, and once during lactation. This study revealed no adverse effects on fetal or preweaning development. *[see Animal Data below]*.

Data

Animal Data

In a developmental toxicity study, female rats were administered 0.25 mL of a conjugated polysaccharide vaccine formulation containing the same conjugated polysaccharides as in CAPVAXIVE. Animals received 42 mcg polysaccharide per dose (a full human dose of CAPVAXIVE contains 84 mcg polysaccharide/dose) by intramuscular injection on four occasions: 28 and 7 days prior to mating, on gestation day 6, and on lactation day 7. There were no embryofetal deaths or fetal malformations, and no adverse effects on female fertility and preweaning development were observed.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of CAPVAXIVE 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 CAPVAXIVE and any potential adverse effects on the breastfed child from CAPVAXIVE 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 CAPVAXIVE in individuals younger than 18 years of age have not been established.

8.5 Geriatric Use

Across studies 1-4, of the 4,556 individuals who received CAPVAXIVE, 1,487 individuals (32.6%) were 65 years of age and older, and 339 individuals (7.4%) were 75 years of age and older. In Study 1, of the 1,379 individuals who received CAPVAXIVE, 590 individuals (42.8%) were 65 years of age and older, and

126 individuals (9.1%) were 75 years of age and older. No clinically meaningful differences in safety of CAPVAXIVE were observed between these individuals and individuals less than 65 years of age. The opsonophagocytic activity (OPA) responses in individuals 65 years of age and older were generally lower than those observed in individuals less than 65 years of age.

11 DESCRIPTION

CAPVAXIVE (Pneumococcal 21-valent Conjugate Vaccine) is an injection for intramuscular use. CAPVAXIVE is a sterile solution of purified capsular polysaccharides from *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B (de-O-acetylated prior to conjugation), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B individually conjugated to CRM197 carrier protein. CRM197 is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

Each *S. pneumoniae* serotype is grown separately in media containing yeast extract, dextrose, salts, and soy peptone. The pneumococcal bacteria are inactivated after growth by addition of phenol to the culture media. Subsequently, each polysaccharide is purified to produce a powder using a series of chemical and physical methods. Serotype 15B polysaccharide is de-O-acetylated (deOAc 15B). The purified polysaccharides are chemically activated. Recombinant *P. fluorescens* expressing CRM197 is grown in a glycerol-based, chemically-defined salt medium. The CRM197 is then purified by chromatography and ultrafiltration. Each polysaccharide is individually conjugated to CRM197 carrier protein to create 21 individual conjugates. The final vaccine is prepared by blending the 21 conjugated polysaccharides in a final buffer containing histidine, polysorbate 20, and sodium chloride.

Each 0.5 mL dose contains a total of 84 mcg of pneumococcal polysaccharide antigen (4 mcg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B (deOAc 15B), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 mcg of CRM197 carrier protein, 1.55 mg L-histidine, 0.50 mg of polysorbate 20, 4.49 mg sodium chloride, and water for injection.

CAPVAXIVE does not contain any preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive pneumococcal disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. CAPVAXIVE induces OPA against 22 *S. pneumoniae* serotypes. The de-O-acetylated polysaccharide from serotype 15B has a molecular structure similar to the polysaccharide from serotype 15C and induces OPA to serotype 15C. The deOAc15B also induces cross-reactive OPA against serotype 15B. An OPA titer that is predictive of protection against invasive pneumococcal disease or pneumococcal pneumonia has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

CAPVAXIVE has not been evaluated for carcinogenic or mutagenic potential or for impairment of male fertility in animals.

14 CLINICAL STUDIES

For studies 1-4, immunogenicity was assessed by serotype-specific opsonophagocytic activity (OPA) responses at 1-month postvaccination. The primary immunogenicity endpoints included OPA geometric mean titers (GMTs) and the proportion of individuals who achieved ≥4-fold rise in OPA responses from prevaccination to 1-month postvaccination.

14.1 Individuals 18 years of age and older

The effectiveness of CAPVAXIVE in individuals 18 years of age and older for the prevention of invasive disease caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B and for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B,

24F, 31, 33F, and 35B was demonstrated based on comparative immunogenicity to a licensed pneumococcal vaccine (Prevnar 20).

Pneumococcal Vaccine-Naïve Individuals 50 years of age and older

In Study 1, 2,362 pneumococcal vaccine-naïve individuals 50 years of age and older were randomized to receive either CAPVAXIVE or Prevnar 20. *[see Adverse Reactions (6.1).]*

Table 4 summarizes the 21 serotype-specific OPA geometric mean antibody titers (GMTs) at 30 days postvaccination. The study demonstrated that CAPVAXIVE is noninferior to Prevnar 20 for the 10 shared serotype polysaccharides and induces statistically significantly greater OPA GMTs compared to Prevnar 20 for 10 of 11 serotype polysaccharides unique to CAPVAXIVE. Serotype 15C did not meet the criterion for statistical significance.

Table 5 summarizes the proportion of individuals who achieved a ≥4-fold rise from prevaccination to 1-month postvaccination for OPA responses. For 10 of 11 serotype polysaccharides unique to CAPVAXIVE, CAPVAXIVE induced statistically significantly greater OPA responses compared to Prevnar 20. Serotype 15C did not meet the criterion for statistical significance.

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

Pneumococcal Serotype	CAPVAXIVE (N = 1179)		Prevnar 20 (N = 1177)		GMT Ratio* (CAPVAXIVE/Prevnar 20) (95% CI)*
	n	GMT*	n	GMT*	
10 Common Serotypes†					
3	1154	274.0	1161	176.7	1.55 (1.40, 1.72)
6A	1148	2302.0	1153	2972.5	0.77 (0.68, 0.88)
7F	1152	3637.4	1158	3429.9	1.06 (0.95, 1.18)
8	1155	2501.3	1158	1811.1	1.38 (1.25, 1.53)
10A	1161	3893.4	1159	4678.0	0.83 (0.75, 0.93)
11A	1145	3232.6	1150	2092.8	1.54 (1.39, 1.72)
12F	1160	2641.2	1161	2499.6	1.06 (0.92, 1.21)
19A	1159	2136.1	1162	2817.8	0.76 (0.69, 0.84)
22F	1147	3874.5	1154	4770.1	0.81 (0.72, 0.92)
33F	1154	13558.9	1157	11742.1	1.15 (1.01, 1.32)
11 Serotypes Unique to CAPVAXIVE ‡					
9N	1147	7470.7	1150	1640.4	4.55 (4.12, 5.04)
15A	1107	5237.2	1102	1589.0	3.30 (2.91, 3.74)
15C	1153	4216.2	1158	2072.3	2.03 (1.77, 2.34)
16F	1151	4868.2	1153	846.3	5.75 (5.16, 6.41)
17F	1148	7764.9	1156	460.4	16.86 (14.90, 19.09)
20A	1161	6099.2	1155	631.1	9.66 (8.66, 10.79)
23A	1132	3737.2	1104	461.5	8.10 (6.86, 9.55)
23B	1160	1082.5	1160	107.3	10.09 (8.48, 12.00)
24F	1153	2728.6	1130	70.5	38.71 (33.87, 44.25)
31	1153	3132.5	1154	144.4	21.69 (18.68, 25.18)
35B	1153	8527.8	1159	1383.0	6.17 (5.59, 6.80)

* GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

† Non-inferiority for the serotypes common to CAPVAXIVE and Prevnar 20 was based on the lower bound of the 2-sided 95% CI for the estimated GMT ratio (CAPVAXIVE/Prevnar 20) being >0.5.

‡ Statistically significantly greater OPA responses for the serotypes unique to CAPVAXIVE compared to Prevnar 20 were based on the lower bound of the 2-sided 95% CI for the estimated GMT ratio (CAPVAXIVE/Prevnar 20) being >2.0.

N=Number of individuals randomized and vaccinated; n=Number of individuals contributing to the analysis.

Table 5: Pneumococcal Vaccine-Naïve Individuals 50 years of Age and Older With a ≥4-Fold Rise in OPA Responses for Serotypes Unique to CAPVAXIVE (Study 1)

Pneumococcal Serotype	CAPVAXIVE (N=1179)	Prevnar 20 (N=1177)	Percentage Point Difference (CAPVAXIVE – Prevnar 20)
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)*,†
9N	64.7 (595/920)	19.9 (195/978)	44.7 (40.7, 48.6)
15A	66.7 (462/693)	35.8 (253/706)	30.9 (25.8, 35.8)
15C	83.4 (794/952)	74.2 (695/937)	9.2 (5.6, 12.9)
16F	71.9 (654/910)	20.8 (200/961)	51.1 (47.1, 54.9)
17F	75.8 (653/862)	9.5 (90/952)	66.3 (62.8, 69.6)
20A	67.3 (675/1003)	9.6 (97/1011)	57.7 (54.2, 61.1)
23A	78.9 (598/758)	36.8 (270/734)	42.2 (37.6, 46.6)
23B	85.5 (873/1021)	49.6 (506/1021)	35.9 (32.1, 39.6)
24F	80.5 (745/925)	6.3 (55/872)	74.2 (71.1, 77.1)
31	76.5 (698/912)	17.9 (171/954)	58.6 (54.8, 62.1)
35B	60.0 (550/917)	6.8 (67/988)	53.2 (49.6, 56.6)

* Estimated difference and CI were based on the stratified Miettinen & Nurminen method.

† Statistically significantly greater OPA responses were based on the lower bound of the 2-sided 95% CI of the differences (CAPVAXIVE – Prevnar 20) between the percentages of individuals with a ≥4-fold rise from prevaccination to 1-month postvaccination being >10 percentage points.

N=Number of individuals randomized and vaccinated; m=Number of individuals with the indicated response; n=Number of individuals contributing to the analysis

In Study 1, 64.7% of individuals 50 years of age and older, who received CAPVAXIVE, had ≥4-fold rise in cross-reactive OPA titers for serotype 15B, which met the prespecified success criterion (lower bound of the 2-sided 95% CI of the proportion of individuals with a ≥4-fold rise in OPA responses is >50%). In a descriptive analysis, the *S. pneumoniae* serotype 15B OPA GMT was 4,400.6 following administration of CAPVAXIVE, and 4,640.0 following administration of Prevnar 20, with a GMT ratio of 0.95 (95% CI: 0.84, 1.07).

Pneumococcal Vaccine-Naïve Individuals 18 through 49 Years of Age

In Study 1, pneumococcal vaccine-naïve individuals 18 through 49 years of age were randomized in a 2:1 ratio to receive CAPVAXIVE or Prevnar 20. *[See Adverse Reactions (6.1).]*

Effectiveness of CAPVAXIVE in individuals 18 through 49 years of age was assessed by a comparison of the OPA responses induced by CAPVAXIVE in this age group to the OPA responses of individuals 50 through 64 years of age. The OPA responses of individuals 18 through 49 years of age to each of 22 *S. pneumoniae* serotypes met the criteria for immunobridging as the lower bound of the 2-sided 95% CI for the GMT ratio for each serotype was >0.5 (see Table 6). The *S. pneumoniae* serotype 15B cross-reactive OPA GMT was 10,976.7 following administration of CAPVAXIVE in individuals 18 through 49 years of age and 5,438.9 following administration of CAPVAXIVE in individuals 50 through 64 years of age, with a GMT ratio of 2.02 (95% CI: 1.57, 2.60).

Table 6: Comparison of Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Individuals 18 through 49 Years of Age to 50 through 64 Years of Age Who Received CAPVAXIVE (Study 1)

Pneumococcal Serotype	18 through 49 years (N = 200)		50 through 64 years (N = 589)		GMT Ratio*,† (18 through 49 years / 50 through 64 years) (95% CI)*
	n	GMT*	n	GMT	
3	194	308.6	572	282.7	1.09 (0.90, 1.33)
6A	196	5289.6	569	2572.9	2.06 (1.61, 2.62)
7F	198	6447.2	571	4278.8	1.51 (1.23, 1.84)
8	197	4516.0	571	3004.7	1.50 (1.26, 1.79)
9N	197	17283.2	570	8791.4	1.97 (1.59, 2.43)
10A	197	6808.1	575	4382.6	1.55 (1.26, 1.92)
11A	196	5871.6	564	3785.8	1.55 (1.26, 1.91)
12F	196	6150.4	574	3561.2	1.73 (1.37, 2.17)
15A	184	11319.2	550	5901.2	1.92 (1.55, 2.37)
15C	195	10194.0	570	5708.0	1.79 (1.36, 2.35)
16F	193	8877.0	571	5720.0	1.55 (1.26, 1.91)
17F	194	16070.6	568	10068.0	1.60 (1.26, 2.02)
19A	198	2773.2	574	2374.6	1.17 (0.97, 1.40)
20A	197	13150.0	575	7562.7	1.74 (1.39, 2.18)
22F	198	9299.6	568	4683.6	1.99 (1.58, 2.49)
23A	192	8848.7	561	4739.5	1.87 (1.43, 2.44)
23B	198	2140.1	575	1420.9	1.51 (1.11, 2.04)
24F	197	4137.6	570	3047.2	1.36 (1.10, 1.67)
31	195	8005.6	570	3820.7	2.10 (1.63, 2.69)
33F	197	34805.5	570	17607.4	1.98 (1.52, 2.57)
35B	198	13933.4	573	9053.9	1.54 (1.26, 1.87)

* GMTs, GMT ratio, and 95% CI were estimated from a Longitudinal Data Analysis model.
† Immunobridging was based on the lower bound of the 2-sided 95% CI for the estimated GMT ratio (18 through 49 years / 50 through 64 years) being >0.5.
N=Number of individuals randomized and vaccinated; n=Number of individuals contributing to the analysis.

Individuals 50 years of age and older with Prior Pneumococcal Vaccination

Study 3, a descriptive Phase 3 study, enrolled individuals 50 years of age and older who were previously vaccinated with other pneumococcal vaccines at least 1 year prior to study entry. Participants were enrolled into 1 of 3 cohorts based on their pneumococcal vaccination history (cohort 1: PNEUMOVAX 23, cohort 2: Prevnar 13, or cohort 3: PNEUMOVAX 23 followed by or preceded by Prevnar 13, PNEUMOVAX 23 preceded by VAXNEUVANCE, or VAXNEUVANCE alone).

Participants in cohort 1 were randomized to receive CAPVAXIVE (n=231) or VAXNEUVANCE (n=119), participants in cohort 2 were randomized to receive CAPVAXIVE (n=176) or PNEUMOVAX 23 (n=85), and participants in cohort 3 were allocated to receive CAPVAXIVE (n=106).

In each of the 3 cohorts, serotype-specific OPA GMTs and the proportion of individuals with ≥4-fold rise in OPA responses from baseline to 1-month postvaccination were assessed. In Cohort 1, CAPVAXIVE elicited OPA responses that were comparable to VAXNEUVANCE for the 6 common serotypes, and higher for the 15 unique serotypes and serotype 15B. In Cohort 2, CAPVAXIVE elicited OPA responses comparable to PNEUMOVAX 23 for the 12 common serotypes and serotype 15B, and higher for the 9 unique serotypes. OPA responses to CAPVAXIVE were similar across the 3 cohorts of participants who previously received one or more pneumococcal vaccines.

14.2 Concomitant Vaccination

In a double-blind study (Study 4), 1,080 individuals 50 years of age and older, with or without a history of prior pneumococcal vaccination, were randomized in a 1:1 ratio. One vaccination group received

CAPVAXIVE and QIV concomitantly, followed by placebo 30 days later (concomitant group). A second vaccination group received QIV and placebo concomitantly, followed by CAPVAXIVE 30 days later (sequential group). Antibody responses were assessed 1-month postvaccination.

The OPA responses to CAPVAXIVE administered concomitantly with QIV were non-inferior to the OPA responses to CAPVAXIVE administered sequentially after QIV for 20 of 21 serotypes [lower bound of the 2-sided 95% CI of the GMT ratio (concomitant group/sequential group) was >0.5]; the non-inferiority was not met for serotype 23B [lower bound of the 2-sided 95% CI of the GMT ratio (concomitant group/sequential group) was 0.44]. The OPA response to serotype 15B was not assessed for non-inferiority. In a descriptive analysis, the OPA GMT in the concomitant group was 3,438.7 and in the sequential group was 4,440.5, with a GMT ratio of 0.77 (95% CI: 0.64, 0.94). The influenza strain-specific hemagglutination inhibition (HAI) responses to QIV administered concomitantly with CAPVAXIVE were non-inferior to the HAI responses to QIV administered alone for 3 of 4 influenza strains [lower bound of the 2-sided 95% CIs for HAI GMT ratios (concomitant group/sequential group) was >0.67 (non-inferiority margin); the lower bound was 0.67 for the A/H3N2 influenza strain].

16 HOW SUPPLIED/STORAGE AND HANDLING

CAPVAXIVE is supplied as follows:
NDC 0006-4347-01: Carton of one single-dose prefilled Luer Lock syringe with tip cap, containing 1 dose of 0.5 mL (NDC 0006-4347-99).
NDC 0006-4347-02: Carton of ten single-dose prefilled Luer Lock syringes with tip caps, each syringe containing 1 dose of 0.5 mL (NDC 0006-4347-99).

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 are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

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

- Inform the patient of the benefits and risks associated with vaccination with CAPVAXIVE.
- Inform the patient that vaccination with CAPVAXIVE may not protect all vaccine recipients.
- Instruct the patient to report any adverse reactions to their healthcare provider or 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 LLC
Rahway, NJ 07065, USA

U.S. license number 0002

For patent information: www.msd.com/research/patent

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