Pages 1-4 inclusive exempt in full under section 22(1) of the FOI Act (irrelevant information)

PRODUCT INFORMATION

Prevenar® 0.5 mL

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_{197} protein. CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β 197) and/or *Corynebacterium diphtheriae* strain C7 (β 197) pPx 350.

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_{197} 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[1, 2] 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.

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
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).
† 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 (≥ 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 etiology 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 4th 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®†	Control*	Prevenar®†	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.

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

PRECAUTIONS

- 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.
- 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.
- 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.
- 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.
- Although some antibody response to diphtheria toxoid may occur, immunisation with this vaccine does not substitute for routine diphtheria immunisation.
- Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents and cytotoxic agents), a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.
- 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.
- 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 REACTIONS).

- 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 REACTIONS).

  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.

- Prevenar is not recommended for use in adult populations. The use of Prevenar does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children over the age of 24 months with asplenia, immunocompromised patients at risk of pneumococcal disease or persons at risk of complications from pneumococcal disease because of chronic illness. 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.

- Do not administer Prevenar intravenously.

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.

If the vaccine is used in subjects deficient in producing antibody, whether due to genetic defect or immunosuppressive therapy, the expected immune response may not be achieved. However, Human Immunodeficiency Virus (HIV) infection is not considered a contraindication for Prevenar.

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.

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, 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.

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 REACTIONS

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 °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 °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.

194

Body System	Very common (≥ 10 %):	Common (≥ 1 % &< 10%)	Uncommon (≥ 0.1% & <1 %)	Rare (≥ 0.01% &< 0.1%)	Very Rare (<0.01%)
Administration site conditions:	Erythema, induration/ swelling, pain/tenderness.	Induration/ swelling or erythema >2.4cm. Tenderness interfering with movement.	-	-	Injection Site dermatitis, injection site urticaria, injection site pruritus.
General disorders:	Fever ≥ 38 °C.	Fever > 39 °C.	-	-	-
Gastrointestinal disorders:	Decreased appetite, vomiting, diarrhoea.	-	-	-	-
Nervous system disorders:	Drowsiness, restless sleep.	-	-	Seizures (including febrile seizures), hypotonic-hyporesponsive episode.	-
Psychiatric disorders:	Irritability.	-	-	-	-
Skin & subcutaneous tissue disorders:	-	-	Rash, urticaria.	-	Angioneurotic oedema, erythema multiforme.
Immune System Disorders:	-	-	-	-	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm, anaphylactic/ anaphylactoid reaction including shock.
Blood and lymphatic system disorders:	-	-	-	-	Lymphadeno-pathy localised to the region of the injection site.

195 **DOSAGE AND ADMINISTRATION**

196 *Do not administer Prevenar intravenously or intradermally. Prevenar is not to be mixed with*
197 *other vaccines or products in the same syringe.*

198 *Before use, shake well to obtain a homogenous white suspension. The vaccine must not be used*
199 *if it cannot be uniformly suspended, or if it is discoloured.*

200 *Prevenar is to be administered immediately after being drawn up into a syringe. The suspension*
201 *contains no antimicrobial agent. Prevenar is for single-use in one patient only. Discard any*
202 *residue.*

203 The dose is 0.5 mL given intramuscularly, preferably into the anterolateral muscles of the thigh
204 of infants and young children, or the deltoid muscle of the upper arm of older children.

For infants the primary vaccination schedule consists of three doses at least 4 weeks apart 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.

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 is no experience with overdosage of Prevenar.

PRESENTATION

Prevenar is presented as a suspension in 0.5 mL single-dose glass vials in packs of 1 and 10.

Registration No: AUST R 73585.

SHELF-LIFE

~~2~~3 years stored at 2 to 8 °C (Refrigerate. Do not freeze)

NAME AND ADDRESS OF SPONSOR

Wyeth Australia Pty Limited, ABN 16 000 296 211
17-19 Solent Circuit, BAULKHAM HILLS NSW 2153

☎(02) 8850 8200 or (02) 9761 8200

® Registered Trade Mark

TGA Approval Date: 12 January 2001

Date of most recent ~~safety~~ notification: ~~4 June 2002~~14 February 2003

[1] Torzillo P. & Gratten M., MJA Vol 173, 2 October 2000, S52
[2] McIntyre P. & Nolan T., MJA Vol 173, 2 October 2000, S55