

5 **Pneumococcal 7-valent Conjugate Vaccine
(Diphtheria CRM₁₉₇ Protein)**

Pprevnar[®]

10 **Rx only**

For Intramuscular Injection Only

15 **DESCRIPTION**

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein), Pprevnar[®], is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ 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 to the protein carrier CRM₁₉₇ to form the glycoconjugate. This is effected by reductive amination. CRM₁₉₇ 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. CRM₁₉₇ is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and are analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

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30 The individual glycoconjugates are compounded to formulate the vaccine, Pprevnar[®]. 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.

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35 Prevnar[®] is manufactured as a liquid preparation. Each 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide); approximately 20 µg of CRM₁₉₇ carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant.

40 After shaking, the vaccine is a homogeneous, white suspension.

CLINICAL PHARMACOLOGY

S. pneumoniae is an important cause of morbidity and mortality in persons of all ages
45 worldwide. The organism causes invasive infections, such as bacteremia and meningitis, as well as pneumonia and upper respiratory tract infections including otitis media and sinusitis. In children older than 1 month, *S. pneumoniae* is the most common cause of invasive disease.¹ Data from community-based studies performed between 1986 and 1995, indicate that the overall annual incidence of invasive pneumococcal disease in the
50 United States (US) is an estimated 10 to 30 cases per 100,000 persons, with the highest risk in children aged less than or equal to 2 years of age (140 to 160 cases per 100,000 persons).^{2,3,4,5,6} Children in group child care have an increased risk for invasive pneumococcal disease.^{7,8} Immunocompromised individuals with neutropenia, asplenia, sickle cell disease, disorders of complement and humoral immunity, human
55 immunodeficiency virus (HIV) infections or chronic underlying disease are also at increased risk for invasive pneumococcal disease.⁸ *S. pneumoniae* is the most common cause of bacterial meningitis in the US.¹ The annual incidence of pneumococcal meningitis in children between 1 to 23 months of age is approximately 7 cases per 100,000 persons.¹ Pneumococcal meningitis in childhood has been associated with 8%
60 mortality and may result in neurological sequelae (25%) and hearing loss (32%) in survivors.⁹

Acute otitis media (AOM) is a common childhood disease, with more than 60% of children experiencing an episode by one year of age, and more than 90% of children
65 experiencing an episode by age 5. Prior to the US introduction of Prevnar[®] in the year 2000, approximately 24.5 million ambulatory care visits and 490,000 procedures for

myringotomy with tube placement were attributed to otitis media annually.^{10,11} The peak incidence of AOM is 6 to 18 months of age.¹² Otitis media is less common, but occurs, in older children. In a 1990 surveillance by the Centers for Disease Control and
70 Prevention (CDC), otitis media was the most common principal illness diagnosis in children 2-10 years of age.¹³ Complications of AOM include persistent middle ear effusion, chronic otitis media, transient hearing loss, or speech delays and, if left untreated, may lead to more serious diseases such as mastoiditis and meningitis. *S. pneumoniae* is an important cause of AOM. It is the bacterial pathogen most commonly
75 isolated from middle ear fluid, identified in 20% to 40% of middle ear fluid cultures in AOM.^{14,15} Pneumococcal otitis media is associated with higher rates of fever, and is less likely to resolve spontaneously than AOM due to either nontypeable *H. influenzae* or *M. catarrhalis*.^{16,17} Prior to the introduction of Prevnar[®], the seven serotypes contained in the vaccine accounted for approximately 60% of AOM due to *S. pneumoniae* (12%-24%
80 of all AOM).¹⁸

The exact contribution of *S. pneumoniae* to childhood pneumonia is unknown, as it is often not possible to identify the causative organisms. In studies of children less than 5 years of age with community-acquired pneumonia, where diagnosis was attempted using
85 serological methods, antigen testing, or culture data, 30% of cases were classified as bacterial pneumonia, and 70% of these (21% of total community-acquired pneumonia) were found to be due to *S. pneumoniae*.^{19,20}

In the past decade the proportion of *S. pneumoniae* isolates resistant to antibiotics has
90 been on the rise in the US and worldwide. In a multi-center US surveillance study, the prevalence of penicillin and cephalosporin-nonsusceptible (intermediate or high level resistance) invasive disease isolates from children was 21% (range <5% to 38% among centers), and 9.3% (range 0%-18%), respectively. Over the 3-year surveillance period (1993-1996), there was a 50% increase in penicillin-nonsusceptible *S. pneumoniae*
95 (PNSP) strains and a three-fold rise in cephalosporin-nonsusceptible strains.⁸ Although generally less common than PNSP, pneumococci resistant to macrolides and trimethoprim-sulfamethoxazole have also been observed.⁴ Day care attendance, a history of ear infection, and a recent history of antibiotic exposure, have also been associated

with invasive infections with PNSP in children 2 months to 59 months of age.^{7,8} There
100 has been no difference in mortality associated with PNSP strains.^{8,9} However, the
American Academy of Pediatrics (AAP) revised the antibiotic treatment guidelines in
1997 in response to the increased prevalence of antibiotic-resistant pneumococci.²¹

Approximately 90 serotypes of *S. pneumoniae* have been identified based on antigenic
105 differences in their capsular polysaccharides. The distribution of serotypes responsible
for disease differ with age and geographic location.²²

Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F have been responsible for approximately
80% of invasive pneumococcal disease in children <6 years of age in the US.¹⁸ These 7
110 serotypes also accounted for 74% of PNSP and 100% of pneumococci with high level
penicillin resistance isolated from children <6 years with invasive disease during a 1993-
1994 surveillance by the CDC.²³

Results of Clinical Evaluations

Efficacy Against Invasive Disease

115 Efficacy was assessed in a randomized, double-blinded 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. Prevnar[®] was administered to 18,906 children and the
120 control vaccine to 18,910 children. Routinely recommended vaccines were also
administered which changed during the trial to reflect changing AAP and Advisory
Committee on Immunization Practices (ACIP) recommendations. A planned interim
analysis was performed upon accrual of 17 cases of invasive disease due to vaccine-type *S.*
pneumoniae (August 1998). Ancillary endpoints for evaluation of efficacy against
125 pneumococcal disease were also assessed in this trial.

Invasive disease was defined as isolation and identification of *S. pneumoniae* from
normally sterile body sites in children presenting with an acute illness consistent with
pneumococcal disease. Weekly surveillance of listings of cultures from the NCKP
Regional Microbiology database was conducted to assure ascertainment of all cases. The
130 primary endpoint was efficacy against invasive pneumococcal disease due to vaccine
serotypes. The per protocol analysis of the primary endpoint included cases which
occurred ≥ 14 days after the third dose. The intent-to-treat (ITT) analysis included all
cases of invasive pneumococcal disease due to vaccine serotypes in children who
received at least one dose of vaccine. Secondary analyses of efficacy against all invasive
135 pneumococcal disease, regardless of serotype, were also performed according to these
same per protocol and ITT definitions. Results of these analyses are presented in Table 1.

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TABLE 1
Efficacy of Pevnar[®] Against Invasive Disease Due to *S. pneumoniae*
in Cases Accrued From October 15, 1995 Through August 20, 1998^{24,25}

	Pevnar[®] Number of Cases	Control* Number of Cases	Efficacy	95% CI
Vaccine serotypes				
Per protocol	0	17	100%	75.4, 100
Intent-to-treat	0	22	100%	81.7, 100
All pneumococcal serotypes				
Per protocol	2	20	90.0%	58.3, 98.9
Intent-to-treat	3	27†	88.9%	63.8, 97.9

*Investigational meningococcal group C conjugate vaccine (MnCC).

†Includes one case in an immunocompromised subject.

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All 22 cases of invasive disease due to vaccine serotype strains in the ITT population were bacteremic. In addition, the following diagnoses were also reported: meningitis (2), pneumonia (2), and cellulitis (1).

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Data accumulated through an extended follow-up period to April 20, 1999, resulted in a similar efficacy estimate (Per protocol: 1 case in Pevnar[®] group, 39 cases in control group; ITT: 3 cases in Pevnar[®] group, 49 cases in the control group).²⁵

Efficacy Against Otitis Media

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The efficacy of Pevnar[®] against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the invasive disease efficacy trial in US infants at Northern California Kaiser Permanente (NCKP).

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The trial in Finland was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either Pevnar[®] or a control vaccine (Hepatitis B vaccine [Hep B]) at 2, 4, 6, and 12-15 months of age. All infants received a DTP-Hib combination vaccine concurrently at 2, 4, and 6 months of age, and Inactivated Poliovirus

Vaccine (IPV) concurrently at 12 months of age. 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.

AOM was defined as a visually abnormal tympanic membrane suggesting effusion in the middle ear cavity, concomitantly with at least one of the following symptoms of acute infection: fever, ear ache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection. A new visit or “episode” was defined as a visit with a study physician at which time a diagnosis of AOM was made and at least 30 days had elapsed since any previous visit for otitis media. The primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per protocol population.

In the NCKP invasive disease efficacy trial, the effectiveness of Prevnar[®] in reducing the incidence of otitis media was assessed from the beginning of the trial in October 1995 through April 1998. During this time, 34,146 infants were randomized to receive either Prevnar[®] (N=17,070), or the control, an investigational meningococcal group C conjugate vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age.

Physician visits for otitis media were identified by physician coding of outpatient encounter forms. Because visits may have included both acute and follow-up care, a new visit or “episode” was defined as a visit that was at least 21 days following a previous visit for otitis media (at least 42 days, if the visit appointment was made > 3 days in advance). Data on placement of ear tubes were collected from automated databases. 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.

Table 2 presents the per protocol and intent-to-treat results of key otitis media analyses for both studies. The per protocol analyses include otitis media episodes that occurred

≥14 days after the third dose. The intent-to-treat analyses include all otitis media episodes in children who received at least one dose of vaccine.

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TABLE 2
Efficacy of Prevnar[®] Against Otitis Media in the Finnish and NCKP Trials^{24,25,26,27}

	Per Protocol		Intent-to-Treat	
	Vaccine Efficacy Estimate*	95% Confidence Interval	Vaccine Efficacy Estimate*	95% Confidence Interval
Finnish Trial	N=1632		N=1662	
AOM due to Vaccine Serotypes	57%	44, 67	54%	41, 64
All culture-confirmed pneumococcal AOM regardless of serotype	34%	21, 45	32%	19, 42
NCKP Trial	N=23,746		N=34,146	
All Otitis Media Episodes regardless of etiology†	7%	4, 10	6%	4, 9

* All vaccine efficacy estimates in the table are statistically significant.

† The vaccine efficacy against all AOM episodes in the Finnish trial, while not reaching statistical significance, was 6% (95% CI: -4, 16) in the per protocol population and 4% (95% CI: -7, 14) in the intent-to-treat population.

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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. The vaccine efficacy against AOM episodes caused by serotypes unrelated to the vaccine was -33% (95% CI: -80, 1) in the per protocol population and -39% (95% CI: -86, -3) in the intent-to-treat population, indicating that children who received Prevnar[®] appear to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine, compared to children who received the control vaccine. However, vaccination with Prevnar[®] reduced pneumococcal otitis media episodes overall.

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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. This observation was supported by a similar trend, although not statistically significant, seen in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of

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tympanostomy tubes in the per protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population.

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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.²⁸

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Immunogenicity

Routine Schedule

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Subjects from a subset of selected study sites in the NCKP efficacy study were approached for participation in the immunogenicity portion of the study on a volunteer basis. Immune responses following three or four doses of Prevnar[®] or the control vaccine were evaluated in children who received either concurrent Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate), (DTP-HbOC), or Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), and Haemophilus b Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate), (HbOC) vaccines at 2, 4, and 6 months of age. The use of Hepatitis B (Hep B), Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV), Measles-Mumps-Rubella (MMR), and Varicella vaccines were permitted according to the AAP and ACIP recommendations.

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Table 3 presents the geometric mean concentrations (GMC) of pneumococcal antibodies following the third and fourth doses of Prevnar[®] or the control vaccine when administered concurrently with DTP-HbOC vaccine in the efficacy study.

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TABLE 3
Geometric Mean Concentrations ($\mu\text{g}/\text{mL}$) of Pneumococcal Antibodies Following the Third and Fourth Doses of Pevnar[®] or Control* When Administered Concurrently With DTP-HbOC in the Efficacy Study^{24,25}

Serotype	Post dose 3 GMC [†] (95% CI for Pevnar [®])		Post dose 4 GMC [‡] (95% CI for Pevnar [®])	
	Pevnar [®] §	Control*	Pevnar [®] §	Control*
	N=88	N=92	N=68	N=61
4	1.46 (1.19, 1.78)	0.03	2.38 (1.88, 3.03)	0.04
6B	4.70 (3.59, 6.14)	0.08	14.45 (11.17, 18.69)	0.17
9V	1.99 (1.64, 2.42)	0.05	3.51 (2.75, 4.48)	0.06
14	4.60 (3.70, 5.74)	0.05	6.52 (5.18, 8.21)	0.06
18C	2.16 (1.73, 2.69)	0.04	3.43 (2.70, 4.37)	0.07
19F	1.39 (1.16, 1.68)	0.09	2.07 (1.66, 2.57)	0.18
23F	1.85 (1.46, 2.34)	0.05	3.82 (2.85, 5.11)	0.09

* Control was investigational meningococcal group C conjugate vaccine (MnCC).

[†] Mean age of Pevnar[®] group was 7.8 months and of control group was 7.7 months.
N is slightly less for some serotypes in each group.

[‡] Mean age of Pevnar[®] group was 14.2 months and of control group was 14.4 months.
N is slightly less for some serotypes in each group.

§ $p < 0.001$ when Pevnar[®] compared to control for each serotype using a Wilcoxon's test.

In another randomized study (Manufacturing Bridging Study, 118-16), immune responses were evaluated following three doses of Pevnar[®] administered concomitantly with DTaP and HbOC vaccines at 2, 4, and 6 months of age, IPV at 2 and 4 months of age, and Hep B at 2 and 6 months of age. The control group received concomitant vaccines only. Table 4 presents the immune responses to pneumococcal polysaccharides observed in both this study and in the subset of subjects from the efficacy study that received concomitant DTaP and HbOC vaccines.

TABLE 4
Geometric Mean Concentrations ($\mu\text{g}/\text{mL}$) of Pneumococcal Antibodies Following the Third Dose of Prevnar[®] or Control* When Administered Concurrently With DTaP and HbOC in the Efficacy Study[†] and Manufacturing Bridging Study^{24,25,29}

Serotype	Efficacy Study		Manufacturing Bridging Study	
	Post dose 3 GMC [‡] (95% CI for Prevnar [®])		Post dose 3 GMC [§] (95% CI for Prevnar [®])	
	Prevnar [®]	Control*	Prevnar [®]	Control*
	N=32	N=32	N=159	N=83
4	1.47 (1.08, 2.02)	0.02	2.03 (1.75, 2.37)	0.02
6B	2.18 (1.20, 3.96)	0.06	2.97 (2.43, 3.65)	0.07
9V	1.52 (1.04, 2.22)	0.04	1.18 (1.01, 1.39)	0.04
14	5.05 (3.32, 7.70)	0.04	4.64 (3.80, 5.66)	0.04
18C	2.24 (1.65, 3.02)	0.04	1.96 (1.66, 2.30)	0.04
19F	1.54 (1.09, 2.17)	0.10	1.91 (1.63, 2.25)	0.08
23F	1.48 (0.97, 2.25)	0.05	1.71 (1.44, 2.05)	0.05

* Control in efficacy study was investigational meningococcal group C conjugate vaccine (MnCC) and in Manufacturing Bridging Study was concomitant vaccines only.

[†] Sufficient data are not available to reliably assess GMCs following 4 doses of Prevnar[®] when administered with DTaP in the NCKP efficacy study.

[‡] Mean age of the Prevnar[®] group was 7.4 months and of the control group was 7.6 months. N is slightly less for some serotypes in each group.

[§] Mean age of the Prevnar[®] group and the control group was 7.2 months.

^{||} $p < 0.001$ when Prevnar[®] compared to control for each serotype using a Wilcoxon's test in the efficacy study and two-sample t-test in the Manufacturing Bridging Study.

In all studies in which the immune responses to Prevnar[®] were contrasted to control, a significant antibody response was seen to all vaccine serotypes following three or four doses, although geometric mean concentrations of antibody varied among serotypes.

260 ^{24,25,27,29,30,31,32,33,34} The minimum serum antibody concentration necessary for protection against invasive pneumococcal disease or against pneumococcal otitis media has not been determined for any serotype. Prevnar[®] induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following three doses. ³⁴

265 **Previously Unvaccinated Older Infants and Children**

To determine an appropriate schedule for children 7 months of age or older at the time of the first immunization with Prevnar[®], 483 children in 4 ancillary studies received Prevnar[®] at various schedules and were evaluated for immunogenicity. GMCs attained using the various schedules among older infants and children were comparable to

270 immune responses of children, who received concomitant DTaP, in the NCKP efficacy study (118-8) after 3 doses for most serotypes, as shown in Table 5. These data support the schedule for previously unvaccinated older infants and children who are beyond the age of the infant schedule. For usage in older infants and children, see **DOSAGE AND ADMINISTRATION**.

TABLE 5
Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following Immunization of Children From 7 Months Through 9 Years of Age With Prevnar[®] ³⁵

Age group, Vaccinations	Study	Sample Size(s)	4	6B	9V	14	18C	19F	23F
7-11 mo. 3 doses	118-12	22	2.34	3.66	2.11	9.33	2.31	1.60	2.50
	118-16	39	3.60	4.63	2.04	5.48	1.98	2.15	1.93
12-17 mo. 2 doses	118-15*	82-84†	3.91	4.67	1.94	6.92	2.25	3.78	3.29
	118-18	33	7.02	4.25	3.26	6.31	3.60	3.29	2.92
18-23 mo. 2 doses	118-15*	52-54†	3.36	4.92	1.80	6.69	2.65	3.17	2.71
	118-18	45	6.85	3.71	3.86	6.48	3.42	3.86	2.75
24-35 mo. 1 dose	118-18	53	5.34	2.90	3.43	1.88	3.03	4.07	1.56
36-59 mo. 1 dose	118-18	52	6.27	6.40	4.62	5.95	4.08	6.37	2.95
5-9 yrs. 1 dose	118-18	101	6.92	20.84	7.49	19.32	6.72	12.51	11.57
118-8, DTaP	Post dose 3	31-32†	1.47	2.18	1.52	5.05	2.24	1.54	1.48

Bold = GMC not inferior to 118-8, DTaP post dose 3 (one-sided lower limit of the 95% CI of GMC ratio ≥0.50).

* Study in Navajo and Apache populations.

† Numbers vary with serotype.

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INDICATIONS AND USAGE

280 Pevnar[®] is indicated for active immunization of infants and toddlers against invasive disease caused by *S. pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). The routine schedule is 2, 4, 6, and 12-15 months of age.

The decision to administer Pevnar[®] should be based primarily on its efficacy in
285 preventing invasive pneumococcal disease. As with any vaccine, Pevnar[®] may not protect all individuals receiving the vaccine from invasive pneumococcal disease.

Pevnar[®] is also indicated for active immunization of infants and toddlers against otitis media caused by serotypes included in the vaccine. However, for vaccine serotypes,
290 protection against otitis media is expected to be substantially lower than protection against invasive disease. Additionally, because otitis media is caused by many organisms other than serotypes of *S. pneumoniae* represented in the vaccine, protection against all causes of otitis media is expected to be low.

295 (See **CLINICAL PHARMACOLOGY** for estimates of efficacy against invasive disease and otitis media).

For additional information on usage, see **DOSAGE AND ADMINISTRATION**.

300 This vaccine is not intended to be used for treatment of active infection.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to use of this vaccine.

305 The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Although a severe or even a moderate febrile illness is sufficient reason to postpone vaccinations,

310 minor illnesses, such as a mild upper respiratory infection with or without low-grade
fever, are not generally contraindications.^{36,37}

WARNINGS

315 THIS VACCINE WILL NOT PROTECT AGAINST *S. PNEUMONIAE* DISEASE
CAUSED BY SEROTYPES UNRELATED TO THOSE IN THE VACCINE, NOR
WILL IT PROTECT AGAINST OTHER MICROORGANISMS THAT CAUSE
INVASIVE INFECTIONS SUCH AS BACTEREMIA AND MENINGITIS OR NON-
INVASIVE INFECTIONS SUCH AS OTITIS MEDIA.

320 This vaccine should not be given to infants or children with thrombocytopenia or any
coagulation disorder that would contraindicate intramuscular injection unless the
potential benefit clearly outweighs the risk of administration. If the decision is made to
administer this vaccine to children with coagulation disorders, it should be given with
caution. (See **DRUG INTERACTIONS**.)

Immunization with Prevnar[®] does not substitute for routine diphtheria immunization.

325 Healthcare professionals should prescribe and/or administer this product with caution to
patients with a possible history of latex sensitivity since the packaging contains dry
natural rubber.

PRECAUTIONS

330 Prevnar[®] is for intramuscular use only. Prevnar[®] SHOULD UNDER NO
CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY. The safety and
immunogenicity for other routes of administration (eg, subcutaneous) have not been
evaluated.

335 Fever, and rarely febrile seizure, have been reported in children receiving Prevnar[®]. For
children at higher risk of seizures than the general population, acetaminophen or other
appropriate antipyretics (dosed according to respective prescribing information) may be
administered around the time of vaccination, to reduce the possibility of post-vaccination
fever.

General

CARE IS TO BE TAKEN BY THE HEALTHCARE PROFESSIONAL FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT.

- 340 1. PRIOR TO ADMINISTRATION OF ANY DOSE OF THIS VACCINE, THE PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE HEALTHCARE PROFESSIONAL SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH
- 345 STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH THIS VACCINE AND TO ALLOW AN ASSESSMENT OF RISKS AND BENEFITS.
- 350 2. BEFORE THE ADMINISTRATION OF ANY BIOLOGICAL, THE HEALTHCARE PROFESSIONAL SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER ADVERSE REACTIONS. This should include a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control
- 355 of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
- 360 3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.^{36,37, 38} (See **DRUG INTERACTIONS.**)
- 365 4. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children \geq 24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised.

Data on sequential vaccination with Prevnar[®] followed by 23-valent pneumococcal polysaccharide vaccine are limited. In a randomized study, 23 children ≥ 2 years of age with sickle cell disease were administered either 2 doses of Prevnar[®] followed by a dose of polysaccharide vaccine or a single dose of polysaccharide vaccine alone. In
370 this small study, safety and immune responses with the combined schedule were similar to polysaccharide vaccine alone.³⁹

5. Since this product is a suspension containing an aluminum adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension prior to withdrawing the dose.

375 6. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

7. The vaccine is to be administered immediately after being drawn up into a syringe.

380 8. Special care should be taken to prevent injection into or near a blood vessel or nerve.

9. Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since the packaging contains dry natural rubber.

385 **Information for Parents or Guardians**

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 **ADVERSE REACTIONS** and **WARNINGS** sections), and the importance of completing the immunization series unless contraindicated. Parents or guardians
390 should be instructed to report any suspected adverse reactions to their healthcare professional. The healthcare professional should provide vaccine information statements prior to each vaccination.

DRUG INTERACTIONS

395 Children receiving therapy with immunosuppressive agents (large amounts of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.^{37,38,40,41} (See **PRECAUTIONS, General.**)

As with other intramuscular injections, Prevnar[®] should be given with caution to children on anticoagulant therapy.

400 **Simultaneous Administration with Other Vaccines**

During clinical studies, Prevnar[®] was administered simultaneously with DTP-HbOC or DTaP and HbOC, OPV or IPV, Hep B vaccines, MMR, and Varicella vaccine. Thus, the safety experience with Prevnar[®] reflects the use of this product as part of the routine immunization schedule.^{24,25,29,31,32,34}

405

The immune response to routine vaccines when administered with Prevnar[®] (at separate sites) was assessed in 3 clinical studies in which there was a control group for comparison. Results for the concurrent immunizations in infants are shown in Table 6 and for toddlers in Table 7. Enhancement of antibody response to HbOC in the infant series was observed. Some suppression of *Haemophilus influenzae* type b (Hib) response was seen at the 4th dose, but over 97% of children achieved titers ≥ 1 $\mu\text{g/mL}$. Although some inconsistent differences in response to pertussis antigens were observed, the clinical relevance is unknown. The response to 2 doses of IPV given concomitantly with Prevnar[®], assessed 3 months after the second dose, was equivalent to controls for poliovirus Types 2 and 3, but lower for Type 1. MMR and Varicella immunogenicity data from controlled clinical trials with concurrent administration of Prevnar[®] are not available.

415

TABLE 6
Concurrent Administration of Prevnar[®] With Other Vaccines to Infants in
Non-Efficacy Studies^{29,32}

Antigen*	GMC*		% Responders†		Study	Vaccine Schedule‡	N	
	Prevnar [®]	Control§	Prevnar [®]	Control§			(mo.)	Prevnar [®]
Hib	6.2	4.4	99.5, 88.3	97.0, 88.1	118-12	2, 4, 6	214	67
Diphtheria	0.9	0.8	100	97.0				
Tetanus	3.5	4.1	100	100				
PT	19.1	17.8	74.0	69.7				
FHA	43.8	46.7	66.4	69.7				
Pertactin	40.1	50.9	65.6	77.3				
Fimbriae 2	3.3	4.2	44.7	62.5				
Hib	11.9	7.8	100, 96.9	98.8, 92.8				
Hep B	--	--	99.4	96.2	118-16	0, 2, 6	156	80
IPV Type 1	--	--	89.0	93.6 [¶]	118-16	2, 4	156	80
Type 2	--	--	94.2	93.6				
Type 3	--	--	83.8	80.8				

* Hib vaccine was HibTITER[®], DTaP vaccine was Acel-Imune[®]. Hib (µg/mL); Dip, Tet (IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) (units/mL).

† Responders = Hib (≥0.15 µg/mL, ≥1.0 µg/mL); Dip, Tet (≥0.1 IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) [4-fold rise]; IPV (≥1:10); Hep B (≥10 mIU/mL).

‡ Schedule for concurrently administered vaccines; Prevnar[®] administered at 2, 4, 6 mos.; blood for antibody assessment attained 1 month after third dose, except for IPV (3 months post-immunization).

§ Concurrent vaccines only.

|| p<0.05 when Prevnar[®] compared to control group using the following tests: ANCOVA for GMCs in 118-12; ANOVA for GMCs in 118-16; and Fisher's Exact test for % Responders in 118-12.

¶ Lower bound of 90% CI of difference >10%.

TABLE 7
Concurrent Administration of Prevnar[®] With Other Vaccines to Toddlers in a Non-Efficacy Study³¹

Antigen*	GMC*		% Responders [†]		Study [‡]	Vaccine Schedule [§] (mo.)	N	
	Prevnar [®]	Control	Prevnar [®]	Control			Prevnar [®]	Control
Hib	22.7	47.9¶	100, 97.9	100, 100	118-7	12-15	47	26
Diphtheria	2.0	3.2¶	100	100				
Tetanus	14.4	18.8	100	100				
PT	68.6	121.2¶	68.1	73.1				
FHA	29.0	48.2¶	68.1	84.6				
Pertactin	84.4	83.0	83.0	96.2				
Fimbriae 2	5.2	3.8	63.8	50.0				

* Hib vaccine was HibTITER[®], DTaP vaccine was Acel-Imune[®]. Hib (µg/mL); Dip, Tet (IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) (units/mL).

[†] Responders = Hib (≥0.15 µg/mL, ≥1.0 µg/mL); Dip, Tet (≥0.1 IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) [4-fold rise].

[‡] Children received a primary series of DTP-HbOC (Tetramune[®]).

[§] Blood for antibody assessment obtained 1 month after dose.

^{||} Concurrent vaccines only.

[¶] p<0.05 when Prevnar[®] compared to control group using a two-sample t-test.

420

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

425

PREGNANCY

Pregnancy Category C

Animal reproductive studies have not been conducted with this product. It is not known whether Prevnar[®] can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. This vaccine is not recommended for use in pregnant women.

430

Nursing Mothers

It is not known whether vaccine antigens or antibodies are excreted in human milk. This vaccine is not recommended for use in a nursing mother.

PEDIATRIC USE

Prevnar[®] has been shown to be usually well-tolerated and immunogenic in infants. The safety and effectiveness of Prevnar[®] in children below the age of 6 weeks or on or after the 10th birthday have not been established. Immune responses elicited by Prevnar[®] among infants born prematurely have not been studied. See **DOSAGE AND ADMINISTRATION** for the recommended pediatric dosage.

GERIATRIC USE

This vaccine is NOT recommended for use in adult populations. It is not to be used as a substitute for the pneumococcal polysaccharide vaccine in geriatric populations.

ADVERSE REACTIONS**Pre-Licensure Clinical Trial Experience**

The majority of the safety experience with Prevnar[®] comes from the NCKP Efficacy Trial in which 17,066 infants received 55,352 doses of Prevnar[®], along with other routine childhood vaccines through April 1998 (see **CLINICAL PHARMACOLOGY** section). The number of Prevnar[®] recipients in the safety analysis differs from the number included in the efficacy analysis due to the different lengths of follow-up for these study endpoints. Safety was monitored in this study using several modalities. Local reactions and systemic events occurring within 48 hours of each dose of vaccine were ascertained by scripted telephone interview on a randomly selected subset of approximately 3,000 children in each vaccine group. The rate of relatively rare events requiring medical attention was evaluated across all doses in all study participants using automated databases. Specifically, rates of hospitalizations within 3, 14, 30, and 60 days of immunization, and of emergency room visits within 3, 14, and 30 days of immunization were assessed and compared between vaccine groups for each diagnosis. Seizures within 3 and 30 days of immunization were ascertained across multiple settings (hospitalizations, emergency room or clinic visits, telephone interviews). Deaths and SIDS were ascertained through April 1999. Hospitalizations due to diabetes, autoimmune disorders, and blood disorders were ascertained through August 1999.

In Tables 8 and 9 the rate of local reactions at the Prevnar[®] injection site is compared at each dose to the DTP or DTaP injection site in the same children.

TABLE 8
Percentage of Subjects Reporting Local Reactions Within 2 Days Following Immunization
With Prevnar[®] and DTP-HbOC* Vaccines at 2, 4, 6, and 12-15 Months of Age^{24,25}

Reaction	Dose 1		Dose 2		Dose 3		Dose 4	
	Prevnar[®] Site	DTP- HbOC Site†	Prevnar[®] Site	DTP- HbOC Site†	Prevnar[®] Site	DTP- HbOC Site†	Prevnar[®] Site	DTP- HbOC Site†
	N=2890	N=2890	N=2725	N=2725	N=2538	N=2538	N=599	N=599
Erythema								
Any	12.4	21.9	14.3	25.1	15.2	26.5	12.7	23.4
>2.4 cm	1.2	4.6	1.0	2.9	2.0	4.4	1.7	6.4
Induration								
Any	10.9	22.4	12.3	23.0	12.8	23.3	11.4	20.5
>2.4 cm	2.6	7.2	2.4	5.6	2.9	6.7	2.8	7.2
Tenderness								
Any	28.0	36.4	25.2	30.5	25.6	32.8	36.5	45.1
Interfered with limb movement	7.9	10.7	7.4	8.4	7.8	10.0	18.5	22.2

* If Hep B vaccine was administered simultaneously, it was administered into the same limb as the DTP-HbOC vaccine. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

† p<0.05 when Prevnar[®] site compared to the DTP-HbOC site using the sign test.

TABLE 9
Percentage of Subjects Reporting Local Reactions Within 2 Days Following Immunization
With Prevnar[®]* and DTaP Vaccines† at 2, 4, 6, and 12-15 Months of Age^{24,25}

Reaction	Dose 1		Dose 2		Dose 3		Dose 4	
	Prevnar[®] Site	DTaP Site	Prevnar[®] Site	DTaP Site	Prevnar[®] Site	DTaP Site	Prevnar[®] Site	DTaP Site‡
	N=693	N=693	N=526	N=526	N=422	N=422	N=165	N=165
Erythema								
Any	10.0	6.7§	11.6	10.5	13.8	11.4	10.9	3.6§
>2.4 cm	1.3	0.4§	0.6	0.6	1.4	1.0	3.6	0.6
Induration								
Any	9.8	6.6§	12.0	10.5	10.4	10.4	12.1	5.5§
>2.4 cm	1.6	0.9	1.3	1.7	2.4	1.9	5.5	1.8
Tenderness								
Any	17.9	16.0	19.4	17.3	14.7	13.1	23.3	18.4
Interfered with limb movement	3.1	1.8§	4.1	3.3	2.9	1.9	9.2	8.0

* HbOC was administered in the same limb as Prevnar[®]. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

† If Hep B vaccine was administered simultaneously, it was administered into the same limb as DTaP. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

‡ Subjects may have received DTP or a mixed DTP/DTaP regimen for the primary series. Thus, this is the 4th dose of a pertussis vaccine, but not a 4th dose of DTaP.

§ p<0.05 when Prevnar[®] site compared to DTaP site using the sign test.

475 Table 10 presents the rates of local reactions in previously unvaccinated older infants and children.

TABLE 10
Percentage of Subjects Reporting Local Reactions Within 3 Days of Immunization With Prevnar® in Infants and Children from 7 Months Through 9 Years of Age³⁵

Age at 1st Vaccination	7 - 11 Mos.						12 - 23 Mos.			24 - 35 Mos.	36 - 59 Mos.	5 - 9 Yrs.
	118-12			118-16			118-9*	118-18		118-18	118-18	118-18
Dose Number	1	2	3†	1	2	3†	1	1	2	1	1	1
Number of Subjects	54	51	24	81	76	50	60	114	117	46	48	49
Reaction												
Erythema												
Any	16.7	11.8	20.8	7.4	7.9	14.0	48.3	10.5	9.4	6.5	29.2	24.2
>2.4 cm‡	1.9	0.0	0.0	0.0	0.0	0.0	6.7	1.8	1.7	0.0	8.3	7.1
Induration												
Any	16.7	11.8	8.3	7.4	3.9	10.0	48.3	8.8	6.0	10.9	22.9	25.5
>2.4 cm‡	3.7	0.0	0.0	0.0	0.0	0.0	3.3	0.9	0.9	2.2	6.3	9.3
Tenderness												
Any	13.0	11.8	12.5	8.6	10.5	12.0	46.7	25.7	26.5	41.3	58.3	82.8
Interfered with limb movement§	1.9	2.0	4.2	1.2	1.3	0.0	3.3	6.2	8.5	13.0	20.8	39.4

* For 118-9, 2 of 60 subjects were ≥24 months of age.

† For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 - 15 mos. of age.

‡ For 118-16 and 118-18, ≥2 cm.

§ Tenderness interfering with limb movement.

Tables 11 and 12 present the rates of systemic events observed in the efficacy study when
 480 Pevnar[®] was administered concomitantly with DTP or DTaP.

TABLE 11
Percentage of Subjects* Reporting Systemic Events Within 2 Days Following Immunization With Pevnar[®] or Control† Vaccine Concurrently With DTP-HbOC Vaccine at 2, 4, 6, and 12-15 Months of Age^{24,25}

<u>Reaction</u>	<u>Dose 1</u>		<u>Dose 2</u>		<u>Dose 3</u>		<u>Dose 4</u>	
	Pevnar[®] N=2998	Control† N=2982	Pevnar[®] N=2788	Control† N=2761	Pevnar[®] N=2596	Control† N=2591	Pevnar[®] N=709	Control† N=733
Fever								
≥38.0°C	33.4	28.7‡	34.7	27.4‡	40.6	32.4‡	41.9	36.9
>39.0°C	1.3	1.3	3.0	1.6‡	5.3	3.4‡	4.5	4.5
Irritability	71.3	67.9‡	69.4	63.8‡	68.9	61.6‡	72.8	65.8‡
Drowsiness	49.2	50.6	32.5	33.6	25.9	23.4‡	21.3	22.7
Restless Sleep	18.1	17.9	27.3	24.3‡	33.3	30.1‡	29.9	28.0
Decreased Appetite	24.7	23.6	22.8	20.3‡	27.7	25.6	33.0	27.4‡
Vomiting	17.9	14.9‡	16.2	14.4	15.5	12.7‡	9.6	6.8
Diarrhea	12.0	10.7	10.9	9.9	11.5	10.4	12.1	11.2
Urticaria-like Rash	0.7	0.6	0.8	0.8	1.4	1.1	1.4	0.8

* Approximately 90% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Investigational meningococcal group C conjugate vaccine (MnCC).

‡ p<0.05 when Pevnar[®] compared to control group using a Chi-Square test.

TABLE 12

Percentage of Subjects* Reporting Systemic Events Within 2 Days Following Immunization With Pevnar[®] or Control† Vaccine Concurrently With DTaP Vaccine at 2, 4, 6, and 12-15 Months of Age^{24,25}

Reaction	Dose 1		Dose 2		Dose 3		Dose 4‡	
	Pevnar[®]	Control†	Pevnar[®]	Control†	Pevnar[®]	Control†	Pevnar[®]	Control†
	N=710	N=711	N=559	N=508	N=461	N=414	N=224	N=230
Fever								
≥38.0°C	15.1	9.4§	23.9	10.8§	19.1	11.8§	21.0	17.0
>39.0°C	0.9	0.3	2.5	0.8§	1.7	0.7	1.3	1.7
Irritability	48.0	48.2	58.7	45.3§	51.2	44.8	44.2	42.6
Drowsiness	40.7	42.0	25.6	22.8	19.5	21.9	17.0	16.5
Restless Sleep	15.3	15.1	20.2	19.3	25.2	19.0§	20.2	19.1
Decreased Appetite	17.0	13.5	17.4	13.4	20.7	13.8§	20.5	23.1
Vomiting	14.6	14.5	16.8	14.4	10.4	11.6	4.9	4.8
Diarrhea	11.9	8.4§	10.2	9.3	8.3	9.4	11.6	9.2
Urticaria-like Rash	1.4	0.3§	1.3	1.4	0.4	0.5	0.5	1.7

* Approximately 75% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Investigational meningococcal group C conjugate vaccine (MnCC).

‡ Most of these children had received DTP for the primary series. Thus, this is a 4th dose of a pertussis vaccine, but not of DTaP.

§ p<0.05 when Pevnar[®] compared to control group using a Chi-Square test.

485 Table 13 presents results from a second study (Manufacturing Bridging Study) conducted at Northern California and Denver Kaiser sites, in which children were randomized to receive one of three lots of Prevnar[®] with concomitant vaccines including DTaP, or the same concomitant vaccines alone. Information was ascertained by scripted telephone interview, as described above.

TABLE 13
Percentage of Subjects* Reporting Systemic Reactions Within 3 Days Following Immunization With Prevnar[®], DTaP, HbOC, Hep B, and IPV vs. Control† In Manufacturing Bridging Study²⁹

Reaction	Dose 1		Dose 2		Dose 3	
	Prevnar [®] N=498	Control† N=108	Prevnar [®] N=452	Control† N=99	Prevnar [®] N=445	Control† N=89
Fever						
≥38.0°C	21.9	10.2‡	33.6	17.2‡	28.1	23.6
>39.0°C	0.8	0.9	3.8	0.0	2.2	0.0
Irritability	59.7	60.2	65.3	52.5‡	54.2	50.6
Drowsiness	50.8	38.9‡	30.3	31.3	21.2	20.2
Decreased Appetite	19.1	15.7	20.6	11.1‡	20.4	9.0‡

* Approximately 72% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Control group received concomitant vaccines only in the same schedule as the Prevnar[®] group (DTaP, HbOC at dose 1, 2, 3; IPV at doses 1 and 2; Hep B at doses 1 and 3).

‡ p<0.05 when Prevnar[®] compared to control group using Fisher's Exact test.

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Fever (≥38.0°C) within 48 hours of a vaccine dose was reported by a greater proportion of subjects who received Prevnar[®], compared to control (investigational meningococcal group C conjugate vaccine [MnCC]), after each dose when administered concurrently with DTP-HbOC or DTaP in the efficacy study. In the Manufacturing Bridging Study, fever within 48-72 hours was also reported more commonly after each dose compared to infants in the control group who received only recommended vaccines. When administered concurrently with DTaP in either study, fever rates among Prevnar[®] recipients ranged from 15% to 34%, and were greatest after the 2nd dose.

500

505 Table 14 presents the frequencies of systemic reactions in previously unvaccinated older infants and children.

TABLE 14
Percentage of Subjects Reporting Systemic Reactions Within 3 Days of Immunization
With Prevnar[®] in Infants and Children from 7 Months Through 9 Years of Age³⁵

Age at 1st Vaccination	7 - 11 Mos.						12 - 23 Mos.			24 - 35 Mos.	36 - 59 Mos.	5 - 9 Yrs.
Study No.	118-12			118-16			118-9*	118-18		118-18	118-18	118-18
Dose Number	1	2	3 [†]	1	2	3 [†]	1	1	2	1	1	1
Number of Subjects	54	51	24	85	80	50	60	120	117	47	52	100
Reaction												
Fever ≥38.0°C	20.8	21.6	25.0	17.6	18.8	22.0	36.7	11.7	6.8	14.9	11.5	7.0
>39.0°C	1.9	5.9	0.0	1.6	3.9	2.6	0.0	4.4	0.0	4.2	2.3	1.2
Fussiness	29.6	39.2	16.7	54.1	41.3	38.0	40.0	37.5	36.8	46.8	34.6	29.3
Drowsiness	11.1	17.6	16.7	24.7	16.3	14.0	13.3	18.3	11.1	12.8	17.3	11.0
Decreased Appetite	9.3	15.7	0.0	15.3	15.0	30.0	25.0	20.8	16.2	23.4	11.5	9.0

* For 118-9, 2 of 60 subjects were ≥24 months of age.

† For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 - 15 mos. of age.

510 Of the 17,066 subjects who received at least one dose of Prevnar[®] in the efficacy trial, there were 24 hospitalizations (for 29 diagnoses) within 3 days of a dose from October 1995 through April 1998. Diagnoses were as follows: bronchiolitis (5); congenital anomaly (4); elective procedure, UTI (3 each); acute gastroenteritis, asthma, pneumonia (2 each); aspiration, breath holding, influenza, inguinal hernia repair, otitis media, febrile seizure, viral syndrome, well child/reassurance (1 each). There were 162 visits to the emergency room (for 182 diagnoses) within 3 days of a dose from October 1995 through April 1998. Diagnoses were as follows: febrile illness (20); acute gastroenteritis (19); trauma, URI (16 each); otitis media (15); well child (13); irritable child, viral syndrome (10 each); rash (8); croup, pneumonia (6 each); poisoning/ingestion (5); asthma, bronchiolitis (4 each); febrile seizure, UTI (3 each); thrush, wheezing, breath holding, choking, conjunctivitis, inguinal hernia repair, pharyngitis (2 each); colic, colitis,

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congestive heart failure, elective procedure, hives, influenza, ingrown toenail, local swelling, roseola, sepsis (1 each).^{24,25}

525 In the large-scale efficacy study, urticaria-like rash was reported in 0.4%-1.4% of children within 48 hours following immunization with Prevnar[®] administered concurrently with other routine childhood vaccines. Urticaria-like rash was reported in 1.3%-6% of children in the period from 3 to 14 days following immunization, and was most often reported following the fourth dose when it was administered concurrently with MMR
530 vaccine. Based on limited data, it appears that children with urticaria-like rash after a dose of Prevnar[®] may be more likely to report urticaria-like rash following a subsequent dose of Prevnar[®].

One case of a hypotonic-hyporesponsive episode (HHE) was reported in the efficacy
535 study following Prevnar[®] and concurrent DTP vaccines in the study period from October 1995 through April 1998. Two additional cases of HHE were reported in four other studies and these also occurred in children who received Prevnar[®] concurrently with DTP vaccine.^{31,34}

540 In the Kaiser efficacy study in which 17,066 children received a total of 55,352 doses of Prevnar[®] and 17,080 children received a total of 55,387 doses of the control vaccine (investigational meningococcal group C conjugate vaccine [MnCC]), seizures were reported in 8 Prevnar[®] recipients and 4 control vaccine recipients within 3 days of immunization from October 1995 through April 1998. Of the 8 Prevnar[®] recipients, 7
545 received concomitant DTP-containing vaccines and one received DTaP. Of the 4 control vaccine recipients, 3 received concomitant DTP-containing vaccines and one received DTaP.^{24,25} In the other 4 studies combined, in which 1,102 children were immunized with 3,347 doses of Prevnar[®] and 408 children were immunized with 1,310 doses of control vaccine (either investigational meningococcal group C conjugate vaccine [MnCC] or
550 concurrent vaccines), there was one seizure event reported within 3 days of immunization.³² This subject received Prevnar[®] concurrent with DTaP vaccine.

Twelve deaths (5 SIDS and 7 with clear alternative cause) occurred among subjects

receiving Prevnar[®], of which 11 (4 SIDS and 7 with clear alternative cause) occurred in
 555 the Kaiser efficacy study from October 1995 until April 20, 1999. In comparison, 21
 deaths (8 SIDS, 12 with clear alternative cause and one SIDS-like death in an older
 child), occurred in the control vaccine group during the same time period in the efficacy
 study.^{24,25,29} The number of SIDS deaths in the efficacy study from October 1995 until
 April 20, 1999 was similar to or lower than the age and season-adjusted expected rate
 560 from the California State data from 1995-1997 and are presented in Table 15.

TABLE 15
Age and Season-Adjusted Comparison of SIDS Rates in the NCKP Efficacy Trial With
the Expected Rate from the California State Data for 1995-1997^{24,25}

Vaccine	<One Week After Immunization		≤Two Weeks After Immunization		≤One Month After Immunization		≤One Year After Immunization	
	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs
Prevnar [®]	1.06	1	2.09	2	4.28	2	8.08	4
Control*	1.06	2	2.09	3†	4.28	3†	8.08	8†

* Investigational meningococcal group C conjugate vaccine (MnCC).

† Does not include one additional case of SIDS-like death in a child older than the usual SIDS age (448 days).

In a review of all hospitalizations that occurred between October 1995 and August 1999
 565 in the efficacy study for the specific diagnoses of aplastic anemia, autoimmune disease,
 autoimmune hemolytic anemia, diabetes mellitus, neutropenia, and thrombocytopenia, the
 numbers of such cases were equal to or less than the expected numbers based on the 1995
 Kaiser Vaccine Safety Data Link (VSD) data set.

Overall, the safety of Prevnar[®] was evaluated in a total of five clinical studies in the US
 570 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. In addition, the safety of Prevnar[®] was evaluated in 831
 Finnish infants using the same schedule, and the overall safety profile was similar to that
 in US infants. The safety of Prevnar[®] was also evaluated in 560 children from 4 ancillary
 studies in the US who started immunization at 7 months to 9 years of age. Tables 16 and
 575 17 summarize systemic reactogenicity data within 2 or 3 days across 4,748 subjects in US
 studies (13,039 infant doses and 1,706 toddler doses) for whom these data were collected

and according to the pertussis vaccine administered concurrently.

TABLE 16
Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days For
The US Efficacy Study and All US Ancillary Studies When Prevnar[®] Administered To
Infants As a Primary Series at 2, 4, and 6 Months of Age^{24,25, 29,31,32,33}

Systemic Event	Prevnar[®] Concurrently With DTP-HbOC (9,191 Doses)*	Prevnar[®] Concurrently With DTaP and HbOC (3,848 Doses) †	DTaP and HbOC Control (538 Doses) ‡
Fever			
≥38.0°C	35.6	21.1	14.2
>39.0°C	3.1	1.8	0.4
Irritability	69.1	52.5	45.2
Drowsiness	36.9	32.9	27.7
Restless Sleep	25.8	20.6	22.3
Decreased Appetite	24.7	18.1	13.6
Vomiting	16.2	13.4	9.8
Diarrhea	11.4	9.8	4.4
Urticaria-like Rash	0.9	0.6	0.3

* Total from which reaction data are available varies between reactions from 8,874-9,191 doses.
Data from studies 118-3, 118-7, 118-8.

† Total from which reaction data are available varies between reactions from 3,121-3,848 doses.
Data from studies 118-8, 118-12, 118-16.

‡ Total from which reaction data are available varies between reactions from 295-538 doses.
Data from studies 118-12 and 118-16.

TABLE 17
Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days
For The US Efficacy Study and All US Ancillary Studies When Prevnar[®]
Administered To Toddlers as a Fourth Dose At 12 to 15 Months of Age^{24,25,31}

Systemic Event	Prevnar[®] Concurrently With DTP-HbOC (709 Doses)*	Prevnar[®] Concurrently With DTaP and HbOC (270 Doses) †	Prevnar[®] Only No Concurrent Vaccines (727 Doses) ‡
Fever			
≥38.0°C	41.9	19.6	13.4
>39.0°C	4.5	1.5	1.2
Irritability	72.8	45.9	45.8
Drowsiness	21.3	17.5	15.9
Restless Sleep	29.9	21.2	21.2
Decreased Appetite	33.0	21.1	18.3
Vomiting	9.6	5.6	6.3
Diarrhea	12.1	13.7	12.8
Urticaria-like Rash	1.4	0.7	1.2

* Total from which reaction data are available varies between reactions from 706-709 doses.
 Data from study 118-8.

† Total from which reaction data are available varies between reactions from 269-270 doses.
 Data from studies 118-7 and 118-8.

‡ Total from which reaction data are available varies between reactions from 725-727 doses.
 Data from studies 118-7 and 118-8.

585 With vaccines in general, including Prevnar[®], it is not uncommon for patients to note within 48 to 72 hours at or around the injection site the following minor reactions: edema; pain or tenderness; redness, inflammation or skin discoloration; mass; or local hypersensitivity reaction. Such local reactions are usually self-limited and require no therapy.

As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks.⁴²

590

Postmarketing Experience

Additional adverse reactions identified from postmarketing experience are listed below:

595 *Administration site conditions:* injection site dermatitis, injection site urticaria, injection site pruritus

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

600

Immune system disorders: hypersensitivity reaction including face edema, dyspnea, bronchospasm; anaphylactic/anaphylactoid reaction including shock

Skin and subcutaneous tissue disorders: angioneurotic edema, erythema multiforme

605

ADVERSE EVENT REPORTING

Any suspected adverse events following immunization should be reported by the healthcare professional to the US Department of Health and Human Services (DHHS).

610 The National Vaccine Injury Compensation Program requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare professional in the vaccine recipient's permanent medical record (or in a permanent office log or file), along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.

615 The US DHHS has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine including, but not limited to, the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The FDA web site is:

<http://www.fda.gov/cber/vaers/vaers.htm>.

620

The VAERS toll-free number for VAERS forms and information is 800-822-7967.⁴³

OVERDOSAGE

625 There have been reports of overdose with Prevnar[®], including cases of administration of a higher than recommended dose and cases of subsequent doses administered closer than recommended to the previous dose. Most individuals were asymptomatic. In general, adverse events reported with overdose have also been reported with recommended single doses of Prevnar[®].

630 DOSAGE AND ADMINISTRATION

For intramuscular injection only. Do not inject intravenously.

The dose is 0.5 mL to be given intramuscularly.

635 **Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. The vaccine should not be used if it cannot be resuspended.**

After shaking, the vaccine is a homogeneous, white suspension.

640 Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (see **DESCRIPTION**). This product should not be used if particulate matter or discoloration is found.

645 The vaccine should be injected intramuscularly. The preferred sites 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. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate and wait to see if any blood appears in the syringe, which will help avoid inadvertent injection into a blood vessel. If blood appears, withdraw the needle and
650 prepare for a new injection at another site.

Vaccine Schedule

For infants, the immunization series of Prevnar[®] consists of three doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth dose should be administered at least 2 months after the third dose.

Previously Unvaccinated Older Infants and Children

For previously unvaccinated older infants and children, who are beyond the age of the routine infant schedule, the following schedule applies:³⁵

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 9 years of age	1

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

† 2 doses at least 2 months apart.

(See **CLINICAL PHARMACOLOGY** section for the limited available immunogenicity data and **ADVERSE EVENTS** section for limited safety data corresponding to the previously noted vaccination schedule for older children).

Safety and immunogenicity data are either limited or not available for children in specific high risk groups for invasive pneumococcal disease (eg, persons with sickle cell disease, asplenia, HIV-infected).

HOW SUPPLIED

Vial, 1 Dose (5 per package) - NDC 0005-1970-67

CPT Code 90669

680 **STORAGE**

DO NOT FREEZE. STORE REFRIGERATED, AWAY FROM FREEZER
COMPARTMENT, AT 2°C TO 8°C (36°F TO 46°F).

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