

PRODUCT INFORMATION

Prevenar[®] 0.5 mL

1 NAME OF VACCINE

2 Pneumococcal conjugate vaccine, 7-valent.

3 DESCRIPTION

4 Prevenar is a sterile, ready to use suspension for intramuscular injection. It contains
 5 saccharides of the capsular antigen of *Streptococcus pneumoniae* (pneumococcus) serotypes
 6 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to diphtheria CRM₁₉₇ protein.
 7 CRM₁₉₇ is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium*
 8 *diphtheriae* strain C7 (β 197) and/or *Corynebacterium diphtheriae* strain C7 (β 197) pPx
 9 350.

10 Active ingredients

11 Each 0.5 mL dose contains 2 micrograms of saccharide for serotypes 4, 9V, 14, 18C, 19F,
 12 and 23F, and 4 micrograms of serotype 6B per dose (16 micrograms total saccharide)
 13 conjugated to CRM₁₉₇ carrier protein and adsorbed on aluminium phosphate (0.5 mg).

14 Excipients

15 Aluminium phosphate
 16 Sodium chloride
 17 Water for injections

18 PHARMACOLOGY

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

24 Surveys^{1,2} have shown that the 7 serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F,
 25 23F) are likely to cover about 67% of invasive isolates in Indigenous Australian children and
 26 80% - 85% of invasive isolates in urban Australian children.

27 Clinical Efficacy

28 Efficacy against invasive disease

29 Efficacy against invasive disease was assessed in a large-scale randomised double-blind
 30 clinical trial in a multiethnic population in Northern California (Kaiser Permanente trial).
 31 More than 37,816 infants were immunised with either Prevenar or a control vaccine
 32 (meningococcal conjugate group C vaccine), at 2, 4, 6 and 12-15 months of age. At the time
 33 of the study, the serotypes included in the vaccine accounted for 89 % of invasive
 34 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 ($\mu\text{g/mL}$) 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.

83 INDICATIONS

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

87 Prevenar is active against *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and
88 23F.

89 CONTRAINDICATIONS

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

93 PRECAUTIONS

- 94 • The decision to administer or delay vaccination because of a current or recent febrile
95 illness depends largely on the severity of the symptoms and their aetiology. Although a
96 severe or even moderate febrile illness is sufficient reason to postpone vaccinations, minor
97 illnesses, such as a mild respiratory infection with or without low-grade fever, are not
98 generally contraindications.
- 99 • Prevenar will not protect against *Streptococcus pneumoniae* serotypes other than those
100 included in the vaccine, nor against other micro-organisms that cause invasive disease or
101 otitis media.
- 102 • Prevenar, as with any intramuscular injection, should be given with caution to infants or
103 children with thrombocytopenia or any coagulation disorder or to those receiving
104 anticoagulant therapy.
- 105 • As with all injectable vaccines, appropriate medical treatment and supervision must
106 always be readily available in case of a rare anaphylactic event following the
107 administration of the vaccine.
- 108 • Although some antibody response to diphtheria toxoid may occur, immunisation with this
109 vaccine does not substitute for routine diphtheria immunisation.
- 110 • Children with impaired immune responsiveness, whether due to the use of
111 immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites,
112 alkylating agents and cytotoxic agents), a genetic ~~defect~~disorder, HIV infection, or other
113 causes, may have reduced antibody response to active immunisation.
- 114 • Safety and immunogenicity data are limited in children with sickle cell disease and are not
115 yet available for children in other specific high-risk groups for invasive pneumococcal
116 disease (e.g. children with congenital and acquired splenic dysfunction, HIV-infected,
117 malignancy, nephrotic syndrome). Vaccination in high-risk groups should be considered
118 on an individual basis.
- 119 • For children from 2 years through 5 years of age, a single dose immunisation schedule
120 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.~~

- 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.

- 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 $\geq 38^{\circ}\text{C}$ 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.

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 (DTaP), 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.

| Body System | Very common (≥ 10 %): | Common (≥ 1 % & < 10%) | Uncommon (≥ 0.1% & < 1 %) | Rare (≥ 0.01% & < 0.1%) | Very Rare (<0.01%) |
|--|--|--|------------------------------|--|--|
| <i>Administration site conditions:</i> | Erythema, induration/ swelling, pain/tenderness. | Induration/ swelling or erythema >2.4cm. Tenderness interfering with movement. | - | - | Injection Site dermatitis, injection site urticaria, injection site pruritus. |
| <i>General disorders:</i> | Fever ≥ 38 °C. | Fever > 39 °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> | Irritability. | - | - | - | - |
| <i>Skin & subcutaneous tissue disorders:</i> | - | - | Rash, urticaria. | - | Angioneurotic oedema, erythema multiforme. |
| <i>Immune System Disorders:</i> | - | - | - | - | Hypersensitivity reaction including face 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

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

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

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

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

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

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

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

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

231 OVERDOSAGE

232 There have been reports of overdose with Prevenar, including cases of administration of a
 233 higher than recommended dose and cases of subsequent doses administered closer than
 234 recommended to the previous dose. Most individuals were asymptomatic. In general, adverse
 235 events reported with overdose have also been reported with recommended single doses of
 236 Prevenar. ✓

237 PRESENTATION

238 Prevenar is presented as a suspension in 0.5 mL single-dose glass vials in packs of 1 and 10.
 239 Registration No: ~~AUST R 73585.~~

240 STORAGE

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

242 NAME AND ADDRESS OF SPONSOR

243 Wyeth Australia Pty Limited, ABN 16 000 296 211
 244 17-19 Solent Circuit, BAULKHAM HILLS NSW 2153
 245 ☎(02) 8850 8200 or (02) 9761 8200

247 TGA Approval Date: ~~12 January 2001~~

~~Date of most recent safety notification: 4 June 2002~~

248 ~~Date of most recent amendment: 3 April 2003~~

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¹ Torzillo P. & Gratten M., MJA Vol 173, 2 October 2000, S52

² McIntyre P. & Nolan T., MJA Vol 173, 2 October 2000, S55

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PRODUCT INFORMATION

Prevenar[®]

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 CRM₁₉₇ protein. CRM₁₉₇ 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 CRM₁₉₇ 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
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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% |
| <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.

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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 disorder, 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, 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.
- 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 $\geq 38^{\circ}\text{C}$ 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.

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 (DTaP), 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.

| Body System | Very common (≥ 10 %): | Common (≥ 1 % & < 10%) | Uncommon (≥ 0.1 % & < 1 %) | Rare (≥ 0.01 % & < 0.1 %) | Very Rare (< 0.01 %) |
|--|--|--|-------------------------------|--|--|
| <i>Administration site conditions:</i> | Erythema, induration/ swelling, pain/tenderness. | Induration/ swelling or erythema > 2.4 cm. Tenderness interfering with movement. | - | - | Injection Site dermatitis, injection site urticaria, injection site pruritus. |
| <i>General disorders:</i> | Fever ≥ 38 °C. | Fever > 39 °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> | Irritability. | - | - | - | - |
| <i>Skin & subcutaneous tissue disorders:</i> | - | - | Rash, urticaria. | - | Angioneurotic oedema, erythema multiforme. |
| <i>Immune System Disorders:</i> | - | - | - | - | Hypersensitivity reaction including face 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

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

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

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

The dose is 0.5 mL given intramuscularly, preferably into the anterolateral muscles of the thigh 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 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 single-dose glass vials in packs of 1 and 10.

STORAGE

Store 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

TGA Approval Date:

® Registered Trade Mark

¹ Torzillo P. & Gratten M., MJA Vol 173, 2 October 2000, S52

² McIntyre P. & Nolan T., MJA Vol 173, 2 October 2000, S55

Marketed Variant Version

PRODUCT INFORMATION

Prevenar[®] 0.5 mL

1 NAME OF VACCINE

2 Pneumococcal conjugate vaccine, 7-valent.

3 DESCRIPTION

4 Prevenar is a sterile, ready to use suspension for intramuscular injection. It contains
5 saccharides of the capsular antigen of *Streptococcus pneumoniae* (pneumococcus) serotypes
6 4, 6B, 9V, 14, 18C, 19F and 23F individually conjugated to diphtheria CRM₁₉₇ protein.
7 CRM₁₉₇ is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium*
8 *diphtheriae* strain C7 (β 197) and/or *Corynebacterium diphtheriae* strain C7 (β 197) pPx
9 350.

10 *Active ingredients*

11 Each 0.5 mL dose contains 2 micrograms of saccharide for serotypes 4, 9V, 14, 18C, 19F,
12 and 23F, and 4 micrograms of serotype 6B per dose (16 micrograms total saccharide)
13 conjugated to CRM₁₉₇ carrier protein and adsorbed on aluminium phosphate (0.5 mg).

14 *Excipients*

15 Aluminium phosphate
16 Sodium chloride
17 Water for injections

18 PHARMACOLOGY

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

24 Surveys^{1,2} have shown that the 7 serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F,
25 23F) are likely to cover about 67% of invasive isolates in Indigenous Australian children and
26 80% - 85% of invasive isolates in urban Australian children.

27 *Clinical Efficacy*

28 **Efficacy against invasive disease**

29 Efficacy against invasive disease was assessed in a large-scale randomised double-blind
30 clinical trial in a multiethnic population in Northern California (Kaiser Permanente trial).
31 More than 37,816 infants were immunised with either Prevenar or a control vaccine
32 (meningococcal conjugate group C vaccine), at 2, 4, 6 and 12-15 months of age. At the time
33 of the study, the serotypes included in the vaccine accounted for 89 % of invasive
34 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.

82

83 **INDICATIONS**

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

87 Prevenar is active against *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and
88 23F.

89 **CONTRAINDICATIONS**

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

93 **PRECAUTIONS**

- 94 • The decision to administer or delay vaccination because of a current or recent febrile
95 illness depends largely on the severity of the symptoms and their aetiology. Although a
96 severe or even moderate febrile illness is sufficient reason to postpone vaccinations, minor
97 illnesses, such as a mild respiratory infection with or without low-grade fever, are not
98 generally contraindications.
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100 included in the vaccine, nor against other micro-organisms that cause invasive disease or
101 otitis media.
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104 anticoagulant therapy.
- 105 • As with all injectable vaccines, appropriate medical treatment and supervision must
106 always be readily available in case of a rare anaphylactic event following the
107 administration of the vaccine.
- 108 • Although some antibody response to diphtheria toxoid may occur, immunisation with this
109 vaccine does not substitute for routine diphtheria immunisation.
- 110 • Children with impaired immune responsiveness, whether due to the use of
111 immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites,
112 alkylating agents and cytotoxic agents), a genetic ~~defect~~disorder, HIV infection, or other
113 causes, may have reduced antibody response to active immunisation.
- 114 • Safety and immunogenicity data are limited in children with sickle cell disease and are not
115 yet available for children in other specific high-risk groups for invasive pneumococcal
116 disease (e.g. children with congenital and acquired splenic dysfunction, HIV-infected,
117 malignancy, nephrotic syndrome). Vaccination in high-risk groups should be considered
118 on an individual basis.
- 119 • For children from 2 years through 5 years of age, a single dose immunisation schedule
120 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.~~

- 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.

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Category B2

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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.

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

166 Use in the Elderly

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

169 Interactions with Other Paediatric Vaccines

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

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

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 188 fever.

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 190 primary series. A higher rate of transient tenderness (36.5 % of which 18.5 % interfered with
 191 limb movement) was reported at the booster dose.

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

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 197 a study, including 1,662 children, fever of $\geq 38^{\circ}\text{C}$ was reported in 41.2 % of children who
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 199 Fever of $> 39^{\circ}\text{C}$ was reported in 3.3 % of children compared to 1.2 % in the control group.

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

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 203 administration of Prevenar. In most cases, Prevenar was administered concomitantly with

other vaccines including diphtheria-tetanus-pertussis (DTP), diphtheria-tetanus-acellular pertussis (DTaP), 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.

| Body System | Very common (≥ 10 %): | Common (≥ 1 % & < 10%) | Uncommon (≥ 0.1% & < 1 %) | Rare (≥ 0.01% & < 0.1%) | Very Rare (<0.01%) |
|--|--|--|------------------------------|--|--|
| <i>Administration site conditions:</i> | Erythema, induration/ swelling, pain/tenderness. | Induration/ swelling or erythema >2.4cm. Tenderness interfering with movement. | - | - | Injection Site dermatitis, injection site urticaria, injection site pruritus. |
| <i>General disorders:</i> | Fever ≥ 38 °C. | Fever > 39 °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> | Irritability. | - | - | - | - |
| <i>Skin & subcutaneous tissue disorders:</i> | - | - | Rash, urticaria. | - | Angioneurotic oedema, erythema multiforme. |
| <i>Immune System Disorders:</i> | - | - | - | - | Hypersensitivity reaction including face 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

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

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

215 *Prevenar is to be administered immediately after being drawn up into a syringe. The*
 216 *suspension contains no antimicrobial agent. Prevenar is for single-use in one patient only.*
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 219 thigh of infants and young children, or the deltoid muscle of the upper arm of older children.

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

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

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

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

231 **OVERDOSAGE**

232 There have been reports of overdose with Prevenar, including cases of administration of a
 233 higher than recommended dose and cases of subsequent doses administered closer than
 234 recommended to the previous dose. Most individuals were asymptomatic. In general, adverse
 235 events reported with overdose have also been reported with recommended single doses of
 236 Prevenar.

237 **PRESENTATION**

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

239 ~~Registration No: AUST R 73585.~~

240 **STORAGE**

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

242 **NAME AND ADDRESS OF SPONSOR**

243 Wyeth Australia Pty Limited, ABN 16 000 296 211
 244 17-19 Solent Circuit, BAULKHAM HILLS NSW 2153
 245 ☎(02) 8850 8200 or (02) 9761 8200

246
 247 TGA Approval Date: ~~12 January 2001~~

~~Date of most recent safety notification: 4 June 2002~~

248 ~~Date of most recent amendment: 3 April 2003~~

249
 250 ® Registered Trade Mark

¹ Torzillo P. & Gratten M., MJA Vol 173, 2 October 2000, S52

² McIntyre P. & Nolan T., MJA Vol 173, 2 October 2000, S55



PRODUCT INFORMATION

Prevenar®**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 CRM₁₉₇ protein. CRM₁₉₇ 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 CRM₁₉₇ 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 disorder, 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, 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.
- 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 $\geq 38^{\circ}\text{C}$ 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.

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 (DTaP), 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.

| Body System | Very common (≥ 10 %): | Common (≥ 1 % & < 10%) | Uncommon (≥ 0.1 % & < 1 %) | Rare (≥ 0.01 % & < 0.1 %) | Very Rare (< 0.01 %) |
|--|--|---|-------------------------------|--|--|
| <i>Administration site conditions:</i> | Erythema, induration/ swelling, pain/tenderness. | Induration/ swelling or erythema > 2.4cm. Tenderness interfering with movement. | - | - | Injection Site dermatitis, injection site urticaria, injection site pruritus. |
| <i>General disorders:</i> | Fever ≥ 38 °C. | Fever > 39 °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> | Irritability. | - | - | - | - |
| <i>Skin & subcutaneous tissue disorders:</i> | - | - | Rash, urticaria. | - | Angioneurotic oedema, erythema multiforme. |
| <i>Immune System Disorders:</i> | - | - | - | - | Hypersensitivity reaction including face 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

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

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

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

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

18

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 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 single-dose glass vials in packs of 1.

STORAGE

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

NAME AND ADDRESS OF SPONSOR

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