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 CRM_{197} Protein])

Suspension for intramuscular injection

Initial U.S. Approval: 2010

INDICATIONS AND USAGE

Prevnar 13 is a vaccine approved for use 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.

Prevnar 13 is also indicated for the prevention of otitis media caused by *Streptococcus 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)

DOSAGE AND ADMINISTRATION

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)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13, Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) or any diphtheria toxoid-containing vaccine. (4)

WARNINGS AND PRECAUTIONS

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. (5.4)

ADVERSE REACTIONS

The most commonly reported solicited adverse reactions (≥20 %) in U.S. clinical trials with Prevnar 13 were redness, swelling and tenderness at the injection site, fever, decreased appetite, irritability, increased sleep, and decreased sleep. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

DRUG INTERACTIONS

- Do not mix with any other vaccine in the same syringe. (7.1)
- Immunosuppressive therapies may reduce immune response to Prevnar 13. (7.2)

USE IN SPECIFIC POPULATIONS

Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks or on or after the 6th birthday have not been established. Prevnar 13 is not approved for use in children in these age groups. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2010

FULL PRESCRIBING INFORMATION: CONTENTS *

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Prevnar 13™ is a vaccine approved for use 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.

Prevnar 13 is also indicated for the prevention of otitis media caused by *Streptococcus 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.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a homogenous, white suspension in the vaccine container. Do not use the vaccine, if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration *[see Description (11)]*. This product should not be used if particulate matter or discoloration is found.

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

2.2 Administration Information

Do not inject intravenously, intradermally, or subcutaneously.

Each 0.5 mL dose is to be injected intramuscularly. The preferred sites for injection are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

2.3 Vaccine Schedule for Infants and Toddlers

Prevnar 13 is to be administered as a four-dose series at 2, 4, 6, and 12-15 months of age.

Table 1: Vaccination Schedule for Infants and Toddlers

Dose	Dose 1*†	Dose 2†	Dose 3†	Dose 4‡
Age at Dose	2 months	4 months	6 months	12-15 months

* Dose 1 may be given as early as 6 weeks of age.
† The recommended dosing interval is 4 to 8 weeks.
‡ The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

2.4 Vaccine Schedule for Unvaccinated Children ≥7 Months of Age

For children who are beyond the age of the routine infant schedule and have not received Prevnar or Prevnar 13, the following catch-up schedule applies:

Table 2: Vaccine Schedule for Unvaccinated Children ≥7 Months of Age

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
24 months through 5 years of age (prior to the 6th birthday)	1

* The first 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.
† Two doses at least 2 months apart.

The immune responses induced by this catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12 to 15 months). In children 24 months through 5 years of age, the catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 3 doses of Prevnar 13 (given at 2, 4, and 6 months).

2.5 Prevnar 13 Vaccine Schedule for Children Previously Vaccinated With Prevnar (*Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)

Children who have received one or more doses of Prevnar may complete the immunization series with Prevnar 13. Children 15 months through 5 years of age who are considered completely immunized with Prevnar may receive one dose of Prevnar 13 to elicit immune responses to the six additional serotypes. This catch-up (supplemental) dose of Prevnar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevnar. The immune responses induced by this Prevnar 13 schedule may result in lower antibody concentrations for the 6 additional serotypes (types 1, 3, 5, 6A, 7F, and 19A), compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12 to 15 months).

3 DOSAGE FORMS AND STRENGTHS

Prevnar 13 is a suspension for intramuscular injection available in 0.5 mL single-dose pre-filled syringes.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13, Prevnar or any diphtheria toxoid-containing vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions or Other Adverse Reactions

Before administration of any dose, all precautions should be taken to prevent allergic or any other adverse reactions. This includes a review of the patient's immunization history for possible sensitivity to the vaccine or similar vaccines and for previous vaccination-related adverse reactions in order to determine the existence of any contraindication to immunization with Prevnar 13 and to allow an assessment of risks and benefits. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following the administration of the vaccine.

5.2 Limitations of Vaccine Effectiveness

Prevnar 13 may not protect all individuals receiving the vaccine. Prevnar 13 will not protect against *Streptococcus pneumoniae* serotypes that are not in the vaccine or serotypes unrelated to those in the vaccine. It will also not protect against other microorganisms. This vaccine does not treat active infection.

Protection against otitis media is expected to be substantially lower than protection against invasive disease. In addition, because otitis media is caused by many organisms other than the 7 serotypes of *Streptococcus pneumoniae* included in the indication, protection against all causes of otitis media is expected to be lower than for pneumococcal otitis media caused by these 7 vaccine serotypes *[see Clinical Studies (14.2)]*.

The duration of protection from immunization is not known.

5.3 Altered Immunocompetence

Data on the safety and effectiveness of Prevnar 13 when administered to children in specific groups at higher risk for invasive pneumococcal disease (e.g., children with congenital or acquired splenic dysfunction, HIV infection, malignancy, nephrotic syndrome) are not available.

Children in these groups may have reduced antibody response to active immunization due to impaired immune responsiveness. Vaccination in high-risk groups should be considered on an individual basis *[see Drug Interactions (7.2)]*.

The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in children ≥24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness or who are otherwise immunocompromised.

5.4 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. As with any vaccine, there is the possibility that broad use of Prevnar 13 could reveal adverse reactions not observed in clinical trials.

6.1 Clinical Trials Experience With Prevnar 13

The safety of Prevnar 13 was evaluated in 13 clinical trials in which 4,729 infants and toddlers 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 7 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 substantive differences in demographic characteristics 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 U.S. evaluated the safety of Prevnar 13 when administered concomitantly with routine U.S. pediatric vaccinations at 2, 4, 6, and 12-15 months of age. Solicited local and systemic adverse events were recorded daily by parents/guardians using an electronic diary for 7 consecutive 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 proportion of Prevnar 13 and Prevnar subjects reporting serious adverse events. Among U.S. 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 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 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 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' system organ class including bronchiolitis (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.

There was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%).

Solicited Adverse Reactions in the Three U.S. Infant and Toddler Studies

A total of 1,907 subjects received at least 1 dose of Prevnar 13 and 701 subjects received at least 1 dose of Prevnar in the three U.S. studies. 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 U.S. infants and toddlers are shown in Tables 3 and 4.

Table 3: Percentage of U.S. Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Local Reaction	**Prevnar 13** (N^b=1375-1612)	**Prevnar** (N^b=516-606)	**Prevnar 13** (N^b=1069-1331)	**Prevnar** (N^b=405-510)	**Prevnar 13** (N^b=998-1206)	**Prevnar** (N^b=348-446)	**Prevnar 13** (N^b=874-1060)	**Prevnar** (N^b=283-379)
Redness[c]								
Any	24.3	26.0	33.3	29.7	37.1	36.6	42.3	45.5
Mild	23.1	25.2	31.9	28.7	35.3	35.3	39.5	42.7
Moderate	2.2	1.5	2.7	2.2	4.6	5.1	9.6	13.4*
Severe	0	0	0	0	0	0	0	0
Swelling[c]								
Any	20.1	20.7	25.2	22.5	26.8	28.4	31.6	36.0*
Mild	17.2	18.7	23.8	20.5	25.2	27.5	29.4	33.8
Moderate	4.9	3.9	3.7	4.9	3.8	5.8	8.3	11.2*
Severe	0	0	0.1	0	0	0	0	0
Tenderness								
Any	62.5	64.5	64.7	62.9	59.2	60.8	57.8	62.5
Interferes with limb movement	10.4	9.6	9.0	10.5	8.4	9.0	6.9	5.7

* Statistically significant difference $p < 0.05$

[a] Data are from three primary U.S. safety studies (the U.S. phase II infant study, the pivotal U.S. non-inferiority study, and the U.S. consistency study). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

[b] Number of subjects reporting Yes for at least 1 day or No for all days.

[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of induration and erythema were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

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Table 4: Percentage of U.S. Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a,b]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Systemic Events	**Prevnar 13** (N^a=1360-1707)	**Prevnar** (N^a=497-640)	**Prevnar 13** (N^a=1084-1469)	**Prevnar** (N^a=409-555)	**Prevnar 13** (N^a=997-1361)	**Prevnar** (N^a=354-521)	**Prevnar 13** (N^a=850-1227)	**Prevnar** (N^a=278-436)
Fever[c]								
Any	24.3	22.1	36.5	32.8	30.3	31.6	31.9	30.6
Mild	23.6	21.7	34.9	31.6	29.1	30.2	30.3	30.0
Moderate	1.1	0.6	3.4	2.8	4.2	3.3	4.4	4.6
Severe	0.1	0.2	0.1	0.3	0.1	0.7	1.0	0
Decreased appetite	48.3	43.6	47.8	43.6	47.6	47.6	51.0	49.4
Irritability	85.6	83.6	84.8	80.4	79.8	80.8	80.4	77.8
Increased sleep	71.5	71.5	66.6	63.4	57.7	55.2	48.7	55.1
Decreased sleep	42.5	40.6	45.6	43.7	46.5	47.7	45.3	40.3

[a] Number of subjects reporting Yes for at least 1 day or No for all days.
[b] Data are from three primary U.S. safety studies (the U.S. phase II infant study, the pivotal U.S. non-inferiority study, and the U.S. consistency study). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.
[c] Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (> 40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 62 to 75% of subjects after any of the 4 doses. There were no statistical differences between the Prevnar 13 and Prevnar groups.

Unsolicited Adverse Reactions in the Three U.S. Infant and Toddler Safety Studies

The following were determined to be adverse drug reactions based on experience with Prevnar 13 in clinical trials:

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 a catch-up study conducted in Poland, 354 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.

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 Vaccination[a]

	7 through 11 months			12 through 23 months		24 months through 5 years
Graded Local Reaction	**Dose 1** N[b]=86 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-82 %	**Dose 1** N[b]=108-110 %	**Dose 2** N[b]=98-106 %	**Dose 1** N[b]=147-149 %
Redness[c]						
Any	48.8	46.0	37.8	70.0	54.7	50.0
Mild	41.9	40.2	31.3	55.5	44.7	37.4
Moderate	16.3	9.3	12.5	38.2	25.5	25.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Swelling[c]						
Any	36.0	32.2	25.0	44.5	41.0	36.9
Mild	32.6	28.7	20.5	36.7	36.2	28.2
Moderate	11.6	14.0	11.3	24.8	12.1	20.3
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness						
Any	15.1	15.1	15.2	33.3	43.7	42.3
Interferes with limb movement	1.2	3.5	6.4	0.0	4.1	4.1

[a] Study conducted in Poland.
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

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 Vaccination[a]

	7 through 11 months			12 through 23 months		24 months through 5 years
Systemic Reaction	**Dose 1** N[b]=86-87 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-81 %	**Dose 1** N[b]=108 %	**Dose 2** N[b]=98-100 %	**Dose 1** N[b]=147-148 %
Fever[c]						
Mild	3.4	8.1	5.1	3.7	5.1	0.7
Moderate	1.2	2.3	1.3	0.9	0.0	0.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Decreased appetite	19.5	17.2	17.5	22.2	25.5	16.3
Irritability	24.1	34.5	24.7	30.6	34.0	14.3
Increased sleep	9.2	9.3	2.6	13.0	10.1	11.6
Decreased sleep	24.1	18.4	15.0	19.4	20.4	6.8

[a] Study conducted in Poland.
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (> 40°C). No other systemic event other than fever was graded.

A U.S. study evaluated the use of Prevnar 13 in children previously immunized with Prevnar. In this open label trial, 284 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 (75.0%), 15.8% were Black or African-American, and 1.6% were Asian; 86.6% of subjects were non-Hispanic and non-Latino and 13.4% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 15 months through 59 months of age are shown in Tables 7 and 8.

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

	15 months through 23 months[a]		24 months through 59 months[b]
Graded Local Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[c]=28-32 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[c]=62-76 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[c]=138-155 %
Redness[d]			
Any	46.9	36.6	34.9
Mild	31.0	31.4	31.5
Moderate	22.6	7.9	9.9
Severe	0.0	0.0	0.0
Swelling[d]			
Any	35.5	21.2	22.2
Mild	26.7	18.8	20.3
Moderate	13.8	7.7	5.7
Severe	0.0	0.0	0.0
Tenderness			
Any	53.1	50.0	61.9
Interferes with limb movement	10.3	6.3	10.6

[a] Dose 2 data not shown.
[b] The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.
[c] Number of subjects reporting Yes for at least 1 day or No for all days.
[d] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

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

	15 through 23 months[a]		24 months through 59 months[b]
Systemic Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[c]=28-33 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[c]=62-75 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[c]=138-151 %
Fever[d]			
Mild	10.7	18.8	5.1
Moderate	7.1	3.2	0.7
Severe	0.0	0.0	0.7
Decreased appetite	56.7	36.2	24.8
Irritability	66.7	57.3	39.7
Increased sleep	30.0	33.8	15.9
Decreased sleep	22.6	22.7	14.0

[a] Dose 2 data not shown.
[b] The data for this age group are only represented as a single result as 95 % of children received 4 doses of Prevnar prior to enrollment.
[c] Number of subjects reporting Yes for at least 1 day or No for all days.
[d] Fever gradings: Mild (≥38ºC but ≤39ºC), Moderate (>39ºC but ≤40ºC), and Severe (> 40ºC). No other systemic event other than fever was graded.

6.2 Clinical Trials Experience With Prevnar®

The safety experience with Prevnar is relevant to Prevnar 13 because the two vaccines share common components.

Generally, the adverse reactions reported in clinical trials with Prevnar 13 were also reported in clinical trials with Prevnar.

Overall, the safety of Prevnar was evaluated in a total of five clinical studies in the U.S. in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age.

Adverse events reported in clinical trials with Prevnar include:

Bronchiolitis, UTI, acute gastroenteritis, asthma, aspiration, breath holding, influenza, inguinal hernia repair, viral syndrome, URI, croup, thrush, wheezing, choking, conjunctivitis, pharyngitis, colic, colitis, congestive heart failure, roseola, sepsis.

6.3 Post-marketing Experience With Prevnar

The following adverse reactions have been reported through passive surveillance since market introduction of Prevnar and therefore, are considered adverse reactions for Prevnar 13 as well. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate its frequency or establish a causal relationship to the vaccine.

Administrative site conditions: Injection-site dermatitis, injection-site pruritus, injection-site urticaria

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

Immune system disorders: Anaphylactic/anaphylactoid reaction including shock

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apnea

The safety of Prevnar given concomitantly with other vaccines as part of routine care was assessed in a three-year observational study performed at Northern California Kaiser Permanente in which 65,927 children received three doses of Prevnar in the first year of life. Primary safety outcomes analyses included an evaluation of pre-defined adverse events occurring in temporal relationship to immunization. Rates of adverse events occurring within various time periods post-vaccination (e.g., 0-2, 0-7, 0-14, and 0-30 days) were compared to the rates of those events occurring within a control time window (i.e., 31-60 days). Secondary safety outcomes analyses included comparisons to a historical control population of infants (1995-1996, N=40,223) prior to the introduction of Prevnar. In addition, the study included extended follow-up of subjects originally enrolled in the NCKP efficacy trial (N=37,866).

The primary safety outcomes analyses did not demonstrate a consistently elevated risk of healthcare utilization for croup, gastroenteritis, allergic reactions, seizures, wheezing diagnoses, or breath-holding across doses, healthcare settings, or multiple time windows. As in prelicensure trials, fever was associated with Prevnar administration. In analyses of secondary safety outcomes, the adjusted relative risk of hospitalization for reactive airways disease was 1.23 (95% CI: 1.11, 1.35). Potential confounders, such as differences in concomitantly administered vaccines, yearly variation in respiratory infections, or secular trends in reactive airways disease incidence, could not be controlled. Extended follow-up of subjects originally enrolled in the NCKP efficacy trial revealed no increased risk of reactive airways disease among Prevnar recipients. In general, the study results support the previously described safety profile of Prevnar.

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

In clinical trials, Prevnar 13 was administered concomitantly with the following U.S. licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first three doses and with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A vaccine, Inactivated] (HepA) for dose 4 *[see Clinical Studies (14.2)]*.

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

Children 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Prevnar 13. It is also not known whether Prevnar 13 can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

8.4 Pediatric Use

Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks or on or after the 6^{th} birthday have not been established. Prevnar 13 is not approved for use in children in these age groups *[see Dosage and Administration (2)]*.

Immune responses elicited by Prevnar 13 among infants born prematurely have not been specifically studied.

8.5 Geriatric Use

The safety and effectiveness of Prevnar 13 in geriatric populations have not been established.

Prevnar 13 is not to be used as a substitute for 23-valent pneumococcal polysaccharide vaccine (PPV23) in geriatric populations.

10 OVERDOSAGE

Overdose with Prevnar 13 is unlikely due to its presentation as a pre-filled syringe. However, there have been reports of overdose with Prevnar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those which have been reported with doses given in the recommended schedules of Prevnar 13.

11 DESCRIPTION

Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM_{197} protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides, which are directly conjugated by reductive amination to the protein carrier CRM_{197}, to form the glycoconjugate. CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

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 of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer and 125 µg aluminum as aluminum phosphate adjuvant.

The tip cap and rubber plunger of the pre-filled syringe do not contain latex.

12 CLINICAL PHARMACOLOGY

A serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL measured one month after the third dose as a single antibody reference concentration was used to estimate the effectiveness of Prevnar 13 against IPD. 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 or the investigational 9-valent CRM_{197} 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 opsonophagocytic assay [OPA]) were also evaluated.

12.1 Mechanism of Action

B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. Prevnar 13, comprised of polysaccharides conjugated to a carrier protein, elicits a T-cell dependent immune response. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. This type of response induces immune memory and elicits booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Prevnar 13 has not been evaluated for any carcinogenic or mutagenic potential, or impairment of fertility.

14 CLINICAL STUDIES

14.1 Prevnar Efficacy Data

Invasive Pneumococcal Disease (IPD)

Prevnar was licensed in the U.S. in 2000, following a randomized, double-blind clinical trial in a multiethnic 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 (an investigational meningococcal group C conjugate vaccine [MnCC]) 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 analysis and 93.9% in the intent-to-treat analysis (95% CI: 82.7% - 99.9% and 79.6% - 98.5%, respectively).

Acute Otitis Media (AOM)

The efficacy of Prevnar against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the pivotal-efficacy trial in U.S. 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 Recombivax HB

(Hepatitis B vaccine (Recombinant) [Hep 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 the 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 receive either Prevnar (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. 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, 19A, 23A), 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 tympanostomy 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 MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

14.2 Evaluation of Prevnar 13 Effectiveness

Prevnar 13 effectiveness against invasive pneumococcal disease was inferred from comparative studies to a U.S. licensed 7-valent pneumococcal conjugate vaccine, Prevnar, in which Prevnar 13 elicited immune responses as measured by antipolysaccharide binding and functional OPA antibodies. These studies were designed to evaluate immunologic non-inferiority of Prevnar 13 to Prevnar.

Clinical trials have been conducted in the U.S. using a 2, 4, 6, and 12 to 15 month schedule.

The pivotal U.S. non-inferiority study was a randomized, double-blind, active-controlled trial in which 2 month-old infants were randomly assigned to receive either Prevnar 13 or Prevnar in a 1:1 ratio. The 2 vaccine groups were well balanced with respect to race, ethnicity, and age and weight at enrollment. Most subjects were White (69.1%), 19.6% were Black or African-American, and 2.4% were Asian; 82.1% of subjects were non-Hispanic and non-Latino and 17.3% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

In the pivotal U.S. non-inferiority study, immune responses were compared in subjects receiving either Prevnar 13 or Prevnar using a set of non-inferiority criteria. Co-primary endpoints included the percentage of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 µg/mL measured one month after the third dose and serum pneumococcal anti-capsular polysaccharide IgG geometric mean concentrations (GMCs) one month after the fourth dose. The assay used for this determination was a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. Responses to the 7 common serotypes in Prevnar 13 and Prevnar recipients were compared directly. Responses to the 6 additional serotypes in Prevnar 13 recipients were each compared to the lowest response observed among the Prevnar serotypes in Prevnar recipients.

Pneumococcal Immune Responses Following Three Doses

In the pivotal U.S. non-inferiority study, the non-inferiority criterion for the proportion of subjects with pneumococcal anti-capsular 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 non-inferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥0.35 µg/mL one month after the third dose is shown below (Table 9).

Table 9: Percentage of Subjects With Anti-capsular Antibody Concentration ≥0.35 µg/mL One Month After Dose 3, U.S. Pivotal Non-inferiority Study[*†]

Serotype	**Prevnar 13** N=249-252 (95% CI)	**Prevnar** N=250-252 (95% CI)	**Difference in % responders** (95% CI)
Prevnar Serotypes			
4	94.4 (90.9, 96.9)	98.0 (95.4, 99.4)	-3.6 (-7.3, -0.1)
6B	87.3 (82.5, 91.1)	92.8 (88.9, 95.7)	-5.5 (-10.9, -0.1)
9V	90.5 (86.2, 93.8)	98.4 (96.0, 99.6)	-7.9 (-12.4, -4.0)
14	97.6 (94.9, 99.1)	97.2 (94.4, 98.9)	0.4 (-2.7, 3.5)
18C	96.8 (93.8, 98.6)	98.4 (96.0, 99.6)	-1.6 (-4.7, 1.2)
19F	98.0 (95.4, 99.4)	97.6 (99.4, 99.1)	0.4 (-2.4, 3.4)
23F	90.5 (86.2, 93.8)	94.0 (90.4, 96.6)	-3.6 (-8.5, 1.2)

Table 9: Percentage of Subjects With Anti-capsular Antibody Concentration ≥0.35 µg/mL One Month After Dose 3, U.S. Pivotal Non-inferiority Study[*†]

Serotype	Prevnar 13 N=249-252 (95% CI)	Prevnar N=250-252 (95% CI)	Difference in % responders (95% CI)
Additional Serotypes[††]			
1	95.6 (92.3, 97.8)	††	2.8 (-1.3, 7.2)
3	63.5 (57.1, 69.4)	††	-29.3 (-36.2, -22.4)
5	89.7 (85.2, 93.1)	††	-3.1 (-8.3, 1.9)
6A	96.0 (92.8, 98.1)	††	3.2 (-0.8, 7.6)
7F	98.4 (96.0, 99.6)	††	5.6 (1.9, 9.7)
19A	98.4 (96.0, 99.6)	††	5.6 (1.9, 9.7)

* Non-inferiority was met when the lower bound of the 95% CI for the difference between groups (Prevnar 13 minus Prevnar) was greater than -10%.
† 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 Prevnar recipients, which for this analysis was serotype 6B (92.8%; 95% CI: 88.9, 95.7).

392 Functional OPA antibody responses were elicited for all 13 serotypes, as shown in Table 10.

Table 10: Pneumococcal OPA Geometric Mean Titers One Month After the Third Dose-Evaluable Immunogenicity Population, U.S. Pivotal Non-inferiority Study*

Serotype	Prevnar 13 N=91-94 (95% CI)	Prevnar N=89-94 (95% CI)
Prevnar Serotypes		
4	359 (276, 468)	536 (421, 681)
6B	1055 (817, 1361)	1514 (1207, 1899)
9V	4035 (2933, 5553)	3259 (2288, 4641)
14	1240 (935, 1646)	1481 (1133, 1934)
18C	276 (210, 361)	376 (292, 484)
19F	54 (40, 74)	45 (34, 60)
23F	791 (605, 1034)	924 (709, 1204)

Table 10: Pneumococcal OPA Geometric Mean Titers One Month After the Third Dose-Evaluable Immunogenicity Population, U.S. Pivotal Non-inferiority Study*

Serotype	Prevnar 13 N=91-94 (95% CI)	Prevnar N=89-94 (95% CI)
Additional Serotypes		
1	52 (39, 69)	4 (4, 5)
3	121 (92, 158)	7 (5, 9)
5	91 (67, 123)	4 (4, 4)
6A	980 (783, 1226)	100 (66, 152)
7F	9494 (7339, 12281)	128 (80, 206)
19A	152 (105, 220)	7 (5, 9)

* The OPA (opsonophagocytic activity) assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.

Pneumococcal Immune Responses Following Four Doses

In the pivotal U.S. non-inferiority study, post-dose 4 antibody concentrations were higher for all 13 serotypes than those achieved after the third dose. The non-inferiority criterion for pneumococcal anti-capsular polysaccharide GMCs after 4 doses was met for 12 of the 13 pneumococcal serotypes. The non-inferiority criterion was not met for the response to serotype 3 (Table 11).

Table 11: Pneumococcal IgG GMCs (µg/mL) One Month After Dose 4, U.S. Pivotal Non-inferiority Study*†

Serotype	Prevnar 13 N=232-236 (95% CI)	Prevnar N=222-223 (95% CI)	GMC Ratio (95% CI)
Prevnar Serotypes			
4	3.73 (3.28, 4.24)	5.49 (4.91, 6.13)	0.68 (0.57, 0.80)
6B	11.53 (9.99, 13.30)	15.63 (13.80, 17.69)	0.74 (0.61, 0.89)
9V	2.62 (2.34, 2.94)	3.63 (3.25, 4.05)	0.72 (0.62, 0.85)
14	9.11 (7.95, 10.45)	12.72 (11.22, 14.41)	0.72 (0.60, 0.86)
18C	3.20 (2.82, 3.64)	4.70 (4.18, 5.28)	0.68 (0.57, 0.81)
19F	6.60 (5.85, 7.44)	5.60 (4.87, 6.43)	1.18 (0.98, 1.41)
23F	5.07 (4.41, 5.83)	7.84 (6.91, 8.90)	0.65 (0.54, 0.78)

Table 11: Pneumococcal IgG GMCs (µg/mL) One Month After Dose 4, U.S. Pivotal Non-inferiority Study[*†]

Serotype	Prevnar 13 N=232-236 (95% CI)	Prevnar N=222-223 (95% CI)	GMC Ratio (95% CI)
Additional Serotypes[††]			
1	5.06 (4.43, 5.80)	††	1.40 (1.17, 1.66)
3	0.94 (0.83, 1.05)	††	0.26 (0.22, 0.30)
5	3.72 (3.31, 4.18)	††	1.03 (0.87, 1.20)
6A	8.20 (7.30, 9.20)	††	2.26 (1.93, 2.65)
7F	5.67 (5.01, 6.42)	††	1.56 (1.32, 1.85)
19A	8.55 (7.64, 9.56)	††	2.36 (2.01, 2.76)

***** Non-inferiority was declared if the lower limit of the 2-sided 95% CI for Geometric Mean Ratio (Prevnar 13:Prevnar) was greater than 0.5.
† 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 Prevnar recipients, which for this analysis was serotype 9V (3.63; 95% CI 3.25, 4.05).

Following the 4th dose, the functional OPA response for each serotype was quantitatively greater than the response following the 3rd dose (see Table 12).

Table 12: Pneumococcal OPA Geometric Mean Titers One Month After the Fourth Dose-Evaluable Toddler Immunogenicity Population, U.S. Pivotal Non-inferiority Study*

Serotype	Prevnar 13 N=88-92 (95% CI)	Prevnar N=92-96 (95% CI)
Prevnar Serotypes		
4	1180 (847, 1643)	1492 (1114, 1999)
6B	3100 (2337, 4111)	4066 (3243, 5098)
9V	11856 (8810, 15955)	18032 (14125, 23021)
14	2002 (1453, 2760)	2366 (1871, 2992)
18C	993 (754, 1308)	1722 (1327, 2236)
19F	200 (144, 276)	167 (121, 230)
23F	2723 (1961, 3782)	4982 (3886, 6387)

Table 12: Pneumococcal OPA Geometric Mean Titers One Month After the Fourth Dose-Evaluable Toddler Immunogenicity Population, U.S. Pivotal Non-inferiority Study*

Serotype	Prevnar 13 N=88-92 (95% CI)	Prevnar N=92-96 (95% CI)
Additional Serotypes		
1	164 (114, 237)	5 (4, 6)
3	380 (300, 482)	12 (9, 16)
5	300 (229, 393)	5 (4, 6)
6A	2242 (1707, 2945)	539 (375, 774)
7F	11629 (9054, 14938)	268 (165, 436)
19A	1024 (774, 1355)	29 (19, 44)

* The OPA (opsonophagocytic activity) assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.

Simultaneous Administration With Other Vaccines

The concomitant administration of routine U.S. infant vaccines *[see Drug Interactions (7.1)]* with Prevnar 13 was evaluated in two studies: the U.S. pivotal non-inferiority study *[see Clinical Studies (14.2)*, *Pneumococcal Immune Responses Following Three Doses]* and the U.S. lot consistency study. In the lot consistency study, 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 (U.S. non-inferiority study) and 1699 (U.S. lot consistency study). 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.

Previously Unvaccinated Older Infants and Children

In an open-label descriptive study of Prevnar 13 in Poland, children 7 through 11 months of age, 12 through 23 months of age and 24 months through 5 years of age (prior to the 6th birthday) who were naïve to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevnar 13 respectively, according to the age-appropriate schedules in Table 1. Serum IgG concentrations were measured one month after the final dose in each age group and the data are shown in Table 13.

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

Serotype	3 doses Prevnar 13 7 through 11 months N=83-84 (95% CI)	2 doses Prevnar 13 12 through 23 months N=104-110 (95% CI)	1 dose Prevnar 13 24 months through 5 years N=135-152 (95% CI)
1	2.88 (2.44, 3.39)	2.74 (2.37, 3.16)	1.78 (1.52, 2.08)
3	1.94 (1.68, 2.24)	1.86 (1.60, 2.15)	1.42 (1.23, 1.64)
4	3.63 (3.11, 4.23)	4.28 (3.78, 4.86)	3.37 (2.95, 3.85)
5	2.85 (2.34, 3.46)	2.16 (1.89, 2.47)	2.33 (2.05, 2.64)
6A	3.72 (3.12, 4.45)	2.62 (2.25, 3.06)	2.96 (2.52, 3.47)
6B	4.77 (3.90, 5.84)	3.38 (2.81, 4.06)	3.41 (2.80, 4.16)
7F	5.30 (4.54, 6.18)	5.99 (5.40, 6.65)	4.92 (4.26, 5.68)
9V	2.56 (2.21, 2.96)	3.08 (2.69, 3.53)	2.67 (2.32, 3.07)
14	8.04 (6.95, 9.30)	6.45 (5.48, 7.59)	2.24 (1.71, 2.93)
18C	2.77 (2.39, 3.23)	3.71 (3.29, 7.19)	2.56 (2.17, 3.03)
19A	4.77 (4.28, 5.33)	4.94 (4.31, 5.65)	6.03 (5.22, 6.97)
19F	2.88 (2.35, 3.54)	3.07 (2.68, 3.51)	2.53 (2.14, 2.99)
23F	2.16 (1.82, 2.55)	1.98 (1.64, 2.39)	1.55 (1.31, 1.85)

Children Previously Vaccinated with Prevnar

In an open-label descriptive study in the U.S., children previously vaccinated with 3 or 4 doses of Prevnar, received 2 doses of Prevnar 13 (children 15 through 23 months of age) or 1 dose of Prevnar 13 (children 24 months through 59 months of age). The data following one dose of Prevnar 13 in children 24 months through 59 months of age are shown in Table 14.

Table 14: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After One Prevnar 13 Catch-Up Dose in Children 24 through 59 Months of Age With 3 or 4 Prior Doses of Prevnar, U.S. Catch-Up Study

Serotype	1 dose Prevnar 13 24 months through 59 months N=173-175 (95% CI)
1	2.43 (2.15, 2.75)
3	1.38 (1.17, 1.61)
5	2.13 (1.89, 2.41)
6A	12.96 (11.04, 15.21)
7F	4.22 (3.74, 4.77)
19A	14.18 (12.37, 16.25)

16 HOW SUPPLIED/STORAGE AND HANDLING

Pre-filled Syringe, 1 Dose (10 per package) – NDC 0005-1971-02.

Store refrigerated at +2ºC to +8ºC (36ºF to 46ºF).

The tip cap and rubber plunger of the pre-filled syringe do not contain latex.

Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

17.1 Potential Benefits and Risks

Prior to administration of this vaccine, the healthcare professional should inform the parent, guardian, or other responsible adult of the potential benefits and risks to the patient *[see Warnings and Precautions (5) and Adverse Reactions (6)]*, and the importance of completing the immunization series unless contraindicated.

17.2 Adverse Reactions

Instruct parents, guardians, or other responsible adults to report any suspected adverse reactions to their healthcare professional.

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(Update W10543C003)
(Update ET01)
(Update Rev Date)

CPT Code 90670
United States Patent Number: 5,614,382.