

# Data Sheet

# Prevenar<sup>®</sup>

## NAME OF VACCINE

Pneumococcal conjugate vaccine, 7-valent.

## DESCRIPTION

Prevenar is a sterile, ready to use suspension for intramuscular injection. It contains saccharides of the capsular antigen of *Streptococcus pneumoniae* (pneumococcus) serotypes 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to diphtheria CRM<sub>197</sub> protein. CRM<sub>197</sub> is a non-toxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β 197) and/or *Corynebacterium diphtheriae* strain C7 (β 197) pPx 3520.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

### *Active ingredients*

Each 0.5 mL dose contains 2 micrograms of saccharide for serotypes 4, 9V, 14, 18C, 19F and 23F and 4 micrograms of serotype 6B per dose (16 micrograms total saccharide) conjugated to CRM<sub>197</sub> carrier protein and adsorbed on aluminium phosphate (0.5 mg).

### *Excipients*

Aluminium phosphate  
Sodium chloride  
Water for injections

## PHARMACOLOGY

*Streptococcus pneumoniae* is an important cause of morbidity and mortality in persons of all ages worldwide. It is a leading cause of death and illness in infants, among the elderly, and in persons who have certain underlying medical conditions. The organism causes invasive infections, including bacteraemia and meningitis, pneumonia and other lower respiratory tract infections, and upper respiratory tract infections including otitis media and sinusitis.

Surveys<sup>1,2</sup> have shown that the 7 serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) are likely to cover about 67% of invasive isolates in Indigenous Australian children and 80% - 85% of invasive isolates in urban Australian children.

In New Zealand, 2002 survey data<sup>3</sup> showed that the 7 serotypes in Prevenar would have covered 91% of invasive isolates found in children under the age of 2 years and 80% of invasive isolates found in children aged 2 to 5 years.

## Clinical efficacy

### Efficacy against invasive disease

Efficacy against invasive disease was assessed in a large-scale randomised double-blind clinical trial in a multiethnic population in Northern California (Kaiser Permanente trial). More than 37,816 infants were immunised with either Prevenar or a control vaccine (meningococcal conjugate group C vaccine), at 2, 4, 6 and 12-15 months of age. At the time of the study, the serotypes included in the vaccine accounted for 89 % of invasive pneumococcal disease (IPD).

A total of 52 cases of invasive disease caused by vaccine serotype had accumulated in a blinded follow-up period through April 20, 1999. The estimate of vaccine serotype specific efficacy was 94% (95% CI = 81- 99) in the intent-to-treat population and 97 % (95% CI = 85 - 100) in the per protocol (fully immunised) population (40 cases).

**TABLE 1: Efficacy of Prevenar® Against Invasive Disease Due to *S. pneumoniae* in Cases Accrued from October 15, 1995 to April 22, 1999**

Cases to April 20, 1999	Prevenar® Number of Cases	Control* Number of Cases	Efficacy	95% CI
<b>Vaccine serotypes</b>				
Per protocol	1	39	97.4%	84.8%, 99.9%
Intent-to-treat	3†	49	93.9%	81.0%, 98.8%
<i>All pneumococcal serotypes</i>				
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).

† Includes one case in a child who developed leukemia and became severely immunocompromised.

‡ Includes one case in an immunocompromised subject.

### Efficacy against pneumonia

In the Kaiser trial, efficacy was 87 % (95 % CI = 7 - 99) against bacteraemic pneumonia due to vaccine serotypes of *S. pneumoniae*.

Effectiveness (no microbiological confirmation of diagnosis was performed) against pneumonia was also assessed. The estimated risk reduction for clinical pneumonia with abnormal X-ray was 33% (95% CI = 6 - 52) and for clinical pneumonia with consolidation was 73 % (95% CI = 36 - 90) in the intent-to-treat analysis.

### Efficacy against acute otitis media

Results from clinical trials support efficacy of Prevenar against otitis media due to vaccine serotypes, but the effectiveness was lower than in invasive disease.

Efficacy of Prevenar against acute otitis media (AOM) was assessed as a primary endpoint in a randomised double blind clinical trial of 1,662 Finnish infants and as a secondary endpoint in the Northern California trial. The estimate for vaccine efficacy against vaccine-serotype AOM in the Finnish trial was 57% (95% CI= 44 - 67). In the intent-to-treat analysis the vaccine efficacy was 54% (95% CI = 41 - 64). A 34% increase in AOM due to non-vaccine serogroups was observed in immunised subjects. However, the overall benefit was a statistically significant reduction (34%) in the incidence of all pneumococcal AOM.

For recurrent otitis media ( $\geq 3$  episodes in 6 months or 4 in 12 months), the impact of the vaccine was a statistically non-significant 16 % reduction (95% CI = -6 - 35) in the Finnish trial. In the Northern California trial, the impact of the vaccine was a statistically significant 9.5 % reduction

(95% CI = 3 - 15). In Northern California, there was also a 20 % (95% CI = 2 - 35) reduction in the placement of ear tubes in vaccine recipients.

In the Finnish trial, the impact of the vaccine on total number of episodes of otitis media regardless of aetiology was a statistically non-significant 6 % reduction (95% CI = -4 - 16) while in the Northern California trial the impact of the vaccine was a statistically significant 7 % reduction (95% CI = 4 - 10).

### Immunogenicity

Vaccine induced antibody to capsular polysaccharide specific of each serotype are considered protective against invasive disease. The minimum protective antibody concentration against invasive disease has not been determined for any serotype.

A significant antibody response was seen following three and four doses to all vaccine serotypes in infants that received Prevenar, although geometric mean concentrations varied among serotypes. For all serotypes, peak primary series responses were seen after 3 doses, with boosting following the 4<sup>th</sup> dose. Prevenar induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following the primary series.

A plain polysaccharide challenge at 13 months, following the primary series with Prevenar, elicited an anamnestic (memory) antibody response for the 7 serotypes included in the vaccine, which is indicative for priming.

**TABLE 2: Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following the Third and Fourth Doses of Prevenar® or Control\* When Administered Concurrently With DTP-HbOC in the Kaiser Efficacy Study and the Finnish Otitis Media Study**

Serotype	Efficacy Study				Finnish Otitis Media Study			
	Post dose 3 GMC (95% CI for Prevenar®)		Post dose 4 GMC (95% CI for Prevenar®)		Post dose 3 GMC (95% CI for Prevenar®)		Post dose 4 GMC (95% CI for Prevenar®)	
	Prevenar® †	Control*	Prevenar® †	Control*	Prevenar® <sup>†</sup>	Control*	Prevenar® <sup>†</sup>	Control*
	N=88	N=92	N=68	N=61	N=54	N=52	N=55	N=54
4	1.46 (1.19, 1.78)	0.03	2.38 (1.88, 3.03)	0.04	1.70 (1.32, 2.20)	0.05	2.56 (2.00, 3.28)	0.11
6B	4.70 (3.59, 6.14)	0.08	14.45 (11.17, 18.69)	0.17	2.00 (1.35, 2.96)	0.09	9.05 (6.50, 12.59)	0.16
9V	1.99 (1.64, 2.42)	0.05	3.51 (2.75, 4.48)	0.06	2.48 (1.97, 3.11)	0.10	3.97 (3.20, 4.91)	0.21
14	4.60 (3.70, 5.74)	0.05	6.52 (5.18, 8.21)	0.06	6.28 (4.78, 8.23)	0.21	10.82 (8.30, 14.09)	0.21
18C	2.16 (1.73, 2.69)	0.04	3.43 (2.70, 4.37)	0.07	3.55 (2.80, 4.49)	0.08	6.51 (5.04, 8.41)	0.10
19F	1.39 (1.16, 1.68)	0.09	2.07 (1.66, 2.57)	0.18	3.28 (2.57, 4.18)	0.22	4.96 (3.86, 6.37)	0.41
23F	1.85 (1.46, 2.34)	0.05	3.82 (2.85, 5.11)	0.09	2.51 (1.84, 3.43)	0.10	6.25 (4.54, 8.61)	0.15

\* Control was investigational meningococcal group C conjugate vaccine (MnCC) in the Kaiser Efficacy Study and Hepatitis B vaccine in the Finnish Otitis Media Study.

† p<0.001 when Prevenar® compared to control for each serotype using a Wilcoxon's test in the Kaiser Efficacy Study. P-values were not calculated in the Finnish Otitis Media Study.

## **Clinical studies with Prevenar and Meningitec**

The concomitant administration of Prevenar and Meningitec at 2 and 6 months of age in different limbs gave immune responses that were similar to administration of either vaccine given alone. In this three-dose primary series clinical trial, the concomitant administration group was compared to a group given three doses of Prevenar or a group given two doses of Meningitec. (All infants also received three doses of Infanrix® hexa, DTPa-HBV-IPV / Hib, vaccine in the primary series.) There was no statistically significant difference in the proportion of infants who achieved a serotype-specific immune response  $\geq 0.35$  mcg/ml for each pneumococcal serotype, whether in the concomitant or the separate administration group. Likewise, there was no statistically significant difference in the percentage of infants with a MnC serum bactericidal activity titre  $\geq 1:8$  (concomitant 99.6% versus separate 98.0%) or  $\geq 1:128$  (concomitant 91.5% versus separate 84.6%). All children received a booster with the respective vaccine(s) given in the primary series.

## **Pharmacokinetic properties**

No pharmacokinetic data are available, as they are not appropriate for vaccines.

## **INDICATIONS**

Prevenar is indicated for the active immunisation of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by *Streptococcus pneumoniae*.

Prevenar is active against *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

## **CONTRAINDICATIONS**

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- The occurrence of an allergic reaction, or anaphylactoid reaction following prior administration of Prevenar.

## **PRECAUTIONS**

- Prevenar is not recommended for use in adult populations.
- Do not administer Prevenar intravenously.
- As with any vaccine, Prevenar may not protect 100% of individuals receiving the vaccine. Prevenar will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine, nor against other micro-organisms that cause invasive disease or otitis media.

### **Patients with minor illnesses**

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 aetiology. Although a severe or even moderate febrile illness is sufficient reason to postpone vaccinations, minor illnesses, such as a mild respiratory infection with or without low-grade fever, are not generally contraindications.

### **Patients with blood disorders**

Prevenar, as with any intramuscular injection, should be given with caution to infants or children with thrombocytopenia or any coagulation disorder or to those receiving anticoagulant therapy.

### **Patients with impaired immune responsiveness**

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents and cytotoxic agents), a genetic disorder, HIV infection, or other causes, may have reduced antibody response to

active immunisation. However, Human Immunodeficiency Virus (HIV) infection is not considered a contraindication for Prevenar.

### **Vaccination in high-risk groups**

Safety and immunogenicity data are limited in children with sickle cell disease and are not yet available for children in other specific high-risk groups for invasive pneumococcal disease (e.g. children with congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome). Vaccination in high-risk groups should be considered on an individual basis.

### **Risk of apnoea**

As with all injectable paediatric vaccines, the potential risk of apnoea should be considered when administering the primary immunisation series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born  $\leq$  30 weeks of gestation), who remain hospitalised 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.

### **Allergic reactions**

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

### **Prophylactic antipyretics**

Prophylactic antipyretic medication is recommended:

- For all children receiving Prevenar simultaneously with vaccines containing whole cell pertussis because of a higher rate of febrile reactions (see ADVERSE EFFECTS).
- For children with seizure disorders or with a prior history of febrile seizures.
- Antipyretic treatment should be initiated whenever warranted or when the temperature rises above 39 C.

### **Carcinogenicity, mutagenicity, impairment of fertility**

Prevenar has not been evaluated for carcinogenicity, mutagenicity, or impairment of fertility.

### **Use in pregnancy**

Category B2

Prevenar is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in animals or humans.

### **Use in lactation**

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

### **Use in children**

Prevenar has been shown to be usually well tolerated and immunogenic in infants from 6 weeks and in children up to 9 years. The safety and effectiveness of Prevenar in children below the age of six weeks or on, or after, the 10th birthday have not been established.

For children from 2 years through 5 years of age, a single dose immunisation schedule was used. Only limited data are available. A higher rate of local reactions, particularly tenderness, has been observed in children older than 24 months of age compared with infants (see ADVERSE EFFECTS).

## Use in the elderly

This vaccine is not recommended for use in any adult populations and is not to be used as a substitute for any pneumococcal polysaccharide 23-valent vaccine in geriatric populations.

## Other vaccinations

Although some antibody response to diphtheria toxoid may occur, immunisation with this vaccine does not substitute for routine diphtheria immunisation.

The use of Prevenar does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children, 24 months of age or older, with conditions such as sickle cell disease, asplenia, HIV infection, chronic illness, or who are immunocompromised, and therefore at higher risk for invasive disease due to *S. pneumoniae*. Consideration may be given to vaccinating these children with a priming dose of Prevenar, followed by a booster dose of the 23-valent pneumococcal polysaccharide vaccine. Based on limited data, the interval between vaccination with Prevenar and vaccination with 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks.

## Interactions with other paediatric vaccines

During clinical studies, Prevenar was administered simultaneously with diphtheria-tetanus-pertussis vaccine (DTP) or diphtheria-tetanus-acellular pertussis vaccine (DTPa), *Haemophilus Influenzae* type B vaccine (Hib), oral polio vaccine (OPV) or inactivated polio vaccine (IPV), hepatitis B vaccines, meningococcal serogroup C conjugate vaccine, measles-mumps-rubella vaccine (MMR) and varicella vaccine. Thus, the safety experience with Prevenar reflects the use of this product as part of the routine immunisation schedule. In some studies, differences in antibody response to some of the antigens have been inconsistently found, however, this is not anticipated to be of any clinical relevance.

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

Immunogenicity data from controlled clinical trials with concurrent administration of Prevenar are not available for Hib (PRP-OMP), Hib (PRP-OMP)-HepB and Tripacel brand DTPa (see Australian Standard Vaccine Schedule).

## ADVERSE EFFECTS

The safety of the vaccine was assessed in different controlled clinical studies in which more than 18,000 healthy infants (6 weeks to 18 months) were included. The majority of the safety experience comes from the efficacy trial in which 17,066 infants received 55,352 doses of Prevenar. Also, safety in previously unvaccinated older children has been assessed. In all studies, Prevenar was administered concurrently with the recommended childhood vaccines.

Amongst the most commonly reported adverse reactions were injection site reactions and fever. No increased local or systemic reactions within repeated doses were seen throughout the primary series. A higher rate of transient tenderness (36.5 % of which 18.5 % interfered with limb movement) was reported at the booster dose.

Limited data are available in older children in whom a higher rate of local reactions, primarily transient in nature, following a single dose has been observed. In children between 36-59 months of age, tenderness has been reported in up to 58 % of children, in which 20 % interfered with limb movement.

Reactogenicity was higher in children receiving whole cell pertussis vaccines concurrently. In a study, including 1,662 children, fever of  $\geq 38^{\circ}\text{C}$  was reported in 41.2 % of children who received Prevenar simultaneously with DTP as compared to 27.9 % in the control group. Fever of  $> 39^{\circ}\text{C}$  was reported in 3.3 % of children compared to 1.2 % in the control group.

Local reactions and systemic events within 2 to 3 days after vaccination have been listed in the following table per body system and per frequency and this for all age groups.

As with other paediatric vaccines, there have been spontaneous reports of apnoea in temporal association with the administration of Prevenar. In most cases, Prevenar was administered concomitantly with other vaccines including diphtheria-tetanus-pertussis (DTP), diphtheria-tetanus-acellular pertussis (DTPa), hepatitis B vaccines, inactivated polio (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.

An increased relative risk of hospitalization for various conditions collected under the term "wheezing diagnoses" has been reported from an observational surveillance study of infants receiving Prevenar when compared to a historical control group. Potential confounders, such as concomitantly administered vaccines, changes in those vaccines, yearly variation in respiratory syncytial virus (RSV) or influenza infections, or secular trends in respiratory disease incidence could not be controlled. Other analyses in this study, as well as the long-term follow-up of the large- scale, multicentre, controlled pivotal efficacy study, did not confirm this finding.

Body System	Very common ( $\geq 10\%$ ):	Common ( $\geq 1\%$ & $< 10\%$ )	Uncommon ( $\geq 0.1\%$ & $< 1\%$ )	Rare ( $\geq 0.01\%$ & $< 0.1\%$ )	Very Rare ( $< 0.01\%$ )
<i>Administration site conditions:</i>	Erythema, induration/ swelling, pain/tenderness.	Induration/ swelling or erythema $> 2.4\text{cm}$ . Tenderness interfering with movement.	-	-	Injection site dermatitis, injection site urticaria, injection site pruritus.
<i>General disorders:</i>	Fever $\geq 38^{\circ}\text{C}$ .	Fever $> 39^{\circ}\text{C}$ .	-	-	-
<i>Gastrointestinal disorders:</i>	Decreased appetite, vomiting, diarrhoea.	-	-	-	-
<i>Nervous system disorders:</i>	Drowsiness, restless sleep.	-	-	Seizures (including febrile seizures), hypotonic-hyporesponsive episode.	-
<i>Psychiatric disorders:</i>	Crying, irritability.	-	-	-	-
<i>Skin &amp; subcutaneous tissue disorders:</i>	-	-	Rash, urticaria or urticaria-like rash.	-	Angioneurotic oedema, erythema multiforme.
<i>Immune system disorders:</i>	-	-	-	-	Hypersensitivity reaction including face

Body System	Very common (≥ 10 %):	Common (≥ 1 % & < 10%)	Uncommon (≥ 0.1% & < 1 %)	Rare (≥ 0.01% & < 0.1%)	Very Rare (<0.01%)
					oedema, dyspnoea, bronchospasm, anaphylactic/ anaphylactoid reaction including shock.
<i>Blood and lymphatic system disorders:</i>	-	-	-	-	Lymphadenopathy localised to the region of the injection site.

## DOSAGE AND ADMINISTRATION

For intramuscular use only. Do not administer Prevenar intravenously, subcutaneously or intradermally, since the safety and immunogenicity of these routes have not been evaluated.

Prevenar is not to be mixed with other vaccines or products in the same syringe.

Prevenar is a suspension containing an adjuvant. Therefore, shake vigorously immediately prior to use to obtain a homogenous white suspension. The vaccine must not be used if it cannot be uniformly suspended. Parenteral products should be inspected visually for particulate matter or discolouration prior to use.

Prevenar is for single-use in one patient only. The suspension contains no antimicrobial agent. Discard any residue.

The dose is 0.5 mL given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred sites are the anterolateral aspect of the thigh of infants and young children, or the deltoid muscle of the upper arm of older children. The vaccine should not be injected in the gluteal area.

Vaccination schedule for infants				
Dose:	Dose 1	Dose 2	Dose 3	Dose 4
Age at Dose:	2 months	4 months	6 months	12-15 months

For infants the primary vaccination schedule consists of three doses beginning at 6 to 8 weeks of age with an interval of at least 4 weeks between doses. A single booster injection should be given in the second year, at least 2 months after the primary series.

Vaccination schedule for previously unvaccinated children ≥7 months of age	
Age at first dose	Total number of 0.5 mL doses
7-11 months of age	3
12-23 months of age	2
≥ 24 months of age	1

Previously unvaccinated infants from 7 to 11 months of age should receive two doses approximately 1 month apart, followed by a third dose in their second year, at least 2 months after the second dose.

Previously unvaccinated children from 12 to 23 months of age should receive two doses at least 2 months apart.

Previously unvaccinated children who are 24 months of age or older should receive a single dose.

## **OVERDOSAGE**

There have been reports of overdose with Prevenar, 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 Prevenar.

## **PRESENTATION**

Prevenar is presented as a suspension in 0.5 mL pre-filled syringes in packs of 1 and 10.

## **STORAGE**

Store at 2° to 8°C. (Refrigerate. Do not freeze).

Store in original package.

## **NAME AND ADDRESS OF SPONSOR**

Pfizer New Zealand Ltd  
P O Box 3998  
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

## **DATE OF PREPARATION**

1 November 2010

® Registered Trade Mark

---

<sup>1</sup> Torzillo P. & Gratten M., MJA Vol 173, 2 October 2000, S52

<sup>2</sup> McIntyre P. & Nolan T., MJA Vol 173, 2 October 2000, S55

<sup>3</sup> Data provided by the Institute of Environmental Science and Research Ltd.