PRODUCT MONOGRAPH

PREVNAR®

Pneumococcal 7-valent Conjugate Vaccine
(Diphtheria CRM_{197} Protein)

Suspension
For Intramuscular Injection

Therapeutic Classification
Active Immunizing Agent

Manufacturer: **Pfizer Inc.**
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Importer/Distributor: **Pfizer Canada Inc.**
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Contents Page

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ACTION AND CLINICAL PHARMACOLOGY

Streptococcus pneumoniae is an important cause of morbidity and mortality in persons of all ages 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. Data from community-based studies performed between 1986 and 1995, indicate that the overall annual incidence of invasive pneumococcal disease in the United States is an estimated 10 to 30 cases per 100,000 population with the highest risk being in children aged less than or equal to 2 years of age (140 to160 cases per 100,000 population).

In the Greater Toronto and Peel regions of Ontario, Canada, overall incidences of invasive pneumococcal disease were determined to be 14.4 per 100,000 population in 1995, 16.1 per 100,000 in 1996, and 11.8 per 100,000 in 1997. Rates of disease were markedly higher in the elderly, and most of the decrease in incidence from 1995 to 1997 was in this age group. In another Canadian study, 2040 consecutive cases of invasive pneumococcal infection seen at 11 pediatric centers across Canada during 1991-98 were analyzed. An overall annual incidence could not be established. Age distribution was determined to be as follows: 61.5% of cases occurred before age 2 years, 26.1% between 2 and 5 years, while 12.3% occurred between 6 and

16 years.

Children in day care have an increased risk for invasive pneumococcal disease. Immunocompromised individuals with neutropenia, asplenia, sickle cell disease, disorders of complement and humoral immunity, Human Immunodeficiency Virus (HIV) infections, or chronic underlying disease are also at increased risk for invasive pneumococcal disease. It was shown in the Canadian multicentre pediatric study that the proportion of children with an underlying condition increased with age, from 15.9% in those under 2 years of age, to 30.4% in those 2-5 years of age, and to 44.5% in those over 5 years of age ($p < 0.001$). Conditions known to predispose to invasive pneumococcal infection were reported in 16.9% of cases, while other conditions were present in 6.4%.

S. pneumoniae is the most common cause of bacterial meningitis in the United States. The annual incidence of pneumococcal meningitis in children between 1 to 23 months of age is approximately 7 cases per 100,000 people. Pneumococcal meningitis in childhood has been associated with 8% mortality and may result in neurological sequelae (25%), and hearing loss (32%) in survivors.

S. pneumoniae is an important cause of acute otitis media, identified in 20 to 40% of middle ear fluid cultures. The seven serotypes account for approximately 60% of acute otitis media due to *S. pneumonia*e (12 - 24% of all acute otitis media). The exact contribution of *S. pneumonia*e 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 serologic methods, antigen testing, and 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*.

In the past decade the portion of *S. pneumoniae* isolates resistant to antibiotics has been on the rise in the United States and world wide. 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. pneumonia*e (PNSP) strains and a three-fold rise in cephalosporin-nonsusceptible strains. Although generally less common than PNSP, pneumococci resistant to macrolides and trimethoprim-sulfamethoxazole have also been observed. 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. There has been no difference in mortality associated with PNSP strains. However, the American Academy of Pediatrics (AAP) revised the antibiotic treatment guidelines in 1997 in response to the increased prevalence of antibiotic-resistant pneumococci.

In 1992 the rate of reduced susceptibility to penicillin in Canada was thought to be less than 5%. Since 1994, reports from eastern Canada have identified rates of 7.3% to 8.1% and one recent national survey reported a rate of 11.7%. In Canada, from April 1993 through March 1994, 154 isolates from blood were evaluated for susceptibility to 9 antibiotics. Of these 40 (26.0%) were found to have reduced susceptibility to one or more of the drugs.

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

Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are responsible for approximately 80% of invasive pneumococcal disease in children <6 years of age in the United States. These 7 serotypes also accounted for 74% of PNSP and 100% of pneumococci isolated from children <6 years with invasive disease during a 1993-1994 surveillance by the Centers for Disease Control.

In the Canadian multicentre pediatric study, of the 2040 cases of invasive pneumococcal infection, serotype data were available for 1,528 isolates, representing 74.9% of cases. Children 6 months to 5 years of age had the highest proportion of serotypes matched by the 7- valent vaccine, at 85.8%. The reduced match among children 0-5 months of age (65.7%) resulted mainly from fewer type 14 isolates, while that among children over 5 years of age (63.6%) resulted mainly from reduced prevalence of types 14 and 6B. Across all age groups, the match with 7-valent vaccine serotypes was better in previously healthy children than in those with

underlying conditions. This rate difference was greatest among those 2-5 years of age (13.6%, P<0.001), and not significant in those 6-23 months of age. No differences were found over large geographic areas: in western and eastern Canada 80.6% and 81.7% of isolates matched vaccine types, respectively.

The match between 7-valent vaccine serotypes and those encountered with various infection syndromes differed as follows: isolated bacteremia cases, 83.4%; meningitis, 78.9%; pneumonia 78.3%. Cases with shock matched least well (74.1%) but included 43 typed isolates. Among 27 typed isolates from fatal cases, 20 (74.1%) matched the 7-valent vaccine.

Results of Clinical Evaluations

EFFICACY

Efficacy was assessed in a randomized, double-blinded clinical trial in a multi-ethnic population at Northern California Kaiser Permanente (NCKP), beginning in October 1995, in which 37,816 infants were randomized to receive either Prevnar (Pneumococcal 7-valent Conjugate Vaccine) 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 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 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 pneumococcal disease were also assessed in this trial.

Efficacy against invasive disease:

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 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 analysis of efficacy against all invasive 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.

TABLE 1

Efficacy of Prevnar
Against Invasive Disease Due to *S. pneumoniae* in cases accrued
From October 15, 1995 Through April 20, 1999.

	Prevnar Number of Cases	Control* Number of Cases	Efficacy (%)	95% CI
Vaccine serotypes				
Per-protocol	**1**	**39**	**97.4**	**84.8, 99.9**
Intent-To-Treat	**3**	**49**	**93.9**	**81.0, 98.8**
All pneumococcal serotypes				
Per-Protocol	**3**	**42**	**92.9**	**77.6, 98.6**
Intent-To-Treat	**6**	**55**	**89.1**	**74.7, 96.2**

*Investigational meningococcal group C conjugate vaccine (MnCC)

Efficacy against Otitis Media (OM):

Physician visits for any 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 at least 21 days following a previous OM visit. Data on placement of ear tubes were collected from automated databases. No routine tympanocentesis was performed. Table 2 presents the results of these OM analyses for both the per-protocol and intent-to-treat analyses.

TABLE 2
Summary of Vaccine Effects on Acute Otitis Media (AOM)

	Per-Protocol Analysis		Intent-To-Treat Analysis	
Acute Otitis Media Outcome	Est. Risk Reduction (95% Conf. Interval)	P-Value	Est. Risk Reduction (95% Conf. Interval)	P-Value
All AOM Episodes - Primary Variable	7.0% (4.1%, 9.7%)	<0.0001	6.4% (3.9%, 8.7%)	<0.0001
First AOM Episodes	5.4% (2.3%, 8.4%)	0.0008	4.9% (2.3%, 7.5%)	0.0003
Frequent AOM	9.5% (3.2%, 15.3%)	0.0035	9.2% (4.3%, 13.9%)	0.0004
Tympanostomy Tube Placement	20.3% (1.8%, 35.4%)	0.0335	20.6% (4.0%, 34.3%)	0.0171
All AOM Visits	8.9% (5.8%, 11.8%)	<0.0001	7.8% (5.2%, 10.5%)	<0.0001
Ruptured Ear Drum with Vaccine Serotype Isolates	55.6% (-59.3%, 90.0%)	0.267	57.1% (-18.7%, 86.5%)	0.115

A significant risk reduction was seen in Prevnar recipients for clinically diagnosed acute otitis media (AOM) episodes, visits, frequent AOM, and the placement of tympanostomy tubes. The estimated reductions for all AOM episodes was 7% which corresponds to 12 episodes prevented per 100 child years. There is evidence of an increased vaccine effect in reducing the risk of more severe cases of recurrent otitis media with the estimated reduction of tympanostomy tube placement of 20.3%.

In a second efficacy study for otitis media performed in Finland, the vaccine was compared to a control vaccine (Hepatitis B vaccine, HBV) when administered at 2,4,6, and 12 months of age. In this study, an episode was defined as a visit to a study clinic at which time acute otitis media was diagnosed by defined symptom criteria and a period of 30 days had elapsed since the previous visit for AOM. Table 3 presents the results of the Finnish efficacy trial analyses.

TABLE 3
Summary of Vaccine Efficacy in the Finnish Otitis Media Study

Episode (follow-up)	Analysis	Episodes		Rate/Person year		Vaccine Efficacy	
		HBV	Prevnar	HBV	Prevnar	Estimate	95% CI
Vaccine serotype AOM	(PP)	250	107	0.21	0.09	0.57	(0.44, 0.67)
Vaccine serotype AOM	(ITT)	292	135	0.20	0.09	0.54	(0.41, 0.64)
Pneumococcal culture-confirmed AOM	(PP)	414	271	0.36	0.23	0.34	(0.21, 0.45)
AOM with Middle Ear Fluid	(PP)	1267	1177	1.16	1.09	0.07	(-0.05, 0.17)
AOM regardless of etiology	(PP)	1345	1251	1.24	1.16	0.06	(-0.04, 0.16)

A significant risk reduction was seen in the incidence of AOM in the Prevnar group versus the control vaccine group regardless of the endpoint assessed. The reduction in all episodes of AOM regardless of etiology in this trial (6%) was similar to that in the Kaiser efficacy study (7%).

Efficacy against pneumonia:

Children with a clinical diagnosis of any pneumonia were identified by physician coding of outpatient encounter forms. Subjects for whom chest x-rays were obtained with -1 to +5 days of clinical diagnosis were identified. Films were defined as abnormal if consolidation, infiltrate, or effusion was present according to the radiology department report. Table 4 presents the results of the pneumonia analyses.

TABLE 4
Summary of Vaccine Effect on Pneumonia

		Per-Protocol Analysis		Intent-to-Treat-Analysis		
Pneumonia Outcome	Cases in 7VPnC/MnCC	Est. Risk Reduction (95% Confidence Interval)	P-value*	Cases in 7VPnC/MnCC	Est. Risk Reduction (95% Confidence Interval)	P-value*
Clinical Pneumonia	500/566	11% (0.8, 21.1)	0.067	615/694	10% (0.1, 19.8)	0.019
Clinical Pneumonia with X-ray taken	323/372	12% (2.2, 24.7)	0.091	393/456	13% (0.2, 24.1)	0.035
Clinical Pneumonia with Abnormal X-ray	45/70	35% (4.2, 56.4)	0.028	61/91	33% (6.2, 52.3)	0.033
Clinical Pneumonia with Consolidation	7/19	63% (8.87)	0.03	7/26	73% (36, 90)	0.001

* P-value calculated using the Exact binomial test (p=0.4975 for per-protocol and 0.4997 for intent-to-treat)

IMMUNOGENICITY

Routine Schedule

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 CRM_{197} Protein Conjugate), (DTP-HbOC), or Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} 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.

Table 5 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.

TABLE 5
Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following the Third and Fourth Doses of Prevnar or Control* When Administered Concurrently with DTP-HbOC in the Efficacy Study

Serotype	Post Dose 3 GMC† (95% CI for Prevnar)		Post Dose 4 GMC‡ (95% CI for Prevnar)	
	Prevnar§	Control*	Prevnar§	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 Prevnar 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 Prevnar 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 Prevnar 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 Prevnar 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 6 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 6
Geometric Mean Concentrations (µg/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

	Efficacy Study		**Manufacturing Bridging Study**	
Serotype	**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 Prevnar group was 7.4 months and of the control group was 7.6 months. N is slightly less for some serotypes.
§ Mean age of Prevnar group and of 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 compared to a control, a significant antibody response was seen to all vaccine serotypes following three or four doses, although geometric mean concentrations varied among serotypes. The minimum serum antibody concentration necessary for protection against invasive pneumococcal disease has not been determined for any serotype. Prevnar induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following three doses.

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. GMCs attained using the various schedules among older infants and children were comparable to immune responses of children, who received concomitant DTaP, in the NCKP efficacy study (D118-P8) after 3 doses for most serotypes, as shown in Table 7. This data supports 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, Previously Unvaccinated Older Infants and Children.

Table 7.
Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following Immunization of Children From 7 months Through 9 Years of Age with Prevnar

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.

The immunogenicity of Prevnar has been investigated in an open label, multicenter study in 49 infants with sickle cell disease. Children were vaccinated with Prevnar (3 doses one month apart from the age of 2 months) and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15-18 months. After primary immunization, 95.6% of the subjects had antibody levels of at least 0.35 µg/ml for all seven serotypes found in Prevnar. A

significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

INDICATIONS AND CLINICAL USE

Prevnar (Pneumococcal 7-valent Conjugate Vaccine) is indicated for the active immunization of infants and children from 6 weeks until 9 years of age against invasive disease, pneumonia and otitis media caused by *S. pneumoniae* due to the 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. For additional information on usage, see DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

This vaccine should not be used in any patient demonstrating hypersensitivity to any component of the vaccine, including diphtheria toxoid.

This vaccine should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection. (See WARNINGS).

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

WARNINGS

Prevnar (Pneumococcal 7-valent Conjugate Vaccine) will not help to protect against *S. pneumoniae* disease other than that caused by the seven serotypes included in the vaccine, nor will it protect against other microorganisms that cause invasive infection such as bacteremia and meningitis, or otitis media and pneumonia.

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 PRECAUTIONS -- Drug Interactions).

Immunization with Prevnar does not substitute for routine diphtheria immunization.

As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunization series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born ≤ 30 weeks of gestation), who remain hospitalized at the time of the recommended administration. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

PRECAUTIONS

General

Minor illnesses, such as mild respiratory infection with or without low-grade fever, are not generally contraindications to vaccination. 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. The administration of Prevnar should be postponed in subjects suffering from acute severe febrile illness. Prior to administration of any dose of Prevnar (Pneumococcal 7-valent Conjugate Vaccine), the parent, guardian, or adult patient should be asked about the personal history, family history, recent health status, and immunization history of the patient to be immunized to determine the existence of any contraindication to immunization with pneumococcal vaccine (see CONTRAINDICATIONS, WARNINGS).

The healthcare professional should also take all known precautions for the prevention of allergic or any other reactions. This includes: a review of the patient's history regarding possible sensitivity, the ready availability of epinephrine 1:1000 and other appropriate agents used for control 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. (See ADVERSE REACTIONS).

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

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

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 a reduced antibody response to active immunization. (See Drug Interactions).

As with any vaccine, Prevnar may not protect 100% of individuals receiving the vaccine.

Prophylactic antipyretic medication is recommended for all children receiving Prevnar simultaneously with vaccines containing whole cell pertussis. Prophylactic antipyretic medication should be considered in children at higher risk for seizures than the general population.

The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children ≥ 24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised, placing them at higher risk for invasive disease due to *S. pneumoniae*. Data on sequential vaccination with Prevnar followed by 23-valent pneumococcal polysaccharide vaccine are limited. In a randomized study, 23 subjects > 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 this small study, safety and immune responses with the combined schedule were similar to polysaccharide vaccine alone.

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

Prevnar is not recommended for use in adult populations and it is not to be used as a substitute for the pneumococcal polysaccharide vaccine, 23-valent in geriatric populations.

Pregnancy

Safety during pregnancy has not been established.

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

Lactation

It is not known whether vaccine antigens or antibodies are excreted in human milk. Prevnar is not recommended for use in a nursing mother. Safety during lactation has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Drug Interactions

Children receiving therapy with immunosuppressive agents (large amounts of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization procedures. (see PRECAUTIONS section).

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

Simultaneous Administration with other Vaccines

During clinical studies, Prevnar was administered simultaneously with DTP-HbOC or DTaP and HbOC, OPV or IPV, Hepatitis B Vaccine(s), meningococcal serogroup C conjugate vaccine, MMR and Varicella vaccine. Thus, the safety experience with Prevnar reflects the use of this product as part of the routine immunization schedule. In some studies, differences in antibody response to some of the antigens have been inconsistently found, however, it is not anticipated to be of any clinical relevance.

Data on concomitant administration of Prevnar with Meningitec (meningococcal C CRM197 protein conjugate vaccine) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as primary series vaccinations.

Concurrent administration of Prevnar with DTaP-IPV/PRP-T vaccine (Pentacel, Sanofi-Aventis) and hepatitis B virus vaccine (Recombivax, Merck), at 2, 4 and 6 months of age, (concurrent administration in two groups of 126 subjects each) was compared to the sequential administration of DTaP-IPV/PRP-T vaccine and hepatitis B virus vaccine at 2, 4 and 6 months of age and Prevnar at 3, 5 and 7 months of age (sequential administration in 124 subjects). There were no significant differences in the antibody response to any Prevnar serotype in either the concurrent (N=123) or the sequential (N=121) group. A significantly lower percentage of responders to hepatitis B (seroprotective level equal to or greater than 10 mIU/mL, measured at 8 weeks post third dose) was noted in the concurrent group, 87.2% (95% CI: 79.7-92.6%), compared to that seen in the sequential group, 96.7% (95% CI: 91.8-99.1%) and statistically significant (p=0.006) higher antibody levels were reported in the sequential group for hepatitis B antibodies. The GMC response to the Haemophilus influenza type b (Hib) antigen was statistically higher in the concurrent group (1.11 mg/mL, CI: 0.82-1.50) compared to the sequential administration group (0.64 mg/mL, CI: 0.48-0.85). The clinical significance of these data is unknown.

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 8 and for toddlers in Table 9. 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 $\geq$ 1 μg/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 slightly lower for types 1. MMR and Varicella immunogenicity data from controlled clinical trials with concurrent administration of Prevnar are not available.

TABLE 8
Concurrent Administration of Prevnar With Other Vaccines to Infants in Non-Efficacy Studies

Antigen*	GMC*		%Responders†		Study	Vaccine Schedule‡	N	
	Prevnar	Control§	Prevnar	Control§		(mo.)	Prevnar	Control§
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	118-16	2,4,6	159	83
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 9
Concurrent Administration of Prevnar With Other Vaccines to Toddlers in a Non-Efficacy Study

Antigen*	GMC*		% Responders†		Study‡	Vaccine Schedule§	N	
	Prevnar	Control//	Prevnar	Control//		(mo.)	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				
Fimbriae2	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.

ADVERSE REACTIONS

Pre-Licensure Clinical Trial Experience

Adverse reactions identified from clinical trial experience are listed below:

ADMINISTRATION SITE CONDITIONS: Very common: (≥10%): Injection site erythema, induration/swelling, pain/tenderness, Common (≥1% and <10%): Injection site induration/swelling or erythema greater than 2.4 cm, pain/tenderness interfering with movement.

GASTROINTESTINAL DISORDERS: Very common: (≥10%): Diarrhea, vomitting.

GENERAL DISORDERS: Very common: (≥10%): Fever, Common (≥1% and <10%): Fever greater than 39°C.

METABOLISM AND NUTRITION DISORDERS: Very common: (≥10%): Decreased appetite.
NERVOUS SYSTEM DISORDERS: Very common: (≥10%): Drowsiness, restless sleep, Rare: (≥0.01% and <0.1%): Seizures (including febrile seizures): hypotonic-hyporesponsive episode.
PSYCHIATRIC DISORDERS: Very common: (≥10%): Irritability.
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Uncommon: (≥0.1% and <1%): Rash, uticaria or uticaria type rash.

The majority of the safety experience with Prevnar (Pneumococcal 7-valent Conjugate Vaccine) 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 hospitalization 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 10 and 11, the rate of local reactions that were common during the first 2 days at the Prevnar injection site (erythema, induration/swelling and pain/tenderness) is compared at each dose to the DTP or DTaP injection site in the same children.

TABLE 10
Percentage of Subjects Experiencing Local Reactions Within 2 Days Following Immunization with Prevnar and DTP-HbOC* Vaccines at 2, 4, 6 and 12-15 Months of Age

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
> 2.4cm	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
> 2.4cm	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 most severe reaction was recorded.
† $p<0.05$ when Prevnar site compared to the DTP-HbOC site using the sign test.

TABLE 11
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

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§
> 2.4cm	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§
> 2.4cm	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 receive 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.

Table 12 presents the rates of local reactions in previously unvaccinated older infants and children.

TABLE 12
Percentage of Subjects Reporting Local Reactions Within 3 Days of Immunization with Prevnar in Infants and Children from 7 Months Through 9 Years of Age.

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	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 movements§	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 13 and 14 present the rates of systemic events observed in the efficacy study when Prevnar was administered concomitantly with DTP or DTaP.

TABLE 13
Percentage of Subjects* Reporting Systemic Events Within 2 Days Following Immunization with Prevnar or Control† Vaccine Concurrently with DTP-HbOC Vaccine at 2, 4, 6, and 12-15 Months of Age

Reaction	Dose 1		Dose 2		Dose 3		Dose 4	
	Prevnar	Control†	Prevnar	Control†	Prevnar	Control†	Prevnar	Control†
	N=2998	N=2982	N=2788	N=2761	N=2596	N=2591	N=709	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
Rash or Hives	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 Prevnar compared to control group using a Chi-Square test.

TABLE 14
Percentage of Subjects* Reporting Systemic Reactions Within 2 Days Following Immunization with Prevnar or Control† Vaccine Concurrently with DTaP Vaccine at 2, 4, 6, and 12-15 Months of Age

Reaction	Dose 1		Dose 2		Dose 3		Dose 4‡	
	Prevnar	Control†	Prevnar	Control†	Prevnar	Control†	Prevnar	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
Rash or Hives	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 a DTaP.
§ $p<0.05$ when Prevnar compared to control group using a Chi-Square test.

Table 15 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 15
Percentage of Subjects* Reporting Systemic Reactions Within 3 Days Following Immunization With Prevnar , DTaP, HbOC, Hep B and IPV vs. Control† In Manufacturing Bridging Study

Reaction	Dose 1		Dose 2		Dose 3	
	Prevnar	Control†	Prevnar	Control†	Prevnar	Control†
	N=498	N=108	N=452	N=99	N=445	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.

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.

Table 16 presents the frequencies of systemic reactions in previously unvaccinated older infants and children.

TABLE 16
Percentage of Subjects Reporting Systemic Reactions Within 3 Days of Immunization in Infants and Children from 7 months Through 9 Years of Age

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.

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, congestive heart failure, elective procedure, hives, influenza, ingrown toenail, local swelling, roseola, sepsis (1 each).

One case of a hypotonic-hyporesponsive episode (HHE) was reported in the efficacy 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 concurrent with DTP vaccine.

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 (including febrile seizures) were reported in 8 Prevnar recipients and 4 control vaccine recipients within 3 days of immunization from October 1995 through April 1999. Of the 8 Prevnar recipients, 7 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. 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 concurrent vaccines), there was one seizure event reported within 3 days of immunization. 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 clear alternative cause) occurred in 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. 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 from the California State data from 1995-1997 and are presented in Table 17.

TABLE 17
Age and Season Adjusted Comparison with SIDS Rates in the NCKP Efficacy Trial With the Expected Rate from the California State Data for 1995 - 1997

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 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 either 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 has been evaluated in a total of five clinical studies 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 560 children from 4 ancillary studies who started immunization at 7 months to 9 years of age. Tables 18 and 19 summarize systemic reactogenicity data within 2 or 3 days across 4,748 subjects (13,039 infant doses and 1,706 toddler doses) for whom these data were collected and according to the pertussis vaccine administered concurrently.

TABLE 18
Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days For Efficacy Study and All Ancillary Studies When Prevnar Administered To Infants As a Primary Series at 2, 4, and 6 Months of Age

Systemic Event	Prevnar Concurrently With DTP-HbOC (9,191 Doses)*	Prevnar Concurrently With DTaP-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**
Rash or Hives	0.9	0.6	**0.3**

* Total from which reaction data are available varies between reactions from 8,874-9,191doses. 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 19
Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days For Efficacy Study and All Ancillary Studies When Prevnar Administered To Toddlers as a Fourth Dose at 12 to 15 Months of Age

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**
Rash or Hives	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.

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.

Post Marketing Experience

Additional adverse reactions identified from post-marketing experience are listed below:

ADMINISTRATION SITE CONDITIONS: Very rare: (<0.01%): injection site dermatitis, injection site urticaria, injection site pruritus.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Very rare: (<0.01%): Lymphadenopathy localized to the region of the injection site.

IMMUNE SYSTEM DISORDERS: Very rare: (<0.01%): hypersensitivity reaction including face edema, dyspnea, bronchospasm; anaphylactic/anaphylactoid reaction including shock.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Very rare: (<0.01%): angioneurotic edema, erythema multiforme

PSYCHIATRIC DISORDERS: Very common: (≥10%): Crying

RESPIRATORY: There have been spontaneous reports of apnoea in temporal association with the administration of Prevnar. In most cases Prevnar was administered concomitantly with other vaccines including diphtheria tetanus pertussis vaccine (DTP), diphtheria tetanus acellular pertussis vaccine (DTaP), hepatitis B vaccines, inactivated polio vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), measles-mumps-rubella vaccine (MMR), and/or varicella vaccine. In addition, in most of the reports, existing medical conditions such as history of apnoea, infection, prematurity, and/or seizure were present.

A large-scale post-marketing surveillance study examined healthcare utilization for adverse reactions occurring in infants (N=65,927) after Prevnar was given concomitantly with other recommended vaccines (diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenzae* type b, and hepatitis B) in the course of routine care. The primary safety outcomes analyses included an evaluation of pre-defined adverse events occurring in temporal relationship to immunization. The secondary safety outcomes analyses included comparisons to a historical control population of infants (1995-1996, N=40,223) who received diphtheria, tetanus, whole-cell pertussis, oral polio, *Haemophilus influenzae* type b, and hepatitis B vaccines prior to the introduction of Prevnar, as well as long-term follow-up of subjects originally enrolled in the NCKP Efficacy Trial (N=37,866).

The primary safety outcomes analyses support the known safety profile of Prevnar. The primary analyses did not demonstrate an increased risk of healthcare utilization for "wheezing diagnoses" in the first thirty days post-vaccination. Analyses of secondary safety outcomes indicated that there was a modest increase in the relative risk of hospitalization for "wheezing diagnoses" including asthma, bronchiolitis and pneumonia, among infants receiving Prevnar in comparison to historical controls. The relative risk of occurrence of these events after Prevnar, compared to historical controls was 1.23 (95% CI: 1.11, 1.35: $p<0.001$) after adjusting for age at first dose, length of follow-up, gender, race and seasonality. Potential confounders, such as concomitantly administered vaccines, changes in vaccine recommendations, yearly variation in respiratory syncytial virus (RSV) or influenza infections, or secular trends in respiratory disease incidence, could not be controlled. The long-term follow-up of subjects originally enrolled in the NCKP Efficacy Trial did not confirm this observation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

DOSAGE AND ADMINISTRATION

Administration

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. This product should not be used if particulate matter or discoloration is found.

Prevnar (Pneumococcal 7-valent Conjugate Vaccine) is a suspension containing an adjuvant. Shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. After shaking, the vaccine is a homogeneous, white suspension. The vaccine should not be used if it cannot be resuspended.

The vaccine is to be administered immediately after being drawn up into a syringe. The recommended dose is 0.5 mL given intramuscularly. This vaccine should not be injected intradermally, subcutaneously or intravenously since the safety and immunogenicity of these routes have not been evaluated.

The preferred sites are the anterolateral aspect of the thigh in infants or in 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. The needle should be long enough to reach the muscle mass and prevent the vaccine from seeping into subcutaneous tissue; but not so long as to involve underlying nerves and blood vessels or bone. Healthcare professionals should be familiar with the anatomy of the area into which they are injecting vaccine. An individual decision on needle size and site of injection must be made for each person on the basis of age, the volume of the material to be administered, the size of the muscle, and the depth below the muscle surface into which the material is to be injected.

Prevnar should not be mixed with other vaccines or products in the same syringe.
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, discard the syringe and prepare for a new injection at another site.

Vaccination Schedule

INFANTS

For infants, the immunization series of Prevnar consists of 3 doses of 0.5 mL each, at approximately 2 month intervals, followed by a fourth dose of 0.5mL 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. In one study, a small sub-population was administered the fourth dose from 15 to 18 months, and Prevnar was found to be both safe and immunogenic.

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 applies:

Age at first dose	**Total number of 0.5mL 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.

Limited safety data and limited immunogenicity data are available for patients treated with the previous vaccination schedule for older children. (See CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

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

PHARMACEUTICAL INFORMATION

Proper name: Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Composition: Prevnar (Pneumococcal 7-valent Conjugate Vaccine) is a sterile solution of saccharides of the capsular antigen of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F and diphtheria CRM_{197} protein.

Description: Individual polysaccharides of the capsular antigen of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to diphtheria CRM_{197} protein. Individual polysaccharides are prepared from purification of the culture broth of each serotype. The saccharides are directly conjugated to the protein carrier CRM_{197} protein by reductive amination. CRM_{197} is a non-toxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae strain C7 (ß197)* and/or *Corynebacterium diphtheriae strain C7 (ß197) pPx 350* grown in a casamino acids and yeast extract-based medium. CRM_{197} is purified through ultra filtration, ammonium sulfate precipitation, and ion-exchange chromatography to high purity. Each serotype is conjugated as a monovalent preparation prior to compounding as a multivalent vaccine. Individual glycoconjugates are analyzed for saccharide to protein ratios, for molecular size, free saccharide and free protein.

Name of Ingredient	Nominal Composition (µg) Per Unit Formula (0.5 mL dose)
Active Ingredients:	
7 Pneumococcal Conjugates (saccharides + CRM197):	
Polysaccharide Serotype 4	**2**
Polysaccharide Serotype 6B	**4**
Polysaccharide Serotype 9V	**2**
Polysaccharide Serotype 14	**2**
Polysaccharide Serotype 18C	**2**
Polysaccharide Serotype 19F	**2**
Polysaccharide Serotype 23F	**2**
CRM197 carrier protein	**~20**
Adjuvant:	**0.5 mg AlPO4**
Aluminum Phosphate	**(0.125 mg Al)**
Other Ingredients:	
Sodium Chloride	**4.5 mg**
Water for injection	**qs to 0.5 mL**

Stability & Storage Recommendations

Prevnar should be stored and shipped under refrigeration between 2°C to 8°C (36°F to 46°F). Stability studies indicate that potency of unopened vaccine is not significantly affected by exposure to temperatures between 8°C and 37°C for up to one week; however, this is not a storage or shipping recommendation. Do not freeze. Discard if the vaccine has been frozen.

Prevnar is stable until the expiration date indicated on the container label.

AVAILABILITY OF DOSAGE FORMS

Prevnar (Pneumococcal 7-Valent Conjugate Vaccine) is supplied as a single dose vial and pre-filled syringe containing 0.5 mL of product. Vials are available in packages containing a single (1) vial or five (5) vials. Pre-filled syringes are available in packages containing a single (1) syringe, five (5) syringes or ten (10) syringes. However not all pack sizes and dosage forms may be available on the Canadian market.

PHARMACOLOGY

The particular capsular polysaccharides of *S. pneumoniae* selected as the antigens in Prevnar (Pneumococcal 7-valent Conjugate Vaccine) are justified by reference to the serotypes known to be common causes of pneumococcal infection in children in developed countries.

Similar to other vaccines, the non-clinical development programme for Prevnar is much simpler than the conventional New Chemical Entity. The absence of certain types of pharmacokinetic and toxicity testing is justified by consideration of the nature of the product as a vaccine which is administered at defined and limited occasions during a lifetime, and by reference to its composition. Also, with vaccines, the animal models that are used to explore preventative activity infection are simplified surrogate indicators of natural diseases as they occur in young children. The nature and intensity [titre] of the clinical antibody response in a carefully standardized laboratory test is a much better indicator of probable clinical prophylactic efficacy.

Immunogenicity

There is considerable evidence from experiments performed in the rabbit, and in the mouse, which supports the following; the conjugates of the seven selected serotypes of *S. pneumoniae* are highly immunogenic; IgG antibodies are reliably generated against each serotype represented in Prevnar after administration to either species; immunological memory [i.e. an indicator of T cell-dependent responses] is stimulated; the dose determines the overall immunogenicity of the preparation; the $AlPO_4$ adjuvant increases the antibody titre. Further, the antibody formed in the rabbit not only binds to the strain specific capsular polysaccharide, as demonstrated by the ELISA, but it also has opsonising activity *in vitro*.

These findings together indicate that the vaccine is an effective immunogen and that it is more potent in the rabbit model than the marketed 23-valent unconjugated polysaccharide vaccine for the specific strains represented in Prevnar.

For a vaccine to be efficacious and safe, it must stimulate the production of an appropriate titre of antibody of the correct class, which does not react with normal body constituents, but does react with the micro-organism against which it is directed.

No specific laboratory experiments were performed to demonstrate the protective effect of the Prevnar vaccine. This was justified by considerable clinical and experimental experience of anti-polysaccharide vaccines of other types, which has shown that the ability of a vaccine to elicit the corresponding, high titre IgG antibody after administration of the intended human dose to the

rabbit is a guide to the immunogenicity and associated efficacy of that vaccine in humans. In addition, there is evidence of the opsonising efficacy of the antibodies produced in animals by this vaccine which is consistent with its performance in humans.

An important point about the value of the experiments in the rabbit concerns the immunogenicity of such a vaccine in young children, whose immune systems are relatively immature. Like young children, adult rabbits respond poorly to unconjugated polysaccharide antigens but develop high titres of antibody in response to conjugated polysaccharide antigens. In this way, the experiments in rabbits provided a good model of the responsiveness of the target population of young children.

The lack of enhanced reactivity with DNA of the antibodies stimulated by Prevnar was shown using sera from immunised humans. It is also true that the lack of cross reactivity between pneumococcal polysaccharide antibodies and normal body constituents has been shown by the absence of immunological reactions in patients with relevant diseases. This has been a common observation from the clinic over many years.

Overall the Prevnar vaccine has expected immunogenicity in pre-clinical laboratory models. The importance of the 7 strains of *S. pneumoniae* against which it raises antibodies has been shown in clinical practice. It has, therefore, the desired properties and activities of a vaccine against pneumococcal disease.

Toxicology

Prevnar (Pneumococcal 7-valent Conjugate Vaccine) has not undergone conventional toxicity testing. There are, however, considerable amounts of data from very large numbers of animals dosed IM or SC with various combinations of diverse pneumococcal polysaccharide conjugates plus $AlPO_4$ adjuvant in doses that match and exceed the human dose of Prevnar.

The animal experiments were mainly done to explore immunogenicity, but information was also obtained about general health and survival, as well as antibody titre after single or multiple doses. Neither in the rabbit nor in the mouse was there any suggestion of untoward responses or harmful effects of 9-valent and 7-valent vaccines, the former including the specific serotypes represented in Prevnar.

The experimental results obtained with single and multivalent conjugate candidate vaccines, which include the seven serotypes in Prevnar, have shown that it does not cause systemic toxicity, it lacks reactogenicity, and it produces only a minimal local reaction at injection sites.

Suggested by the experimental results, the vaccine has acceptably low toxicity. This is further supported by the composition and the general experience of other conjugated oligo- and polysaccharide vaccines and by the very extensive historical database on the lack of reactogenicity of pneumococcal polysaccharides as antigens.

Prevnar is a conjugate of polysaccharides with a non-toxic variant protein from C. *diphtheriae* CRM_{197}. The safety of each batch of the latter is demonstrated by showing, amongst other properties, that it lacks the specific toxic property of ADP-ribosyl transferase enzymatic activity inherent to active diphtheria toxin. Additional standard tests of safety, namely freedom from abnormal toxicity, 'general safety' and pyrogenicity, have been conducted.

Despite the varied nature of the available experimental data, Prevnar is regarded as not carrying a risk of local or systemic toxicity. It has also been shown that Prevnar does not lead in humans to the development of anti-DNA autoantibodies.

The lack of formal tests of genotoxicity, of reproduction toxicity and of carcinogenicity is considered acceptable in view of the nature and composition of Prevnar and its use as a single dose on up to four occasions, as well as being consistent with the general recommendations.

Overall, Prevnar is regarded as a safe and effective vaccine against pneumococcal infection, appropriate for administration to infants and young children.

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