Standing Orders for Administering Pneumococcal Vaccine (PCV13 and PPSV23) to Adults 65 Years of Age or Older

**Purpose:** To potentially reduce pneumococcal disease by vaccinating adults aged 65 or older who meet the criteria established by the Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP).

**Policy:** Under these standing orders, eligible nurses and other healthcare professionals (e.g., pharmacists), where allowed by state law, may vaccinate adults who meet any of the criteria below.

**Criteria:**
1. Identify adults in need of pneumococcal vaccination based on the following criteria:
   a. Adults aged 65 years or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 (13-valent pneumococcal conjugate vaccine) first, followed by a dose of PPSV23 (23-valent pneumococcal polysaccharide vaccine)
   b. Adults previously vaccinated with PPSV23 at age 65 years or older should receive a dose of PCV13
   c. Adults previously vaccinated with PPSV23 before age 65 years who are now aged 65 years or older should receive a dose of PCV13, followed by a dose of PPSV23
   d. Adults aged 65 years or older who have already received a dose of PCV13, but not a dose of PPSV23 at or after the age of 65, should receive a dose of PPSV23

2. Screen all patients for contraindications and precautions to pneumococcal vaccine:
   a. Contraindication: A history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of the pneumococcal vaccine (PCV13 or PPSV23) being administered, to any vaccine component, or to any diphtheria toxoid-containing vaccine (PCV13). For information on vaccine components, refer to the manufacturer’s package insert
   b. Precaution: Moderate or severe acute illness with or without fever

3. Document each patient’s vaccine administration information and follow up in the following places:
   a. For PCV13, administer intramuscularly into the deltoid muscle
   b. For PPSV23, administer intramuscularly or subcutaneously into the deltoid muscle or lateral mid-thigh

4. Prior receipt of PPSV23 within 1 year results in diminished immune responses to Prevnar 13® compared to PPSV23-naive individuals.

5. Ensure that the standing orders are approved by either an institution, physician, or another authorized practitioner who are due or overdue

6. Participate in local/regional/state immunization registry (IIS)

7. Prior to patient visits, review the immunization record for each patient and flag charts of those due for vaccination.

8. Train staff to administer multiple vaccinations to patients who are due for multiple vaccinations

9. Ensure vaccines are consistently available (by putting a system in place to order vaccines in a timely manner)

10. Designate an immunization “champion” in your practice to keep staff up-to-date on current recommendations

11. Maintain a comprehensive immunization record in a visible location in each patient’s chart (e.g., the front administering clinic)

12. Participate in local/regional/state immunization registry (IIS)

Implementing standing orders has been shown to increase vaccination rates by 17%.

Empower your staff and increase vaccination rates by establishing standing orders in your practice.

The enclosed Standing Orders provide direction on:

- The CDC’s ACIP recommendations for pneumococcal vaccination of adults aged 65 years and older
- Administration considerations for pneumococcal vaccination
- Criteria for identifying appropriate patients for pneumococcal vaccination
- Documenting vaccine administration
The CDC’s Advisory Committee on Immunization Practices (ACIP) pneumococcal recommendations for immunocompetent adults aged 65 and older. As stated by the CDC’s ACIP:

- For adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or coelhilar implants, the recommended interval between Prevnar 13® and Pneumovax® 23 is ≥8 weeks.
- The 2 vaccines (Prevnar 13® and Pneumovax® 23) should not be coadministered. If a dose of Pneumovax® 23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.

Prior receipt of Pneumovax® 23 within 1 year results in diminished immune responses to Prevnar 13® as compared to Pneumovax® 23-naïve individuals.

Limitations of Use and Effectiveness

- In adults, antibody responses to Prevnar 13® were diminished when given with inactivated influenza vaccine, trivalent (IIV3) influenza vaccines, and other conjugate vaccines.
- Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody responses.
- Inadvertently given earlier than the recommended interval, the dose need not be repeated.

4 simple suggestions to help improve vaccination rates in your practice

The following tips can be used to improve the integration of standing orders into your practice, thereby helping to increase efficiency and vaccination rates.

1. **Authorize the standing orders**
   - Ensure that the standing orders are approved by either an institution, physician, or another authorized practitioner.

2. **Keep staff up-to-date with current recommendations**
   - Post the current, official ACIP U.S. immunization schedule for adults or variations thereof (for example, the official schedule of a medical society or of a state health department).
   - Designate an immunization “champion” in your practice to keep staff up-to-date on current recommendations and to ensure standing orders are in place.
   - Familiarize staff with special vaccination recommendations for certain patient populations.

3. **Keep patient records up-to-date**
   - Maintain a comprehensive immunization record in a visible location in each patient’s chart (e.g., the front of the chart if paper files are kept), or print the patient’s immunization record from the immunization registry or Immunization Information System (IIS).
   - Participate in local/regional/state immunization registry (IIS).

4. **Be proactive about avoiding “missed opportunities”**
   - Prior to patient visits, review the immunization record for each patient and flag charts of those who are due or overdue.
   - Train staff to administer multiple vaccinations to patients who are due for multiple vaccinations.
   - Ensure vaccines are consistently available (by putting a system in place to order vaccines in a timely manner).

References:

Prevnar® 13 is a registered trademark of Wyeth LLC.

Manufactured by Wyeth Pharmaceuticals Inc. Marketed by Pfizer Inc.
Standing Orders for Administering Pneumococcal Vaccine (PCV13 and PPSV23) to Adults 65 Years of Age or Older

**Purpose:** To potentially reduce pneumococcal disease by vaccinating adults aged 65 or older who meet the criteria established by the Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP).

**Policy:** Under these standing orders, eligible nurses and other healthcare professionals (eg, pharmacists), where allowed by state law, may vaccinate adults who meet any of the criteria below.

### Criteria

1. Identify adults in need of pneumococcal vaccination based on the following criteria:
   a. Adults aged 65 years or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 (13-valent pneumococcal conjugate vaccine) first, followed by a dose of PPSV23 (23-valent pneumococcal polysaccharide vaccine).
   b. Adults previously vaccinated with PPSV23 at age 65 years or older should receive a dose of PCV13.
   c. Adults previously vaccinated with PPSV23 before age 65 years who are now aged 65 years or older should receive a dose of PCV13, followed by a dose of PPSV23.
   d. Adults aged 65 years or older who have already received a dose of PCV13, but not a dose of PPSV23 at or after the age of 65, should receive a dose of PPSV23.

### Administration considerations

For adults aged 65 years or older in need of both PCV13 and PPSV23, administer PCV13 first, followed by PPSV23 at least 1 year later. If previously vaccinated with PPSV23, give PCV13 at least 1 year after the most recent dose of PPSV23. If previously vaccinated with PCV13, no additional dose is necessary. For those patients aged 65 years or older for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given at least 1 year after PCV13 and at least 5 years after the most recent dose of PPSV23. The two vaccines should not be coadministered. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated. For adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants, the recommended interval between PCV13 followed by PPSV23 is ≥8 weeks. Prior receipt of PPSV23 within 1 year results in diminished immune responses to Prevnar 13® compared to PPSV23-naïve individuals.

2. Screen all patients for contraindications and precautions to pneumococcal vaccine.
   a. **Contraindication:** A history of a severe allergic reaction (eg, anaphylaxis) after a previous dose of the pneumococcal vaccine (PCV13 or PPSV23) being administered, to any vaccine component, or to any diphtheria toxoid–containing vaccine (PCV13). For information on vaccine components, refer to the manufacturer’s package insert.
   b. **Precaution:** Moderate or severe acute illness with or without fever.

3. Provide all patients with a copy of the most current federal Vaccine Information Statement (VIS) for the vaccine administered. Provide non–English-speaking patients with a copy of the VIS in their native language, if available and preferred; these can be found at www.immunize.org/vis.

4. Administer PCV13 or PPSV23 according to the following:
   a. For PCV13, administer intramuscularly into the deltoid muscle.
   b. For PPSV23, administer intramuscularly or subcutaneously into the deltoid muscle or lateral mid-thigh.
   c. The two vaccines should not be coadministered.

5. Document each patient’s vaccine administration information and follow up in the following places:
   a. **Medical chart:** Record the date the vaccine was administered, the manufacturer and lot number, the vaccination site and route, and the name and title of the person who administered the vaccine. If a vaccine was not given, record the reason(s) for nonreceipt of the vaccine (eg, medical contraindication or patient refusal).
   b. **Personal immunization record card:** Record the date of vaccination and the name and location of the administering clinic.

6. Be prepared for management of a medical emergency related to the administration of vaccine by having a written emergency medical protocol available, as well as equipment and medications.

7. Report all adverse reactions to PCV13 and PPSV23 to the federal Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or by calling 1-800-822-7967. VAERS report forms are available at www.vaers.hhs.gov.

This policy and procedure shall remain in effect for all patients of the name of practice or clinic until rescinded or until date.

Signature: ____________________________ Effective date: ____________________________

Adapted with permission from the Immunization Action Coalition.

Please see Important Safety Information on next page and accompanying full Prescribing Information for Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]).
The CDC's Advisory Committee on Immunization Practices (ACIP) pneumococcal recommendations for immunocompetent adults aged 65 and older¹,²

The information below represents the ACIP recommendations to complete the pneumococcal vaccination sequence

Not previously vaccinated or unknown vaccination history

Administer Prevnar 13 first

At least 1 year later

Administer dose of Pneumovax 23

Previously vaccinated with Pneumovax 23

At or after age 65

Administer Prevnar 13 (at least 1 year after the most recent dose of Pneumovax 23)

Before age 65 who are now 65 or older

Administer Prevnar 13 (at least 1 year after the most recent dose of Pneumovax 23)

At least 1 year later

Administer subsequent dose of Pneumovax 23 (no sooner than 5 years after the most recent dose of Pneumovax 23)

*An attempt should be made to locate missing records. However, if not possible within a reasonable time frame, do not postpone vaccination.⁶

As stated by the CDC's ACIP:

- For adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants, the recommended interval between Prevnar 13 followed by Pneumovax 23 is ≥8 weeks¹
- The 2 vaccines (Prevnar 13 and Pneumovax 23) should not be coadministered. If a dose of Pneumovax 23 is inadvertently given earlier than the recommended interval, the dose need not be repeated¹

Prior receipt of Pneumovax 23 within 1 year results in diminished immune responses to Prevnar 13 compared to Pneumovax 23-naive individuals⁴

In accordance with the CDC’s ACIP recommendations for adults aged 65 and older, administer both Prevnar 13 and Pneumovax 23 to help protect against pneumococcal pneumonia and IPD¹

INDICATION

- In adults 18 years of age and older, Prevnar 13 is indicated for active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Limitations of Use and Effectiveness

- Prevnar 13 will only help protect against S pneumoniae serotypes in the vaccine

IMPORTANT SAFETY INFORMATION

- Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine is a contraindication
- Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response
- In adults, antibody responses to Prevnar 13 were diminished when given with inactivated influenza vaccine, trivalent (IIV3)
- In adults, the most commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle pain, joint pain, decreased appetite, vomiting, fever, chills, and rash

Please see accompanying full Prescribing Information for Prevnar 13.


Pneumovax is a registered trademark of Merck & Co., Inc.
Prevnar 13 is a registered trademark of Wyeth LLC.

Manufactured by Wyeth Pharmaceuticals Inc.

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The Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP) specifically recommends standing orders for pneumococcal vaccination.

Standing orders can help your practice by:
- Enabling assessment and vaccination without the need for direct order at the time of the patient interaction
- Establishing a process in your office for the administration of one or more specific vaccines to patients

Implementing standing orders has been shown to increase vaccination rates by 17%.

Empower your staff and increase vaccination rates by establishing standing orders in your practice.

The enclosed Standing Orders provide direction on:
- The CDC’s ACIP recommendations for pneumococcal vaccination of adults aged 65 years and older
- Criteria for identifying appropriate patients for pneumococcal vaccination
- Administration considerations for pneumococcal vaccination
- Documenting vaccine administration
4 simple suggestions to help improve vaccination rates in your practice

The following tips can be used to improve the integration of standing orders into your practice, thereby helping to increase efficiency and vaccination rates:¹,³

1. **Authorize the standing orders**
   - Ensure that the standing orders are approved by either an institution, physician, or another authorized practitioner

2. **Keep staff up-to-date with current recommendations**
   - Post the current, official ACIP U.S. immunization schedule for adults or variations thereof (for example, the official schedule of a medical society or of a state health department)
   - Designate an immunization “champion” in your practice to keep staff up-to-date on current recommendations and to ensure standing orders are in place
   - Familiarize staff with special vaccination recommendations for certain patient populations

3. **Keep patient records up-to-date**
   - Maintain a comprehensive immunization record in a visible location in each patient's chart (eg, the front of the chart if paper files are kept), or print the patient’s immunization record from the immunization registry or Immunization Information System (IIS)
   - Participate in local/regional/state immunization registry (IIS)

4. **Be proactive about avoiding “missed opportunities”**
   - Prior to patient visits, review the immunization record for each patient and flag charts of those who are due or overdue
   - Train staff to administer multiple vaccinations to patients who are due for multiple vaccinations
   - Ensure vaccines are consistently available (by putting a system in place to order vaccines in a timely manner)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PREVNAR 13 safely and effectively. See full prescribing information for PREVNAR 13.

PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
Suspension for intramuscular injection

Initial US Approval: 2010

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**INDICATIONS AND USAGE**

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 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, and 23F. (1.1)
- Active immunization for the prevention of otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)
- In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age (prior to the 18th birthday), Prevnar 13 is indicated for:
  - Active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. (1.2)
- In adults 18 years of age and older, Prevnar 13 is indicated for:
  - Active immunization for the prevention of pneumonia and invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, and 19A. (1.1)

Limitations of Prevnar 13 Use and Effectiveness

- Prevnar 13 does not protect against disease caused by S. pneumoniae serotypes that are not in the vaccine. (1.4)

**DOSAGE AND ADMINISTRATION**

**Children 6 weeks through 5 years of age:**
- The four-dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6, and 12-15 months of age. (2.3)
- Children 6 through 17 years of age: a single dose. (2.6)
- Adults 18 years and older: a single dose. (2.7)

**0.5 mL suspension for intramuscular injection, supplied in a single-dose prefilled syringe.** (3)

**Recent Major Changes**

- In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 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, and 23F. (1.1)
  - Active immunization for the prevention of otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)
- In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age (prior to the 18th birthday), Prevnar 13 is indicated for:
  - Active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. (1.2)
- In adults 18 years of age and older, Prevnar 13 is indicated for:
  - Active immunization for the prevention of pneumonia and invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, and 19A. (1.1)

**INDICATIONS AND USAGE**

- In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 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, and 23F. (1.1)
  - Active immunization for the prevention of otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)
- In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age (prior to the 18th birthday), Prevnar 13 is indicated for:
  - Active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. (1.2)
- In adults 18 years of age and older, Prevnar 13 is indicated for:
  - Active immunization for the prevention of pneumonia and invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, and 19A. (1.1)

Limitations of Prevnar 13 Use and Effectiveness

- Prevnar 13 does not protect against disease caused by S. pneumoniae serotypes that are not in the vaccine. (1.4)

**DOSAGE AND ADMINISTRATION**

**Children 6 weeks through 5 years of age:**
- The four-dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6, and 12-15 months of age. (2.3)
- Children 6 through 17 years of age: a single dose. (2.6)
- Adults 18 years and older: a single dose. (2.7)

**0.5 mL suspension for intramuscular injection, supplied in a single-dose prefilled syringe.** (3)

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**REFERENCES**

- **14 CLINICAL STUDIES**
  - 14.1 Efficacy Data
  - 14.2 Prevnar 13 Clinical Trials in Children 6 Weeks Through 17 Years of Age
  - 14.3 Prevnar 13 Immunogenicity Clinical Trials in Adults
  - 14.4 Concomitant Vaccine Administration

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**7 DRUG INTERACTIONS**

- 7.1 Concomitant Immunizations
- 7.2 Immunosuppressive Therapies
- 7.3 Antipyretics
- 7.4 Prior Vaccination with PPSV23

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**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 High Risk Populations

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**11 DESCRIPTION**

- **12 CLINICAL PHARMACOLOGY**
  - 12.1 Mechanism of Action

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**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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**17 PATIENT COUNSELING INFORMATION**

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*Sectons or subsections omitted from the full prescribing information are not listed.*
2.7 Vaccination Schedule for Adults 18 Years of Age and Older
Prevnar 13 is administered as a single dose.

3 DOSAGE FORMS AND STRENGTHS
Prevnar 13 is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

4 CONTRAINDICATIONS
[Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine [see Description (11)].

5 WARNINGS AND PRECAUTIONS
5.1 Management of Allergic Reactions
Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 13.

5.2 Altered Immunocompetence
Individuals with altered immunocompetence, including those at higher risk for invasive pneumococcal disease (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome), may have reduced antibody responses to immunization with Prevnar 13 [see Use in Specific Populations (8.6)].

5.3 Apnea in Premature Infants
Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS
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.

6.1 Clinical Trials Experience With Prevnar 13 in Children 6 Weeks Through 17 Years of Age
The safety of Prevnar 13 was evaluated in 13 clinical trials in which 4,729 infants (6 weeks through 11 months of age) and toddlers (12 months through 15 months of age) received at least one dose of Prevnar 13 and 2,760 infants and toddlers received at least one dose of Prevnar active control. Safety data for the first three doses are available for all 13 infant studies; dose 4 data are available for 10 studies; and data for the 6-month follow-up are available for 4 studies. The vaccination schedule and concomitant vaccinations used in these infant trials were consistent with country-specific recommendations and local clinical practice. There were no statistically significant differences in the distribution and frequency of adverse reactions between the vaccine groups. By race, 84.0% of subjects were White, 6.0% were Black or African-American, 5.8% were Asian and 3.8% were of ‘other race’ (most of these being biracial). Overall, 52.3% of subjects were male infants.

Three studies in the US (Studies 1, 2 and 3) evaluated the safety of Prevnar 13 when administered concomitantly with routine US pediatric vaccinations at 2, 4, 6, and 12-15 months of age. Solicited local and systemic adverse reactions were recorded daily by parents/guardians using an electronic diary and solicited reactions occurring 4-6 days following each vaccination. For unsolicited adverse events, study subjects were monitored from administration of the first dose until one month after the infant series, and for one month after the administration of the toddler dose. Information regarding unsolicited and serious adverse events, newly diagnosed chronic medical conditions, and hospitalizations since the last visit were collected during the clinic visit for the fourth-study dose and during a scripted telephone interview 6 months after the fourth-study dose. Serious adverse events were also collected throughout the study period. Overall, the safety data show a similar pattern of adverse events for Prevnar 13 and Prevnar subjects reporting serious adverse events. Among US study subjects, a similar proportion of Prevnar 13 and Prevnar recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

Serious Adverse Events in All Infant and Toddler Clinical Studies
Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting period may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13 recipients and 7.2% among Prevnar recipients. Serious adverse events observed during different study periods for Prevnar 13 and Prevnar respectively were: 1) 3.7% and 3.5% from dose 1 to the bleed approximately 1 month after the infant series; 2) 3.6% and 2.7% from the bleed after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the bleed approximately 1 month after the toddler dose and 4) 2.5% and 2.8% during the 6 month follow-up period after the last dose. The most commonly reported serious adverse events were in the ‘infections and infestations’ and ‘systemic disorders and administration site conditions’ categories including bronchitis (0.9%, 1.1%), gastroenteritis, (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Prevnar 13 and Prevnar respectively.

There were 3 (0.063%) deaths among Prevnar 13 recipients, and 1 (0.036%) death in Prevnar recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age specific background rates of SIDS from the year 2000. Among 6,339 subjects who received at least 1 dose of Prevnar 13 in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4,204 subjects who received at least 1 dose of Prevnar in clinical trials conducted globally, there were 4 reported events associated with a minor to moderate respiratory distress (0.09%). Most subjects were White (77.3%), 14.2% were Black or African-American, and 1.7% were Asian; 79.1% of subjects were non-Hispanic and non-Latino and 14.6% were Hispanic or Latino. Overall, 53.6% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13 or Prevnar administered to US infants and toddlers are shown in Tables 3 and 4.
The following were determined to be adverse drug reactions based on experience with Prevnar 13. After dose 3, fever was reported in 8.0-9.6% on day 1 and 9.1-10.5% on day 2. After dose 2, fever was reported in 12.3-13.1% on day 1 and 12.5-12.8% on day 2. After dose 1, fever was reported in 11.0-12.7% on day 1 and 6.4-6.8% on day 2. After dose 2, fever was reported in 12.3-13.1% on day 1 and 12.5-12.8% on day 2. After dose 3, fever was reported in 8.0-9.6% on day 1 and 9.1-10.5% on day 2. After dose 1, fever was reported in 11.0-12.7% on day 1 and 6.4-6.8% on day 2.

### Table 3: Percentage of US Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Agea,b

<table>
<thead>
<tr>
<th>Grade of Reaction</th>
<th>Dose 1 (N=1375)</th>
<th>Dose 2 (N=1360)</th>
<th>Dose 3 (N=1084)</th>
<th>Dose 4 (N=497)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Redness</td>
<td></td>
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</tr>
<tr>
<td>Any</td>
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<td>22.1</td>
<td>22.1</td>
</tr>
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<tr>
<td>Moderate</td>
<td>22.1</td>
<td>22.1</td>
<td>22.1</td>
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</tr>
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<td>Swelling</td>
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<td>Moderate</td>
<td>4.9</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Tenderness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>62.5</td>
<td>64.5</td>
<td>64.5</td>
<td>64.5</td>
</tr>
<tr>
<td>Interferes with limb movement</td>
<td>10.4</td>
<td>9.6</td>
<td>10.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

* Data are from three primary US safety studies (the US Phase 2 infant study [National Clinical Trial (NCT) number NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

### Table 4: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Agea,b,c

<table>
<thead>
<tr>
<th>Systemic Reaction</th>
<th>Dose 1 (N=1360)</th>
<th>Dose 2 (N=1360)</th>
<th>Dose 3 (N=1084)</th>
<th>Dose 4 (N=497)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>24.3</td>
<td>22.1</td>
<td>22.1</td>
<td>22.1</td>
</tr>
<tr>
<td>Mild</td>
<td>23.1</td>
<td>23.1</td>
<td>22.1</td>
<td>22.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>22.1</td>
<td>22.1</td>
<td>22.1</td>
<td>22.1</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>48.3</td>
<td>43.6</td>
<td>43.6</td>
<td>43.6</td>
</tr>
<tr>
<td>Irritability</td>
<td>85.6</td>
<td>83.6</td>
<td>84.8</td>
<td>84.8</td>
</tr>
<tr>
<td>Increased sleep</td>
<td>71.5</td>
<td>71.5</td>
<td>68.6</td>
<td>63.4</td>
</tr>
<tr>
<td>Decreased sleep</td>
<td>42.5</td>
<td>40.6</td>
<td>45.6</td>
<td>43.7</td>
</tr>
</tbody>
</table>

* Data are from three primary US safety studies (the US Phase 2 infant study [NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

### Table 5: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Local Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccinationa

<table>
<thead>
<tr>
<th>Grade of Reaction</th>
<th>Dose 1 (N=86)</th>
<th>Dose 2 (N=86)</th>
<th>Dose 3 (N=78)</th>
<th>Dose 4 (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Redness</td>
<td>48.8</td>
<td>46.0</td>
<td>37.8</td>
<td>50.0</td>
</tr>
<tr>
<td>Mild</td>
<td>41.9</td>
<td>40.2</td>
<td>31.3</td>
<td>44.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>16.3</td>
<td>9.3</td>
<td>12.5</td>
<td>25.3</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Swelling</td>
<td>36.0</td>
<td>32.2</td>
<td>25.0</td>
<td>44.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>32.6</td>
<td>28.7</td>
<td>20.5</td>
<td>36.7</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Tenderness</td>
<td>15.1</td>
<td>15.1</td>
<td>15.2</td>
<td>43.7</td>
</tr>
</tbody>
</table>

* Data are from three primary US safety studies (the US Phase 2 infant study [NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

### Table 6: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Systemic Adverse Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccinationa,b,c

<table>
<thead>
<tr>
<th>Systemic Reaction</th>
<th>Dose 1 (N=86)</th>
<th>Dose 2 (N=86)</th>
<th>Dose 3 (N=78)</th>
<th>Dose 4 (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Fever</td>
<td>3.4</td>
<td>8.1</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.2</td>
<td>2.3</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19.5</td>
<td>17.2</td>
<td>17.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Irritability</td>
<td>24.1</td>
<td>34.5</td>
<td>24.7</td>
<td>30.6</td>
</tr>
<tr>
<td>Increased sleep</td>
<td>9.2</td>
<td>9.3</td>
<td>2.5</td>
<td>10.1</td>
</tr>
<tr>
<td>Decreased sleep</td>
<td>24.1</td>
<td>18.4</td>
<td>15.0</td>
<td>20.4</td>
</tr>
</tbody>
</table>

* Data are from three primary US safety studies (the US Phase 2 infant study [NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

A US study (Study 5) evaluated the use of Prevnar 13 in children previously immunized with Prevnar. In this open label trial, 596 healthy children 15 through 59 months of age previously vaccinated with at least 3 doses of Prevnar, received 1 or 2 doses of Prevnar 13. Children 15 months through 23 months of age (group 1) received 2 doses, and children 24 months through 59 months of age (group 2) received one dose. Most subjects were White (74.3%), 14.9% were Black or African-American, and 1.2% were Asian; 89.3% of subjects were non-Hispanic and non-Latino and 10.7% were Hispanic or Latino. Overall, 52.2% of subjects were male. The incidence and severity of solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13 administered to children 15 months through 59 months of age are shown in Tables 7 and 8.

Reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash. Reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

Safety Assessments in the Catch-Up Studies in Infants and Children Through 5 Years of Age

In a catch-up study conducted in Poland (Study 4), 554 children (7 months through 5 years of age) receiving at least one dose of Prevnar 13 were also monitored for safety. All subjects in this study were White and non-Hispanic. Overall, 49.6% of subjects were male infants. The incidence and severity of solicited adverse reactions that occurred within 4 days following each dose of Prevnar 13 administered to pneumococcal-vaccine naïve children 7 months through 5 years of age are shown in Tables 5 and 6.
The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 was evaluated in children 5 through 9 years of age in a US study. In this open label trial, 592 children, including those with asthma, received a single dose of Prevnar 13.

### Table 7: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Doses of Prevnar, Reporting Solicited Local Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination

<table>
<thead>
<tr>
<th>Local Reaction</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 prior Prevnar doses</td>
<td>4 prior Prevnar doses</td>
<td>3 or 4 prior Prevnar doses</td>
<td>3 or 4 prior Prevnar doses</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Redness</td>
<td>26.4</td>
<td>28.2</td>
<td>35.4</td>
<td>31.1</td>
</tr>
<tr>
<td>Mild</td>
<td>11.4</td>
<td>7.5</td>
<td>12.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe</td>
<td>1.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Swelling</td>
<td>23.9</td>
<td>19.6</td>
<td>20.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Mild</td>
<td>18.6</td>
<td>16.4</td>
<td>17.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>8.8</td>
<td>8.1</td>
<td>7.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Tenderness</td>
<td>48.6</td>
<td>47.3</td>
<td>62.6</td>
<td>10.7</td>
</tr>
</tbody>
</table>

### Table 8: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Doses of Prevnar, Reporting Solicited Systemic Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination

<table>
<thead>
<tr>
<th>Systemic Reaction</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
<th>1 dose Prevnar 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 prior Prevnar doses</td>
<td>4 prior Prevnar doses</td>
<td>3 or 4 prior Prevnar doses</td>
<td>3 or 4 prior Prevnar doses</td>
</tr>
<tr>
<td>Fever</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Any</td>
<td>19.1</td>
<td>19.9</td>
<td>8.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Mild</td>
<td>16.2</td>
<td>17.4</td>
<td>7.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>6.1</td>
<td>3.9</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44.4</td>
<td>39.3</td>
<td>28.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Irritability</td>
<td>73.3</td>
<td>65.1</td>
<td>45.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Increased sleep</td>
<td>35.2</td>
<td>35.3</td>
<td>18.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased sleep</td>
<td>25.0</td>
<td>29.7</td>
<td>14.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Clinical Trials Experience With Prevnar 13 in Children 5 Through 17 Years of Age

In a US study, the safety of Prevnar 13 was assessed in children 5 through 9 years of age previously immunized with at least one dose of Prevnar, and in children 10 through 17 years of age with no prior pneumococcal vaccination. In this open label trial, 592 children, including those with asthma, received a single dose of Prevnar 13. The percentage of children 5 through 9 years of age who received 3 and 4 prior doses of Prevnar was 29.1% and 54.5% respectively. Most subjects were White (72.8%), 21.8% were Black or African-American, and 1.5% were Asian; 91.4% of subjects were non-Hispanic and non-Latino and 8.6% were Hispanic or Latino. Overall, 51.2% of subjects were male.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 5 through 17 years of age are shown in Tables 9 and 10.

6.2 Clinical Trials Experience With Prevnar 13 in Adults ≥18 Years of Age

The safety of Prevnar 13 was assessed in 7 clinical studies (Studies 6-12) conducted in the US and Europe which included 91,593 adults (48,806 received Prevnar 13) ranging in age from 18 through 101 years.

6 Clinical safety study was randomized and compared the safety and immunogenicity of Prevnar 13 with PPSV23 in different sequential order in PPSV23 naive adults aged 60 through 64 years old. One clinical safety study (Study 9) of Prevnar 13 conducted in PPSV23 previously vaccinated adults ≥68 years was a single arm study. Two studies, one in the US10 (Study 10) in adults aged 50 through 59 years and the other in Europe (Study 11) in adults aged ≥65 years, evaluated the concomitant administration of Prevnar 13 with inactivated influenza vaccine, trivalent (Fluarix®, A/H1N1, A/H3N2, and B, Fall 2007/Spring 2008: IIV3) in these two age groups in sequential order in PPSV23 naive adults aged 60 through 64 years old.
In the safety and immunogenicity studies, 5, 6, 11 subjects were excluded from study participation due to prior receipt of diphtheria toxoid-containing vaccines within 6 months of study vaccine. However, the time of prior receipt of a diphtheria toxoid-containing vaccine was not recorded.

Solicited adverse reactions for Prevnar 13 in the safety and immunogenicity studies were monitored by subjects recording local adverse reactions and systemic reactions daily using an electronic diary for 14 consecutive days following vaccination. Unsolicited serious and non-serious adverse events were collected for one month after each vaccination. In addition, serious adverse events were collected for an additional 5 months after each vaccination (at the 6-month follow-up phone contact) in all studies except Study 11.

**Efficacy Study**

Study 12 was a randomized double-blind placebo-controlled study conducted in the Netherlands in community-dwelling adults aged 65 years and older with no prior pneumococcal vaccination history. A total of 49,466 subjects received either a single dose of Prevnar 13 (42,240) or placebo (42,256) in a 1:1 randomization. Among the 49,466 subjects, 58,072 (68.7%) were >65 to <75 years of age, 23,461 (27.9%) were ≥75 and <85 years of age, and 2,943 (3.5%) were ≥85 years of age. In the total study population, more males (55.9%) were enrolled than females. The racial distribution was 98.5% White, 0.3% Black, 0.7% Asian, 0.5% Other, with <0.1% having missing data.

Adults with immunocompromising conditions or receiving immunosuppressive therapy and adults residing in a long-term care facility or requiring semiskilled nursing care were excluded. Adults with pre-existing medical conditions, as well as subjects with a history of smoking were eligible for enrollment. In the safety population, 42.3% of subjects had pre-existing medical conditions including heart disease (25.4%), lung disease or asthma (15.1%) and type 1 and type 2 diabetes mellitus (12.5%). Smoking was reported at baseline by 12.3% of the subjects.

For a subset of 2,011 subjects (1,006 Prevnar 13 recipients and 1,005 placebo recipients), solicited adverse reactions were monitored by recording local and systemic events using electronic diaries for 7 days after vaccination; unsolicited adverse events were collected for 28 days after vaccination, and serious adverse events were collected for 6 months after vaccination. For the remaining 41,231 Prevnar 13 and 41,250 placebo vaccinated subjects, serious adverse events were collected for 28 days after vaccination.

**Serious Adverse Events in Adult Clinical Studies**

**Safety and Immunogenicity Studies**

Across the 6 safety and immunogenicity studies, 5, 6, 11 serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5,057 subjects vaccinated with Prevnar 13, and in 0.4%-1.7% of 1,124 subjects vaccinated after an initial study dose of PPSV23. From 1 month to 6 months after an initial study dose, serious adverse events were reported in 0.2%-5.8% of subjects vaccinated during the studies with Prevnar 13 and in 2.4%-5.5% of subjects vaccinated after an initial study dose in 0.2%-1.4% of 5,057 subjects vaccinated with Prevnar 13 and 0.4%-1.7% of 1,124 subjects vaccinated after an initial study dose of PPSV23.

**Efficacy Study**

In Study 12, 13 subjects 65 years and older, serious adverse events within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Prevnar 13 recipients (352 events) and in 314 of 42,225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1,066 (7%) Prevnar 13 vaccinated subjects (90 events) and 60 of 1,005 (6%) placebo vaccinated subjects (89 events) reported serious adverse events. During the follow-up period (average of 4 years) for case accumulation there were 3,006 deaths (7.1%) in the Prevnar 13 group and 3,005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevnar 13 group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Prevnar 13 group and 144 deaths (0.3%) in the placebo group within 29 days – 6 months following vaccination. These data do not provide evidence for a causal relationship between deaths and vaccination with Prevnar 13.

**Solicited Adverse Reactions in Adult Clinical Studies**

The incidence and severity of solicited adverse reactions that occurred within 7 or 14 days following each dose of Prevnar 13, PPSV23, or placebo administered to adults in 5 studies are shown in Tables 11 and 12.

**Study 12**

The commonly reported local adverse reactions after Prevnar 13 vaccination in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were redness, swelling, and pain at the injection site, or limitation of arm movement (Tables 11 and 12). The commonly reported systemic adverse reactions in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain (Tables 13 and 14).

**Table 11 - Percentage of Subjects With Solicited Local Adverse Reactions Within 7 or 14 Days in PPSV23 Unvaccinated Adults**

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Study 6</th>
<th>Study 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevnar 13</td>
<td>PPSV23</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>18-49</td>
<td>268-270</td>
<td>22.0-22.4</td>
</tr>
<tr>
<td>50-59</td>
<td>152-202</td>
<td>11.2-14.2</td>
</tr>
<tr>
<td>60-64</td>
<td>193-331</td>
<td>6.4-9.9</td>
</tr>
<tr>
<td>≥65</td>
<td>201-370</td>
<td>9.7-12.2</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>Mild</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>30.5</td>
<td>26.4</td>
</tr>
<tr>
<td>PPSV23</td>
<td>30.5</td>
<td>26.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>30.5</td>
<td>26.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>Mild</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>39.4</td>
<td>37.2</td>
</tr>
<tr>
<td>PPSV23</td>
<td>39.4</td>
<td>37.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>39.4</td>
<td>37.2</td>
</tr>
</tbody>
</table>

**Table 12 - Percentage of Subjects With Solicited Local Adverse Reactions in PPSV23 Previously Vaccinated Adults**

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Study 7</th>
<th>Study 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevnar 13</td>
<td>PPSV23</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>N=306-362</td>
<td>N=324-383</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>Mild</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>10.8</td>
<td>9.5</td>
</tr>
<tr>
<td>PPSV23</td>
<td>10.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>Mild</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>10.4</td>
<td>8.9</td>
</tr>
<tr>
<td>PPSV23</td>
<td>10.4</td>
<td>8.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Studies conducted in US NCT00424785 (Study 6) and NCT00574548 (Study 8) reported local reactions within 14 days. Study conducted in the Netherlands NCT00744263 (Study 12) reported local reactions within 7 days.

Open label administration of Prevnar 13.

Number of subjects with known values (number of subjects reporting yes for at least one day or no for all days).

Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+.

Moderate intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and Severe >10.0 cm.

Mild = awareness of symptom but easily tolerated, Moderate = discomfort enough to cause interference with usual activity, Severe = incapacitating with inability to do usual activity.

Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder; and Severe = unable to move arm above shoulder.

Statistically significant difference p<0.05. No adjustments for multiplicity.
Table 13 - Percentage of Subjects With Solicited Systemic Events in PPSV23 Unvaccinated Adults

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Study 6</th>
<th>Study 7</th>
<th>Study 8</th>
<th>Study 9</th>
<th>Study 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevnar 13</td>
<td>Prevnar 13</td>
<td>Prevnar 13</td>
<td>Prevnar 13</td>
<td>Prevnar 13</td>
</tr>
<tr>
<td>Systemic Event</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fever ≥38.0°C</td>
<td>7.2</td>
<td>1.5</td>
<td>4.0</td>
<td>1.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Fever 38.0°C to 38.4°C</td>
<td>4.2</td>
<td>1.5</td>
<td>4.0</td>
<td>1.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Fever 38.5°C to 38.9°C</td>
<td>1.9</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Fever ≥40.0°C</td>
<td>1.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Chills</td>
<td>80.5</td>
<td>63.3</td>
<td>63.2</td>
<td>61.5</td>
<td>50.5</td>
</tr>
<tr>
<td>Headache</td>
<td>81.4</td>
<td>65.9</td>
<td>54.0</td>
<td>54.4</td>
<td>49.7</td>
</tr>
<tr>
<td>Rash</td>
<td>38.1</td>
<td>19.6</td>
<td>23.5</td>
<td>24.1</td>
<td>19.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21.3</td>
<td>14.2</td>
<td>16.5</td>
<td>13.0</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Table 14 - Percentage of Subjects With Systemic Events in PPSV23 Previously Vaccinated Adults

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Study 7</th>
<th>Study 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥70</td>
<td>≥85</td>
</tr>
<tr>
<td></td>
<td>Prevnar 13</td>
<td>PPSV23</td>
</tr>
<tr>
<td></td>
<td>N=299-350</td>
<td>N=303-367</td>
</tr>
<tr>
<td>Systemic Event</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fever ≥39.0°C</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Fever 38.0°C to 38.4°C</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Fever 38.5°C to 38.9°C</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fever ≥40.0°C</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3.4</td>
<td>43.3</td>
</tr>
<tr>
<td>Chills</td>
<td>3.7</td>
<td>26.0</td>
</tr>
<tr>
<td>Rash</td>
<td>7.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Generalized muscle pain</td>
<td>36.8</td>
<td>44.7</td>
</tr>
<tr>
<td>Generalized increased joint pain</td>
<td>20.6</td>
<td>27.5</td>
</tr>
<tr>
<td>Generalized increased joint pain</td>
<td>12.6</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Prevnar 13 and IPV (Fluarix)

The safety of concomitant administration of Prevnar 13 with IPV3 was assessed in 2 studies in PPSV23 unvaccinated adults aged 50 through 59 years (Study 10) and aged ≥65 years (Study 11). Frequencies of local reactions within 14 days post-vaccination in adults aged 50 through 59 years and in adults aged ≥65 years were similar after Prevnar 13 was administered with IPV3 compared to Prevnar 13 administered alone, with the exception of mild redness at the injection site, which was increased when Prevnar 13 was administered concomitantly with IPV3 and mild limitation of arm movement, which was increased when Prevnar 13 was administered alone.

An increase in some solicited systemic reactions within 14 days post-vaccination was noted when Prevnar 13 was administered concomitantly with IPV3 compared with IPV3 given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with Prevnar 13 given alone (fatigue, headache, chills, decreased appetite, and joint pain).

6.3 Post-marketing Experience With Prevnar 13 in Infants and Toddlers

The following adverse events have been reported through passive surveillance since market introduction of Prevnar 13. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Prevnar 13 vaccine.

Administration site conditions: Vaccination-site dermatitis, vaccination-site pruritus, vaccination-site urticaria

Blood and lymphatic system disorders: Lymphadenopathy localized to the region of the injection site

Cardiac disorders: Cyanosis

Immune system disorders: Anaphylactic/anaphylactoid reaction including shock

Nervous system disorders: Hypotonia

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apeana

Vascular disorders: Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

In clinical trials with infants and toddlers, Prevnar 13 was administered concomitantly with the following US licensed vaccines: Pediarix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombimant) and Inactivated Poliovirus Vaccine Combined) (DTPa-HB-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-OMP, M-M-R II [Mesolice, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella and Varicella Virus Vaccine Live] (MMRV) and VATGA [Hepatitis A vaccine, Inactivated] (Hepa) for dose 4 [see Clinical Studies (14.2) and Adverse Reactions (6.1)].

In children and adolescents, data are insufficient to assess the concomitant administration of Prevnar 13 with Human Papillomavirus Vaccine (HPV), Meningococcal Conjugate Vaccine (MCV4) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap).

In adults, Prevnar 13 was administered concomitantly with US licensed Fluarix (IV3) for the 2007/2008 influenza season [see Clinical Studies (14.3) and Adverse Reactions (6.2)]. There are no data on the concomitant administration of Prevnar 13 with diptheria toxoid-containing vaccines and other vaccines licensed for use in adults 50 years of age and older.

When Prevnar 13 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

7.2 Immunosuppressive Therapies

Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

7.3 Antipyretics

A post-marketing clinical study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. The data showed that 3 doses of acetaminophen (the first dose administered at the time of each vaccination and the subsequent doses at 8 to 6 hour intervals) reduced the antibody response to some serotypes following the third dose of Prevnar 13, compared with responses among infants who received antipyretics only as needed for treatment. Reduced antibody responses were not observed after the fourth dose of Prevnar 13 when acetaminophen was administered prophylactically.

7.4 Prior Vaccination with PPSV23

Prior receipt of Pneumovax®23 (23 valent pneumococcal vaccine polyvalent, PPSV23) within 1 year results in diminished immune responses to Prevnar 13 compared to PPSV23 naïve individuals [see Clinical Studies (14.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Prevnar 13 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rabbits administered Prevnar 13 prior to mating and during gestation. Each dose was approximately 20 times the human dose. This study revealed no evidence of harm to the fetus due to Prevnar 13 (see 8.1 Data).
The individual glycoconjugates are compounded to formulate Prevnar 13. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens and by the saccharide to protein ratios in the individual glycoconjugates. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 μg of each *Strepococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 μg of 6B saccharides, 34 μg CRM197 carrier protein, 100 μg polysorbate 80, 29.5 μg sucrose buffer and 125 μg aluminum phosphate adjuvant. The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prevnar 13, comprised of pneumococcal polysaccharides conjugated to a carrier protein (CRM197), elicits a T-cell independent immune response. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response.

Nonclinical and clinical data support opsonophagocytic activity, as measured by opsonophagocytic activity (OPA) assay, as a contributor to protection against pneumococcal disease. The OPA assay provides an in vitro measurement of the ability of antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease. OPA antibody titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

In infants that have received Prevnar 13, opsonophagocytic activity correlates well with serotype specific anti-capsular polysaccharide IgG levels as measured by ELISA. A serum anti-capsular polysaccharide antibody concentration of 0.3 μg/mL as measured by ELISA one month after the third dose as a single antibody reference concentration was used to estimate the effectiveness of Prevnar 13 against invasive pneumococcal disease (IPD) in infants and children. The assay used for this determination is a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. The single antibody reference value was based on pooled efficacy estimates from three placebo-controlled IPD efficacy trials with either Prevnar 13 or the 9-valent CRM197 conjugate pneumococcal polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis. Functional antibodies elicited by the vaccine (as measured by a dribble opsonophagocytic activity [dOPA] antibody assay) were also evaluated in infants.

In adults, an anti-polysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined. Noninferiority trials for Prevnar 13 were designed to show that functional OPA antibody responses (as measured by a microcytotoxicity OPA [mOPA] antibody assay for the Prevnar 13 serotypes noninferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23). OPA antibody titers measured in the mOPA antibody assay cannot be directly compared to titers measured in the dOPA antibody assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Prevnar 13 has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a study in rabbits, no vaccine-related effects were found regarding reproductive performance including female fertility [see Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

14.1 Efficacy Data

Prevnar Efficacy Data

Invasive Pneumococcal Disease (IPD)

Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM197 Protein]) was licensed in the US for infants and children in 2000, following a randomized, double-blind clinical trial in a multicentric population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either Prevnar or a control vaccine (investigational meningococcal group C conjugate vaccine [MCCgCV]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of Prevnar against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% CI: 75.4%, 100% and 81.7%, 100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.4% in the per-protocol population and 93.9% in the intent-to-treat analysis (95% CI: 82.7%, 99.9% and 79.6%, 99.5%, respectively).

Acute Otitis Media (AOM)

The vaccine efficacy of otitis media was assessed in two clinical trials: a trial in Finnish children at the National Public Health Institute and the efficacy trial in US infants at Northern California Kaiser Permanente (NCKP).

The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either Prevnar or a control vaccine Reombvac HB (Hepatitis B Vaccine [Reombinant] [Heb B]) at 2, 4, 6, and 12-15 months of age. In this study, conducted between December 1995 and March 1999, parents of study participants were asked to bring their children to study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of Prevnar against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to either Prevnar or the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at 2, 4, 6, and 12-15 months of age. In this trial, conducted between December 1995 and March 1999, parents of study participants were asked to bring their children to study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). The trial did not achieve accrual goals in the US pediatric population; the primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population. The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial, was 57% (95% CI: 44%, 67%) in the per-protocol population and 54% (95% CI: 41%, 64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 18A 23A) was also assessed in the Finnish trial, was 51% (95% CI: 27, 67) in the per-protocol population and 44% (95% CI: 20, 62) in the intent-to-treat population. There was a nonsignificant increase in AOM...
episodes caused by serotypes unrelated to the vaccine in the per-protocol population, compared to children who received the control vaccine, suggesting that children who received Prevnar appeared to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine. However, vaccination with Prevnar reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI: 4%, 10%) and 6% (95% CI: 4%, 9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the two trials.

Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI: 3%, 15% in per-protocol and 95% CI: 4%, 14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of tympanometry tubes in the per-protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in Prevnar group and 18,941 in MenCC control group), resulting in similar otitis media efficacy estimates for all endpoints.

Prevnar 13 Adult Efficacy Data

The efficacy of Prevnar 13 against vaccine-type (VT) pneumococcal community-acquired pneumonia (CAP) and IPD was assessed in a randomized, double-blind, placebo-controlled study conducted over 4 years in the Netherlands (Study 2). A total of 84,496 subjects 65 years and older received a single dose of either Prevnar 13 or placebo in a 1:1 randomization; 42,240 subjects were vaccinated with Prevnar 13 and 42,256 subjects were vaccinated with placebo.

The primary objective was to demonstrate the efficacy of Prevnar 13 in the prevention of the first episode of confirmed VT-CAP (defined as presence of ≥2 specified clinical criteria; chest X-ray consistent with CAP as determined by a central committee of radiologists, and positive VT-specific urinary antigen detection assay (UAD) or isolation of VT S. pneumoniae from blood or other sterile site). The secondary objectives were to demonstrate the efficacy of Prevnar 13 in the prevention of: (1) confirmed nonbacteremic/noninvasive (NB/NI) VT-CAP (an episode of VT-CAP from blood or other sterile site), (2) VT-IPD (the presence of S. pneumoniae in a sterile site).

Surveillance for suspected pneumonia and IPD began immediately after vaccination and continued through identification of a prespecified number of cases. Subjects who had a CAP or IPD episode with symptom onset less than 14 days after vaccination were excluded from all analyses.

The median duration of follow up per subject was 3.93 years. Prevnar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing first episodes of VT pneumococcal CAP, nonbacteremic/noninvasive (NB/NI) VT pneumococcal CAP, and VT-IPD (Table 15).

### Table 15 - Vaccine Efficacy for the Primary and Secondary Efficacy Endpoints – Per-Protocol Population

<table>
<thead>
<tr>
<th>Vaccine Group</th>
<th>Prevnar 13</th>
<th>Placebo</th>
<th>VE (%)</th>
<th>(95.2% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint: First case of confirmed VT pneumococcal CAP</td>
<td>139</td>
<td>49</td>
<td>90</td>
<td>45.6 (21.8, 62.5)</td>
</tr>
<tr>
<td>Secondary endpoint: First episode of confirmed NB/NI VT pneumococcal CAP</td>
<td>93</td>
<td>33</td>
<td>60</td>
<td>45 (14.2, 65.3)</td>
</tr>
<tr>
<td>Secondary episode of VT-IPD</td>
<td>35</td>
<td>7</td>
<td>28</td>
<td>75 (41.1, 90.9)</td>
</tr>
</tbody>
</table>

### Functional dOPA antibody responses were elicited for all 13 serotypes, as shown in Table 17.

### Table 17: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2

![Table 17](image2.png)

### Pneumococcal Immune Responses Following Four Doses

In Study 2, post-dose 4 antibody concentrations were higher for all 13 serotypes than those achieved after the third dose. The noninferiority criterion for pneumococcal anti-capillary polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose was met for 10 of the 13 serotypes. The exceptions were serotypes 6B, 9V, and 3. Although the response to serotypes 6B and 9V did not meet the pre-specified noninferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capillary polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose is shown below (Table 16).

### Table 16: Percentage of Subjects With Anti-capillary Polysaccharide Antibody Concentration ≥0.35 μg/mL One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2

![Table 16](image3.png)

### Pneumococcal Immune Responses Following Three Doses

In Study 2, the noninferiority criterion for the proportion of subjects with pneumococcal anti-capillary polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose was met for 10 of the 13 serotypes. The exceptions were serotypes 6B, 9V, and 3. Although the response to serotypes 6B and 9V did not meet the pre-specified noninferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capillary polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose is shown below (Table 16).

### Table 16: Percentage of Subjects With Anti-capillary Polysaccharide Antibody Concentration ≥0.35 μg/mL One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2

![Table 16](image4.png)
Table 18: Pneumococcal IgG GMCs (μg/mL) One Month After a Four Dose Series Administered at 2, 4, 6 and 12-15 Months, Study 2ab,c,d

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Prevnar 13</th>
<th>Prevenar</th>
<th>GMC Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=223-236</td>
<td>N=222-223</td>
<td></td>
</tr>
<tr>
<td>Prevenar Serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.73 (3.28, 4.24)</td>
<td>5.49 (4.91, 6.13)</td>
<td>0.68 (0.57, 0.80)</td>
</tr>
<tr>
<td>6B</td>
<td>11.53 (9.99, 13.30)</td>
<td>15.63 (13.80, 17.69)</td>
<td>0.74 (0.61, 0.89)</td>
</tr>
<tr>
<td>9V</td>
<td>2.62 (2.34, 2.94)</td>
<td>3.63 (3.25, 4.05)</td>
<td>0.72 (0.62, 0.85)</td>
</tr>
<tr>
<td>14</td>
<td>9.11 (7.95, 10.45)</td>
<td>12.72 (11.22, 14.41)</td>
<td>0.72 (0.60, 0.86)</td>
</tr>
<tr>
<td>18C</td>
<td>3.20 (2.82, 3.64)</td>
<td>4.70 (4.18, 5.28)</td>
<td>0.68 (0.57, 0.81)</td>
</tr>
<tr>
<td>19F</td>
<td>6.60 (5.85, 7.44)</td>
<td>5.60 (4.87, 6.43)</td>
<td>0.98 (0.86, 1.14)</td>
</tr>
<tr>
<td>23F</td>
<td>5.07 (4.41, 5.83)</td>
<td>7.84 (6.91, 8.90)</td>
<td>0.65 (0.54, 0.76)</td>
</tr>
<tr>
<td>Additional Serotypesa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.06 (4.43, 5.80)</td>
<td>e</td>
<td>1.40 (1.17, 1.66)</td>
</tr>
<tr>
<td>3</td>
<td>0.94 (0.83, 1.05)</td>
<td>e</td>
<td>0.26 (0.22, 0.30)</td>
</tr>
<tr>
<td>5</td>
<td>3.72 (3.31, 4.18)</td>
<td>e</td>
<td>1.03 (0.87, 1.20)</td>
</tr>
<tr>
<td>6A</td>
<td>8.20 (7.30, 9.20)</td>
<td>e</td>
<td>2.26 (1.93, 2.65)</td>
</tr>
<tr>
<td>7F</td>
<td>5.67 (5.01, 6.42)</td>
<td>e</td>
<td>1.56 (1.32, 1.85)</td>
</tr>
<tr>
<td>19A</td>
<td>8.55 (7.64, 9.56)</td>
<td>e</td>
<td>2.36 (2.01, 2.76)</td>
</tr>
</tbody>
</table>

a Studies conducted in US NCT00373958 (Study 2).  
b Evaluative Immunogenicity Population.  
c Noninferiority was declared if the lower limit of the 2-sided 95% CI for Geometric Mean Ratio (Prevnar 13: Prevenar) was greater than 0.5.  
d Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.  
Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevenar recipients, which for this analysis was serotype 9N (3.63; 95% CI 3.25, 4.05).

Table 19: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After the Fourth Dose of Prevenar 13 in Children 24 Months through 59 Months of Age Are shown in Table 21.

Table 20: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (μg/mL) One Month After the Final Prevnar 13 Catch-Up Dose in Pneumococcal Vaccine Naive Children 7 Months Through 5 Years of Age by Age Group, Study 4ab

Following the fourth dose, the functional dOPA antibody response for each serotype was quantitatively greater than the response following the third dose (see Table 19).

Table 19: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After the Fourth Dose of Prevenar 13 Evaluable Toddler Immunogenicity Population, Study 2ab,c,d

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Prevnar 13</th>
<th>Prevenar</th>
<th>GMC Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=98-92</td>
<td>N=92-96</td>
<td></td>
</tr>
<tr>
<td>Prevenar Serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1180 (847, 1643)</td>
<td>1492 (1114, 1999)</td>
<td></td>
</tr>
<tr>
<td>6B</td>
<td>3100 (2337, 4111)</td>
<td>4066 (3243, 5098)</td>
<td></td>
</tr>
<tr>
<td>9V</td>
<td>11856 (8810, 15955)</td>
<td>18032 (14125, 23021)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2002 (1453, 2760)</td>
<td>2366 (1871, 2992)</td>
<td></td>
</tr>
<tr>
<td>18C</td>
<td>993 (754, 1308)</td>
<td>1722 (1327, 2326)</td>
<td></td>
</tr>
<tr>
<td>19F</td>
<td>200 (144, 276)</td>
<td>167 (121, 230)</td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>2723 (1961, 3782)</td>
<td>4982 (3886, 6387)</td>
<td></td>
</tr>
<tr>
<td>Additional Serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>164 (114, 237)</td>
<td>5 (4, 6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>380 (300, 482)</td>
<td>12 (9, 16)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>300 (229, 393)</td>
<td>5 (4, 6)</td>
<td></td>
</tr>
<tr>
<td>6A</td>
<td>2242 (1707, 2945)</td>
<td>539 (375, 774)</td>
<td></td>
</tr>
<tr>
<td>7F</td>
<td>11629 (9054, 14383)</td>
<td>268 (164, 436)</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>1024 (774, 1355)</td>
<td>29 (19, 44)</td>
<td></td>
</tr>
</tbody>
</table>

a Studies conducted in US NCT00737985 (Study 2).  
b The dOPA (epoxysphingobactin) activity assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of S. pneumoniae by phagocytic cells.
Prevnar 13 was compared to other pneumococcal vaccines in a number of Phase 3 trials. The response to the additional serotype 6A, which is contained in Prevnar 13 but not in PPSV23, was assessed by determination of a >4-fold increase in the anti-6A mcOPA antibody titer above preimmunization levels. A statistically significantly greater response for Prevnar 13 was defined for the difference in percentages (Prevnar 13 minus PPSV23) of adults achieving a >4-fold increase in anti-6A mcOPA antibody titer, as the lower limit of the 2-sided 95% CI greater than zero. For comparison, the mcOPA antibody GMTs for serotype 6A were defined as the lower limit of the 2-sided 95% CI of the GMT ratio (Prevnar 13/PPSV23) greater than 2.

Of the 5 Phase 3 clinical trials, 2 noninferiority trials were conducted in which the immune responses to Prevnar 13 were compared with the immune responses to PPSV23; one in PPSV23 vaccinated adults aged 18 through 64 years (Study 6), and one in PPSV23 vaccinated adults aged 65 and older (Study 7). A third study compared immune responses to a single dose of Prevnar 13 to the response to Prevnar 13 administered one year after a dose of PPSV23 in adults aged 60 through 64 years who were PPSV23 unvaccinated at enrollment (Study 8). The study also compared immune responses to PPSV23 as a single dose to responses to PPSV23 administered one year after a dose of Prevnar 13. Two studies assessed the concomitant administration of Prevnar 13 with seasonal inactivated influenza (IVS) in the US (Study 10) and Europe (Study 11).

Overall across the clinical studies evaluating the immunogenicity of Prevnar 13 in adults, persons 18 through 64 years of age responded at least as well as persons 65 years and older, the age group evaluated in a clinical endpoint efficacy trial.

### Clinical Trials Conducted in PPSV23 Unvaccinated Adults

In an active-controlled modified double-blind clinical trial (Study 6) of Prevnar 13 in the US, PPSV23 unvaccinated adults aged 60 through 64 years were randomly assigned (1:1) to receive Prevnar 13 or PPSV23. In addition, adults aged 18 through 49 years and 50 through 59 years were enrolled and received one dose of Prevnar 13 (open-label).

In adults aged 60 through 64 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines (see Table 24). In addition, the lower limit of the 95% confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 8 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a >4-fold increase after Prevnar 13 (88.5%) was statistically significantly higher than after PPSV23 (49.3%) in PPSV23-unvaccinated adults aged 60 through 64 years. OPA antibody GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared to PPSV23 after 1 year (see Table 25). The mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 50 through 59 years were noninferior to the corresponding mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

In adults aged 18 through 49 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

### Table 24: Comparison of Pneumococcal mcOPA GMTs One Month After Vaccination, Prevnar 13, in Children 10 through 17 Years of Age Relative to Prevnar 13 in Children 5 through 9 Years of Age

<table>
<thead>
<tr>
<th>Vaccine Group (as Enrolled)</th>
<th>Prevnar 13</th>
<th>Prevnar 13 Post-Toddler Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td>n</td>
<td>GMTc (95% CI)</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Common</td>
<td>1</td>
<td>189 9312 (6101, 7831)</td>
</tr>
<tr>
<td>6A</td>
<td>183 14224 (12136, 16247)</td>
<td>181 4699 (3713, 5648)</td>
</tr>
<tr>
<td>9V</td>
<td>186 4485 (4001, 5208)</td>
<td>180 4733 (4205, 5328)</td>
</tr>
<tr>
<td>14A</td>
<td>184 6789 (6207, 7884)</td>
<td>178 4759 (4120, 5490)</td>
</tr>
<tr>
<td>18C</td>
<td>189 6354 (5346, 7215)</td>
<td>179 4662 (7338, 10041)</td>
</tr>
<tr>
<td>19F</td>
<td>184 2286 (1944, 2668)</td>
<td>178 1891 (1336, 1893)</td>
</tr>
<tr>
<td>23A</td>
<td>187 3100 (2335, 3939)</td>
<td>178 3121 (2643, 3765)</td>
</tr>
</tbody>
</table>

* Studies conducted in US NCT00761631 (Study 5).
* n: Number of subjects with a detectable antibody titer for the specified serotype.
* Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
* Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
* Ratio of GMTs: Prevnar 13 (10 through 17 years of age) to Prevnar 13 (5 through 9 years of age).
* Evaluative Immunogenicity Population.
* Noninferiority was declared if the lower limit of the 95% CI for geometric mean ratio was greater than 0.5.

### Table 25: mcOPA Antibody GMTs in PPSV23-Unvaccinated Adults

<table>
<thead>
<tr>
<th>Vaccine Group (as Enrolled)</th>
<th>Prevnar 13</th>
<th>Prevnar 13 Post-Toddler Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td>n</td>
<td>GMTc (95% CI)</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Common</td>
<td>1</td>
<td>189 327 (275, 378)</td>
</tr>
<tr>
<td>6A</td>
<td>181 114 (101, 130)</td>
<td>179 203 (182, 226)</td>
</tr>
<tr>
<td>9V</td>
<td>183 360 (286, 436)</td>
<td>179 498 (437, 568)</td>
</tr>
<tr>
<td>18A</td>
<td>185 9923 (8451, 11650)</td>
<td>179 7514 (6351, 8891)</td>
</tr>
<tr>
<td>19F</td>
<td>187 1358 (7812, 7473)</td>
<td>180 10334 (9068, 11737)</td>
</tr>
<tr>
<td>23A</td>
<td>187 1276 (1132, 1439)</td>
<td>180 1108 (1046, 1172)</td>
</tr>
</tbody>
</table>

* Studies conducted in US NCT00761631 (Study 5).
Clinical Trials Conducted in PPSV23 Previously Vaccinated Adults

In a Phase 3 active-controlled, modified double-blind clinical trial (Study 7) of Prevnar 13 in the US and Sweden, PPSV23 prevaccinated adults aged ≥70 years who had received one dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either Prevnar 13 or PPSV23.

The mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common, when Prevnar 13 or PPSV23 were administered at a minimum of 5 years after a prior dose of PPSV23. In addition, the lower limit of the 95% confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 9 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a ≥4-fold increase in mcOPA antibody titers after Prevnar 13 (71.1%) was statistically significantly greater than after PPSV23 (27.3%) in the PPSV23-prevaccinated adults aged ≥70 years. mcOPA antibody GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥70 years and prevaccinated with PPSV23 ≥5 years prior, vaccination with Prevnar 13 elicited noninferior immune responses as compared with re-vaccination with PPSV23 (see Table 26).

14.4 Concomitant Vaccine Administration

Infants and Toddlers

The concomitant administration of routine US infant vaccines [see Drug Interactions (7.1)] with Prevnar 13 was evaluated in two studies: Study 2 [see Clinical Studies (14.2)], Pneumococcal Immune Responses Following Three Doses and the US lot consistency study (Study 3). In Study 3, subjects were randomly assigned to receive one of 3 lots of Prevnar 13 or Prevnar in a 2:2:2:1 ratio. The total number of infants vaccinated was 663 (Study 2) and 1699 (Study 3). Immune responses to concomitant vaccine antigens were compared in infants receiving Prevnar and Prevnar 13. Responses to diphtheria toxoid, tetanus toxoid, pertussis, polio types 1, 2, and 3, hepatitis B, PRP-T, PRP-OMP, measles, and varicella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

Adulthood

Two randomized, double-blind clinical trials evaluated the immunogenicity of Prevnar 13 given with ILV3 (Fall 2007/Spring 2008 Fluarix, A/H1N1, A/H3N2, and B strains) in PPSV23 unvaccinated adults aged 50 through 59 years of age in Study 7 (conducted in the U.S.) and in adults ≥65 years of age (Study 11, conducted in Europe).

In each clinical trial one group received Prevnar 13 and ILV3 concurrently, followed approximately one month later by placebo. The other group received ILV3 and placebo concurrently, followed approximately one month later by Prevnar 13.

Antibody responses elicited by ILV3 were measured by hemagglutination inhibition assay (HAI) one month after ILV3 vaccination. The proportion of subjects achieving a ≥4-fold increase in HAI titer (responder) for each ILV3 strain was evaluated 1 month after vaccination.

Noninferiority was demonstrated for each ILV3 vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders between the two groups [concomitant minus Placebo] was greater than -10%.

In subjects 50 through 59 years of age, noninferiority was demonstrated for each of the 3 ILV3 strains after Prevnar 13 given concurrently with ILV3 compared with ILV3 given alone in subjects ≥65 years of age, noninferiority was demonstrated for A/H1N1 and B strains, but not for A/H3N2, which had a lower limit of the 95% CI of -10.4%.

The studies also assessed the antibody responses of Prevnar 13 when Prevnar 13 was given concomitantly with ILV3 compared with Prevnar 13 alone. The antipolysaccharide binding antibody responses (sIgG) were measured by ELISA sIgG one month after Prevnar 13 vaccination in a subset of subjects. Noninferiority was demonstrated if the lower limit of the 2-sided, 95% CI for the sIgG GMC ratios (Prevnar 13 / ILV3 relative to Prevnar 13 alone) was >0.5. In a post hoc analysis, mcOPA antibody response was evaluated using the same criterion.

In subjects 50 through 59 years of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for all 13 serotypes after Prevnar 13 was given concomitantly with ILV3 compared with Prevnar 13 given alone, and noninferiority of the mcOPA antibody GMT ratios was observed for 10 of 13 serotypes.

In subjects ≥65 years of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for 12 of 13 serotypes after Prevnar 13 was given concomitantly with ILV3 compared with Prevnar 13 given alone, and noninferiority of the mcOPA antibody GMT ratios was observed for all of the 13 serotypes.

Table 28: mcOPA Antibody GMTs for the Prevnar 13 Serotypes in PPSV23-Prevaccinated Adults Aged 60 Through 64 Years Given PPSV23

To study conducted in US NCT00574548 (Study 8).

A mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were measured.

McOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at LLOQ for the purpose of calculating the mcOPA antibody GMT.

Clinical Trial of Sequential Vaccination of Prevnar 13 and PPSV23 in PPSV23 Unvaccinated Adults

In a randomized clinical trial conducted in PPSV23-unvaccinated adults 60 through 64 years of age (Study 8); 223 subjects received PPSV23 followed by Prevnar 13 one year later (PPSV23/ Prevnar 13) and 478 received only Prevnar 13; mcOPA antibody titers were measured 1 month after vaccination with Prevnar 13 and are shown in Table 26. mcOPA antibody GMTs in those that received Prevnar 13 one year after PPSV23 were diminished when compared to those who received Prevnar 13 alone. Similarly, in exploratory analyses in PPSV23-pre-vaccinated adults ≥70 years of age in Study 7, diminished mcOPA antibody GMTs were observed in those that received Prevnar 13 one year after PPSV23 when compared to those who received Prevnar 13 alone.

Table 26: mcOPA Antibody GMTs in PPSV23-Prevaccinated Adults Aged ≥70 Years Given Prevnar 13 or PPSV23 (Study 7)
15 REFERENCES
ClinicalTrials.gov identifiers for studies included below:
1. Study 1 NCT00205803
2. Study 2 NCT00373958
3. Study 3 NCT00444457
4. Study 4 NCT00452452
5. Study 5 NCT00761631
6. Study 6 NCT00427895
7. Study 7 NCT00546572
8. Study 8 NCT00574548
9. Study 9 NCT00506026
10. Study 10 NCT00521586
11. Study 11 NCT00492557
12. Study 12 NCT00744263

16 HOW SUPPLIED/STORAGE AND HANDLING
Prefilled Syringe, 1 Dose (10 per package) – NDC 0005-1971-02.
Prefilled Syringe, 1 Dose (1 per package) – NDC 0005-1971-05.
After shipping, Prevnar 13 may arrive at temperatures between 2ºC to 25ºC (36ºF to 77ºF).
Upon receipt, store refrigerated at 2ºC to 8ºC (36ºF to 46ºF).
Do not freeze. Discard if the vaccine has been frozen.
The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION
Prior to administration of this vaccine, inform the individual, parent, guardian, or other responsible
adult of the following:
• The potential benefits and risks of immunization with Prevnar 13 [see Warnings and
  Precautions (5) and Adverse Reactions (6)].
• The importance of completing the immunization series unless contraindicated.
• Any suspected adverse reactions should be reported to their healthcare professional.
Provide the Vaccine Information Statements, which are available free of charge at the Centers for
Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
This product’s label may have been updated. For current full prescribing information, please visit

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LAB-0469-14.0
CPT Code 90670