PRODUCT INFORMATION

Prevenar 13®

NAME OF THE MEDICINE

Prevenar 13

Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

DESCRIPTION

The vaccine is a ready to use homogeneous white suspension for intramuscular injection, supplied as a pre-filled syringe.

Active ingredients

Each 0.5 mL dose contains:

2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F

4.4 µg of pneumococcal purified capsular polysaccharides for serotype 6B.

Each serotype is individually conjugated to non-toxic diphtheria CRM_{197} protein and adsorbed on aluminium phosphate (0.565 mg).

Excipients

Succinic acid, polysorbate 80, aluminium phosphate, sodium chloride in water for injections.

PHARMACOLOGY

Burden of Disease

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.

Infants and children less than 5 years of age

Based on serotype surveillance performed before the introduction of Prevenar (7-valent), Prevenar 13 is estimated to cover 93.3% of serotypes causing IPD (Invasive Pneumococcal Disease) among children less than 5 years of age in Australia (Watson M. et al., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 92.8% in New Zealand (Heffernan H.M., et al., *Epidemiology of Infections* 2007; 1-8.)

Prevenar 13 is estimated to cover over 90% of serotypes causing antibiotic resistant IPD.

Adults

The incidence of invasive pneumococcal disease (IPD) in adults increases with age from 18 years, risk factors (smoking status or alcohol use), and underlying co-morbidities (see Special populations below). Bacteraemic pneumonia, bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults.

Based on serotype surveillance performed before the introduction of Prevenar (7-valent), Prevenar 13 is estimated to cover 81.9% of serotypes causing IPD among adults aged 65 years and older in Australia (Watson M. et al., Communicable Disease Intelligence 2004; 28(4): 455-464) and 77.4% in New Zealand (Heffernan H.M., et al., Epidemiology of Infections 2007; 1-8.).

Following the introduction of Prevenar (7-valent) on to the National Immunisation Program (NIP) for children, Prevenar 13 is estimated to cover 62.2% of serotypes causing IPD among adults aged 65 years and older in Australia, based on National Notifiable Diseases Surveillance System data from 2008.

Special populations

The risk for invasive pneumococcal disease is increased in individuals with anatomical or functional asplenia, diabetes mellitus, asthma, chronic cardiovascular, pulmonary, kidney or liver disease, and it is highest in those who are immune-suppressed such as those with malignant haematological diseases or HIV infection.

Pharmacodynamics

Pharmacotherapeutic group: pneumococcal vaccines.

Prevenar 13 contains the 7 pneumococcal capsular polysaccharides that are in Prevenar (7-valent) conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM_{197} carrier protein.

Mode of action

The protection afforded by Prevenar 13 vaccination is mediated by the induction of antibodies against the pneumococcal capsular serotypes in the vaccine.

B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. The immune response to most antigens is T-dependent and involves the collaboration of CD4+ T-cells and B-cells, recognizing the antigen in a linked fashion. CD4+ T-cells (T-helper cells) provide signals to B-cells directly through cell surface protein interactions, and indirectly through the release of cytokines. These signals result in proliferation and differentiation of the B-cells, and production of high-affinity antibodies. CD4+ T-cell signaling is a requisite for the generation of long-lived B-cells called plasma cells, which continuously produce antibodies of several isotypes (with an IgG component) and memory B-cells that rapidly mobilize and secrete antibodies upon re-exposure to the same antigen.

Bacterial capsular polysaccharides (PSs), while varied in chemical structure, share the common immunological property of being largely T-independent antigens. In the absence of T-cell help,

PS-stimulated B-cells predominantly produce IgM antibodies; there is generally no affinity maturation of the antibodies, and no memory B-cells are generated. As vaccines, PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of PSs to a protein carrier overcomes the T-cell–independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of *Streptococcus pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody response and induces immune memory. This has been demonstrated to elicit booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not available for vaccines.

CLINICAL TRIALS

Prevenar 13 immunogenicity clinical trials in infants and children

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide IgG antibody concentration of 0.35 µg/mL using an enzyme-linked immunosorbent assay, measured one month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against IPD. This recommendation is largely based upon the observed correlation between immunogenicity and IPD efficacy from three placebo-controlled trials with either Prevenar (7-valent) or the investigational 9-valent CRM_{197} conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

Immune responses following a three-dose primary infant series

Clinical trials have been conducted in a number of European countries and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL and opsonophagocytic activity (OPA) antibody titers ³ 1:8, one month after a three-dose primary series (at 2, 4 and 6 months) and after booster dosing, from representative studies are presented below (Table 1):

Table 1: Percentage of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations ³ 0.35 µg/mL and OPA antibody titer ³ 1:8 following Prevenar 13 administration in a 2, 4, 6 month primary schedule

Serotype		Primary Schedule (2, 4, 6 months)	Booster
		IgG (N=897-924) OPA (N=91-94)	IgG (N=458-479) OPA (N=88-92)
1	IgG ³ 0.35 µg/mL	95.6-99.3%	98.7-100.0%
	OPA Antibody ³ 1:8	98.9%	98.9%
3	IgG ³ 0.35 µg/mL	63.5-90.3%	90.5-92.2%
	OPA Antibody ³ 1:8	96.8%	97.8%
4	IgG ³ 0.35 µg/mL	94.4-98.9%	99.1-99.2%

	OPA Antibody [3] 1:8	97.8%	98.9%
5	IgG [3] 0.35 µg/mL	89.7-97.3%	99.1-99.6%
	OPA Antibody [3] 1:8	92.3%	98.9%
6A	IgG [3] 0.35 µg/mL	96.0-98.2%	99.1-100.0%
	OPA Antibody [3] 1:8	100.0%	98.9%
6B	IgG [3] 0.35 µg/mL	87.3-98.5%	99.6%
	OPA Antibody [3] 1:8	98.9%	98.9%
7F	IgG [3] 0.35 µg/mL	98.4-100.0%	98.8-99.6%
	OPA Antibody [3] 1:8	100.0%	100.0%
9V	IgG [3] 0.35 µg/mL	90.5-99.3%	99.1-100.0%
	OPA Antibody [3] 1:8	100.0%	98.9%
14	IgG [3] 0.35 µg/mL	97.4-98.2%	98.7-100.0%
	OPA Antibody [3] 1:8	100.0%	100.0%
18C	IgG [3] 0.35 µg/mL	96.8-98.1%	98.7-99.6%
	OPA Antibody [3] 1:8	100.0%	98.9%
19A	IgG [3] 0.35 µg/mL	98.4-99.6%	100.0%
	OPA Antibody [3] 1:8	100.0%	97.8%
19F	IgG [3] 0.35 µg/mL	98.0-99.3%	99.6-100.0%
	OPA Antibody [3] 1:8	90.4%	96.7%
23F	IgG [3] 0.35 µg/mL	87.2-94.6%	99.1-99.6%
	OPA Antibody [3] 1:8	98.9%	98.9%

In Prevenar 13 recipients, antipolysaccharide binding antibody for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically active antibody).

Immune responses following a two-dose primary infant series

The immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥ 0.35 mg/mL one month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) and 23F (55.8% to 68.6%). Compared to a three-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a two-dose infant series for most serotypes.

Booster responses following two-dose and three-dose primary infant series

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. Antibody responses to booster doses following two-dose or three-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged from 7 months to 5 years, age appropriate catch-up immunisation schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

Preterm Infants

Safety and immunogenicity of Prevenar 13 given at 2, 3, 4 and 12 months was assessed in 100 prematurely born infants (Estimated Gestational Age [EGA] mean, 31 weeks; range, 26 to 36 weeks) and compared with 100 infants born at term (EGA mean, 39 weeks; range, 37 to 42 weeks). More than 85% achieved a pneumococcal polysaccharide IgG binding antibody concentration ≥0.35 μg/mL 1 month after the infant series, except for serotypes 5 (71.7%), 6A (82.7%), and 6B (72.7%) in the preterm group. For these 3 serotypes, the proportion of responders among preterm infants was significantly lower than among term infants. One month after the toddler dose, evidence of priming was observed as the proportion of subjects in each group achieving this same antibody concentration threshold was >97%, except for serotype 3 (71% in preterm infants and 79% in term infants). In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

Effect on nasopharyngeal S. pneumoniae serotypes

Prevenar 13 is associated with the prevention of nasopharyngeal colonisation of vaccine type serotypes and this may contribute to protection against pneumococcal disease.

In a randomised double-blind study, 930 infants received Prevenar 13 and 933 received Prevenar (7-valent) at 2, 4, 6 and 12 months of age in Israel. The proportion of subjects with a newly identified nasopharyngeal (NP) acquisition in each vaccine group was assessed at 7, 12, 13, 18 and 24 months. Prevenar 13 significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with Prevenar. Among the common serotypes, a significant reduction in the proportion of subjects with newly identified NP acquisition of serotype 19F was observed in the Prevenar13 group compared with the Prevenar group. For the remaining 6 common serotypes, similar rates of NP acquisition were observed in both vaccines groups.

Children and Adolescents 5 to 17 years of age

In an open-label study in 592 healthy children and adolescents including those with asthma who may be predisposed to pneumococcal infection, Prevenar 13 elicited immune responses to all 13 serotypes. A single dose of Prevenar 13 was given to children 5 to 10 years of age previously vaccinated with at least 1 dose of Prevenar, and children and adolescents 10 to 17 years of age who had never received a pneumococcal vaccine.

In both the children 5 to 10 years of age and children and adolescents aged 10 to 17 years, the immune response to Prevenar 13 was non-inferior (i.e. the lower limit of the 2-sided 95% CI for the GMR >0.5) to Prevenar for the 7 common serotypes and to Prevenar 13 for the 6 additional serotypes, compared to the immune response after the fourth dose in infants vaccinated at 2, 4, 6 and 12-15 months of age as measured by serum IgG.

Table 2: Comparison of Pneumococcal IgG GMC (µg/mL) post vaccination – *Evaluable Immunogenicity Population*

	13vPnC Group 3c (Study 3011)			7vPnC (Study 3005)			Ratio
Serotype	**n**	**GMC**	**95% CI**	**n**	**GMC**	**95% CI**	
7vPnC							
4	169	8.45	7.24, 9.87	173	2.79	2.45, 3.18	3.03 (2.48, 3.71)
6B	171	53.56	45.48, 63.07	173	9.47	8.26, 10.86	5.66 (4.57, 6.99)
9V	171	9.51	8.38, 10.78	173	1.97	1.77, 2.19	4.83 (4.10, 5.70)
14	169	29.36	24.78, 34.78	173	8.19	7.31, 9.18	3.58 (2.93, 4.39)
18C	171	8.23	7.13, 9.51	173	2.33	2.05, 2.65	3.53 (2.91, 4.29)
19F	171	17.58	14.95, 20.67	173	3.31	2.87, 3.81	5.31 (4.29, 6.58)
23F	169	11.26	9.79, 12.95	173	4.49	3.86, 5.23	2.51 (2.04, 3.08)

Table 3: Comparison of Pneumococcal IgG GMC (µg/mL) post-vaccination – *Evaluable Immunogenicity Population*

	13vPnC Group 3c (Study 3011)			13vPnC (Study 3005)			Ratio
Serotype	**n**	**GMC**	**95% CI**	**n**	**GMC**	**95% CI**	
Additional							
1	171	3.57	3.05, 4.18	1068	2.90	2.75, 3.05	1.23 (1.07, 1.42)
3	171	2.38	2.07, 2.74	1065	0.75	0.72, 0.79	3.17 (2.78, 3.62)
5	171	5.52	4.82, 6.32	1068	2.85	2.72, 2.98	1.94 (1.71, 2.20)
6A	169	21.51	18.15, 25.51	1063	7.11	6.78, 7.46	3.03 (2.64, 3.47)
7F	170	6.24	5.49, 7.08	1067	4.39	4.18, 4.61	1.42 (1.24, 1.62)
19A	170	17.18	15.01, 19.67	1056	8.44	8.05, 8.86	2.03 (1.78, 2.32)

In children and adolescents aged 10 to17 years of age, OPA Geometric Mean Titres (GMTs) 1 month after vaccination were non-inferior (i.e. the lower limit of the 2-sided 95% CI for the GMR >0.5) to OPA GMTs in the 5-10 year old age group for 12 of the 13 serotypes (except serotype 3).

Table 4: Comparison of Pneumococcal OPA GMTs post-vaccination – *Evaluable Immunogenicity Population*

	Prevenar 13 (10 through 17 years of age)			Prevenar 13 (5 through 9 years of age)			Ratio
Serotype	**n**	**GMT**	**95% CI**	**n**	**GMT**	**95% CI**	
7vPnC							
4	188	6912	6101, 7831	181	4629	4017, 5334	1.5 (1.24, 1.80)
6B	183	14224	12316, 16427	178	14496	13164, 17083	0.9 (0.78, 1.15)
9V	186	4485	4001, 5027	180	4733	4203, 5328	0.9 (0.80, 1.12)
14	187	6894	6028, 7884	176	4759	4120, 5497	1.4 (1.19, 1.76)
18C	182	6263	5436, 7215	175	8815	7738, 10041	0.7 (0.59, 0.86)
19F	184	2280	1949, 2668	178	1559	1293, 1879	1.5 (1.15, 1.86)
23F	187	3808	2255, 4323	176	3245	2819, 3736	1.2 (0.97, 1.42)
Additional							

1	189	319	271, 376	179	187	160, 219	1.7 (1.35, 2.13)
3	181	114	100, 129	178	202	181, 226	0.6 (**0.48**, 0.67)
5	183	336	270, 418	178	491	426, 565	0.7 (0.53, 0.89)
6A	182	9928	8457, 11655	178	7514	6351, 8891	1.3 (1.05, 1.67)
7F	185	6584	5829, 7436	178	10334	9099, 11737	0.6 (0.53, 0.76)
19A	187	1276	1132, 1439	180	1180	1048, 1329	1.1 (0.91, 1.28)

Prevenar (7-valent) protective efficacy

The efficacy of Prevenar (7-valent) was evaluated in two major trials – the Northern California Kaiser Permanente (NCKP) trial and the Finnish Otitis Media trial (FinOM). Both trials were randomised, double-blind, active-control trials in which infants were randomised to receive either Prevenar (7-valent) or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a four-dose series at 2, 4, 6, and 12 - 15 months of age. The various efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 5).

Table 5: Summary of efficacy of Prevenar (7-valent)

Test	Study	N	VE*	95% CI
Invasive Pneumococcal Disease (IPD)				
Per-protocol	NCKP	30,258	97%	85, 100
Intent-to-treat		37,866	94%	81, 99
Pneumonia (Per-protocol)				
With bacteraemia			87.5%	7, 99
C*linical pneumonia with abnormal chest X-ray*			35%	4, 56
Acute Otitis Media (AOM)				
Per-protocol (reduction of)	NCKP	37,868		
Total episodes			7%	4, 10
Recurrent AOM (3 episodes in 6 mo. or 4 episodes in 1 yr.)			9%	3, 15
Recurrent AOM (5 episodes in 6 mo. or 6 episodes in 1 yr.)			23%	7, 36
Tympanostomy tube placement			20%	2, 35
Per-protocol (reduction of)	FinOM	1662		
Total episodes			6%	-4, 16
All pneumococcal AOM			34%	21, 45
Vaccine-serotype AOM			57%	44, 67
Intent-to-treat				
Vaccine-serotype AOM			54%	41, 64

*Vaccine efficacy

Prevenar (7-valent) effectiveness

The effectiveness of Prevenar (7-valent) against pneumococcal disease (comprising the protection afforded by vaccination and from herd immunity due to reduced transmission of vaccine serotypes in the population) has been evaluated in routine paediatric immunisation programmes

that employ either three-dose or two-dose primary infant series, each with booster doses. This surveillance will continue with Prevenar 13.

Data from several countries is summarised in Table 6. It is important to note that as countries continually update the data from their surveillance systems, values included in this table may change over time.

Table 6. Summary of effectiveness of Prevenar (7-valent) for invasive pneumococcal disease

Country	Year of Introduction	Recommended Schedule	Disease Reduction, %	95% CI
USA	2000	2, 4, 6, 12 - 15 months		
Children <5[a]			Vaccine serotypes: 98% All serotypes: 77%	97, 99% 73, 79%
Persons ≥65[b]			Vaccine serotypes: 76.2% All serotypes: 38.2%	NA
Canada (Quebec)[c]	2004	2, 4 and 12 months	All serotypes: 72.5%	NA
UK (England and Wales)[d]	2006	2, 4 and 13 months	Two doses under age 1: 85%	49, 95%
Australia [e]	2002	2, 4 and 6 months	Vaccine serotypes: 89.6%	NA

[a] 2005 data.
[b] 2004 data.
[c] Children < 5 years of age. 2006 data.
[d] Children <2 years of age. Calculated vaccine effectiveness as of May 2008 (Broome method). Complete effectiveness for routine 2+1 schedule not yet available.
[e] Roche et al., *Communicable Disease Intelligence*. 2008; 32:18-30.

Effectiveness of Prevenar (7-valent) in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42.7%, and prescriptions for AOM by 41.9%, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52.4% and 41.1%, respectively. For those events specifically identified as pneumococcal pneumonia, the observed reductions in hospitalisations and ambulatory visits were 57.6% and 46.9%, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99).

While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar (7-valent) plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Prevenar 13 immunogenicity clinical trials in adults

In adults, an antibody threshold of serotype-specific pneumococcal polysaccharide IgG binding antibody concentration associated with protection has not been defined. For all pivotal clinical trials, a serotype-specific opsonophagocytosis assay (OPA) was used as a surrogate to assess potential efficacy against invasive pneumococcal disease and pneumonia. OPA geometric mean titres (GMTs) measured 1-month after each vaccination were calculated. OPA titres are expressed

as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

Pivotal trials for Prevenar 13 were designed to show that functional OPA antibody responses for the 13 serotypes are non-inferior, and for some serotypes superior, to the 12 serotypes in common with the licensed 23-valent pneumococcal polysaccharide vaccine (23vPPV) [1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F]. The response to serotype 6A, which is unique to Prevenar 13, was assessed by demonstration of a 4-fold increase in the specific OPA titre above pre-immunised levels.

Five clinical studies were conducted in Europe and the USA evaluating the immunogenicity of Prevenar 13 in different age groups ranging from 18-95 years of age. Clinical studies with Prevenar 13 currently provide immunogenicity data in adults aged 18 years and older, including adults aged 65 and older previously vaccinated with one or more doses of 23vPPV, 5 years prior to enrolment. Each study included healthy adults and immunocompetent adults with stable underlying conditions known to predispose individuals to pneumococcal infection (i.e., chronic cardiovascular disease, chronic pulmonary disease, renal disorders and diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism).

Immunogenicity and safety of Prevenar 13 has been demonstrated in adults aged 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

Adults not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

In a head-to-head, comparative trial conducted in adults aged 60-64 years, subjects received a single dose of either Prevenar 13 or 23vPPV. In the same study another group of adults aged 50-59 years and another group of adults aged 18-49 years received a single dose of Prevenar 13.

Table 7 compares the OPA GMTs, 1-month post-dose, in 60-64 year olds given either a single dose of Prevenar 13 or 23vPPV, and in 50-59 year olds given a single dose of Prevenar 13.

Table 7: OPA GMTs in adults aged 60-64 years given Prevenar 13 or pneumococcal polysaccharide vaccine (23vPPV) and in adults aged 50-59 years given Prevenar 13[a,b,c]

	Prevenar 13 50-59 Years N=350-384	Prevenar 13 60-64 Years N=359-404	23vPPV 60-64 Years N=367-402	Prevenar 13, 50-59 Relative to 60-64 Years		Prevenar 13 Relative to 23vPPV, 60-64 Years	
Serotype	GMT	GMT	GMT	GM Ratio	(95% CI)	GM Ratio	(95% CI)
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6A†	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] For serotype 6A†, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR being greater than 2.

In adults aged 60-64 years, OPA GMTs to Prevenar 13 were non-inferior to the OPA GMTs elicited to the 23vPPV for the twelve serotypes common to both vaccines. For 8 of the serotypes in common, the OPA titres were shown to be statistically significantly greater in Prevenar 13 recipients. In addition, OPA GMTs for serotype 6A were statistically significantly greater in Prevenar 13 recipients.

In adults aged 50-59 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years. For 9 serotypes, immune responses were related to age, with adults in the 50-59 years group showing statistically significantly greater responses than adults aged 60-64 years.

In adults aged 60-64 years, antibody levels one year after vaccination were greater after Prevenar 13 compared to antibody levels after 23vPPV for 7 of 12 serotypes in common. In adults aged 50-59 years, antibody levels one year after vaccination with Prevenar 13 were greater for 12 of 13 serotypes compared to vaccination with Prevenar 13 in 60-64 year olds.

Table 8 shows OPA GMTs 1-month post-dose in 18-29 year olds, 30-39 year olds, and 40-49 year olds given a single dose of Prevenar 13 and compares the OPA GMTs in 18-49 year olds and in 60-64 year olds.

Table 8: OPA GMTs in adults aged 18-49 years and 60-64 years given Prevenar 13[a,b]

	18-29 Years N=276-290	30-39 Years N=276-288	40-49 Years N=279-290	18-49 Years N=836-866	60-64 Years N=359-404	18-49 Years Relative to 60-64 Years	
Serotype	GMT[b]	GMT[b]	GMT[b]	GMT[b]	GMT[b]	GM Ratio	(95% CI[c])
1	409	353	305	353	146	2.4	(2.03, 2.87)
3	112	93	72	91	93	1.0	(0.84, 1.13)
4	7152	4589	3229	4747	2062	2.3	(1.92, 2.76)
5	567	375	271	386	199	1.9	(1.55, 2.42)
6A	8476	6131	3626	5746	2593	2.2	(1.84, 2.67)
6B	14134	10180	6571	9813	1984	4.9	(4.13, 5.93)
7F	3741	3276	2792	3249	1120	2.9	(2.41, 3.49)
9V	5086	3208	2292	3339	1164	2.9	(2.34, 3.52)
14	4452	2919	2049	2983	612	4.9	(4.01, 5.93)
18C	5240	3841	3171	3989	1726	2.3	(1.91, 2.79)
19A	2162	1504	1209	1580	682	2.3	(2.02, 2.66)
19F	2251	1507	1076	1533	517	3.0	(2.44, 3.60)
23F	2954	1606	814	1570	375	4.2	(3.31, 5.31)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] Confidence intervals (CI) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

In adults aged 18-49 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years. For 12 serotypes, immune responses were related to age, with adults aged 18-49 years showing statistically significantly greater responses than adults aged 60-64 years. Similarly, statistically significantly greater responses for 12 serotypes were observed for adults in age subgroups 18-29 years, 30-39 years and 40-49 years compared with adults aged 60-64 years. OPA GMTs were highest in the 18-29 years old and lowest in the 60-64 years old.

One year after vaccination with Prevenar 13 OPA titers had declined compared to one month after vaccination, however OPA titers for all serotypes remained higher than levels at baseline.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

Immune responses to Prevenar 13 and 23vPPV were compared in a head to head trial in adults aged ≥ 70 years, who had received a single dose of pneumococcal polysaccharide vaccine at least 5 years before study vaccination.

Table 9 compares the OPA GMTs, 1-month post-dose, in pneumococcal polysaccharide vaccinated adults aged ≥ 70 years given a single dose of either Prevenar 13 or 23vPPV.

Table 9: OPA GMTs in pneumococcal polysaccharide (23vPPV) vaccinated adults aged ≥ 70 years given either Prevenar 13 or 23vPPV[a,b,c]

	Prevenar 13 N=400-426	23vPPV N=395-445	Prevenar 13 OPA GMT Relative to 23vPPV	
Serotype	**OPA GMT**	**OPA GMT**	**Ratio**	**(95% CI)**
1	81	55	1.5	(1.17 , 1.88)
3	55	49	1.1	(0.91 , 1.35)
4	545	203	2.7	(1.93 , 3.74)
5	72	36	2.0	(1.55 , 2.63)
6A†	903	94	9.6	(7.00 , 13.26)
6B	1261	417	3.0	(2.21 , 4.13)
7F	245	160	1.5	(1.07 , 2.18)
9V	181	90	2.0	(1.36 , 2.97)
14	280	285	1.0	(0.73 , 1.33)
18C	907	481	1.9	(1.42 , 2.50)
19A	354	200	1.8	(1.43 , 2.20)
19F	333	214	1.6	(1.17 , 2.06)
23F	158	43	3.7	(2.69 , 5.09)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] For serotype 6A†, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GM ratio greater than 2.

In adults vaccinated with pneumococcal polysaccharide vaccine at least 5 years prior to the clinical study, OPA GMTs to Prevenar 13 were non-inferior to the 23vPPV responses for the 12 serotypes in common. Furthermore, in this study statistically significantly greater OPA GMTs were demonstrated for 10 of the 12 serotypes in common. Immune responses to serotype 6A were statistically significantly greater following vaccination with Prevenar 13 than after 23vPPV.

Additional immunogenicity data

In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar 13 can be given concomitantly with trivalent inactivated influenza vaccine (TIV). The responses to all three TIV antigens were comparable when TIV was given alone or concomitantly with Prevenar 13.

When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone. The clinical significance of this is unknown. In adults aged 50-59, non-inferiority was met for all serotypes. In adults aged 65 years and over, non-inferiority was met for all serotypes except serotype 19F.

Immune responses in special populations

Individuals with the conditions described below have an increased risk of pneumococcal disease.

Children and adolescents with sickle cell disease

An open label single arm study with 2 doses of Prevenar 13 given 6 months apart was conducted in 158 children and adolescents ≥6 to <18 years of age with sickle cell disease who were previously vaccinated with one or more doses of 23vPPV at least 6 months prior to enrolment. After the first vaccination, Prevenar 13 elicited antibody levels measured by both IgG GMCs and

OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second dose immune responses were comparable to the ones after the first dose.

OPA GMTs in subjects with SCD, before and after each dose are presented in Table 10 for the evaluable immunogenicity population. In general, antibodies increased in response to dose 1, declined over the 6 months between doses 1 and 2, but remained higher than before dose 1 levels for all serotypes. OPA GMTs then increased in response to dose 2. The OPA GMTs after dose 2 were similar to or higher than those after dose 1 for subjects in the evaluable immunogenicity population for all serotypes.

Table 10. Pneumococcal OPA GMTs at Dose 1 and Dose 2 - Evaluable Immunogenicity Population

Serotype	Pre-Dose 1 N[a]=95-131 GMT[b]	Pre-Dose 1 (95% CI[c])	Post-Dose 1 N[a]=89-123 GMT[b]	Post-Dose 1 (95% CI[c])	Post-Dose 2 N[a]=89-118 GMT[b]	Post-Dose 2 (95% CI[c])
1	7	(5.7, 8.8)	56	(41.0, 77.4)	78	(59.5, 101.2)
3	13	(10.1, 17.5)	115	(93.0, 142.1)	105	(87.2, 127.2)
4	215	(129.6, 357.2)	2670	(2128.1, 3351.1)	3051	(2536.7, 3670.3)
5	10	(7.8, 13.9)	277	(198.4, 385.8)	273	(213.9, 349.2)
6A	246	(149.0, 404.8)	7845	(6581.6, 9349.9)	7633	(6439.6, 9048.6)
6B	626	(377.5, 1037.4)	7535	(6320.5, 8983.5)	7601	(6392.6, 9038.6)
7F	344	(220.5, 537.9)	3348	(2881.9, 3888.5)	3723	(3276.2, 4230.1)
9V	234	(137.6, 398.7)	2312	(1684.0, 3172.8)	3467	(2784.0, 4317.6)
14	628	(425.8, 925.7)	2288	(1906.6, 2745.0)	2081	(1770.5, 2446.0)
18C	426	(235.7, 771.4)	4326	(3250.3, 5756.8)	5271	(4267.8, 6510.1)
19A	137	(100.0, 187.4)	1449	(1164.2, 1804.3)	1314	(1084.4, 1592.6)
19F	94	(55.0, 160.7)	1429	(1043.5, 1957.3)	1507	(1139.9, 1992.2)
23F	34	(21.5, 54.8)	1607	(1227.4, 2102.7)	2330	(1880.4, 2887.0)

a. N = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

Additional Prevenar (7-valent) immunogenicity data: children with sickle cell disease

The immunogenicity of Prevenar has been investigated in an open-label, multicentre study in 49 infants with sickle cell disease. Children were vaccinated with Prevenar (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23vPPV at the age of 15-18 months. After primary immunisation, 95.6% of the subjects had antibody levels of at least 0.35 mg/mL for all seven serotypes found in Prevenar (7-valent). A significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

Adults with HIV infection

Immune responses were assessed in 329 HIV-infected adults ≥18 years of age (CD4 >200 cells/mL and viral load <50,000 copies/mL) previously vaccinated with 23vPPV administered at least 6 months prior to enrolment. Subjects received 3 doses of Prevenar 13, at enrolment, 6 months and 12 months after the first dose of Prevenar 13. After the first vaccination, Prevenar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second and third dose

of Prevenar 13, immune responses were comparable or higher than those after the first dose. Subjects who received two or more previous doses of 23vPPV showed a similar immune response compared with subjects who received a single previous dose. The immune responses to Prevenar 13 observed in HIV infected adults were lower than the immune responses reported for healthy adults.

OPA GMTs in adults with HIV, before and after each vaccine dose are presented in Table 11 for the evaluable population. In general, the OPA GMTs after vaccine dose 2 and vaccine dose 3 were similar to or higher than those after vaccine dose 1 for subjects in the evaluable population.

Table 11. Pneumococcal OPA Antibody GMTs – Evaluable Immunogenicity Population

	Pre-Dose 1[a] N[b]=230-253		Post-Dose 1[a] N[b]=247-255		Post-Dose 2[a] N[b]=238-246		Post-Dose 3[a] N[b]=217-228	
Serotype	GMT[c]	(95% CI[d])	GMT[c]	(95% CI[d])	GMT[c]	(95% CI[d])	GMT[c]	(95% CI[d])
1	7	(5.7, 7.6)	38	(30.9, 47.6)	40	(32.3, 49.2)	48	(38.7, 58.6)
3	6	(5.5, 6.9)	28	(23.3, 33.4)	43	(36.3, 50.9)	54	(45.9, 63.9)
4	26	(19.2, 36.4)	631	(491.4, 810.9)	701	(575.4, 855.1)	743	(605.1, 912.1)
5	7	(6.3, 8.7)	63	(49.0, 81.1)	63	(50.0, 80.5)	71	(55.9, 91.2)
6A	17	(12.6, 22.4)	952	(698.8, 1296.6)	1704	(1339.4, 2166.8)	2117	(1706.8, 2624.5)
6B	83	(58.0, 117.5)	1050	(783.1, 1408.4)	1807	(1465.4, 2228.2)	2388	(1975.6, 2887.4)
7F	42	(30.1, 59.7)	769	(595.5, 992.1)	939	(777.3, 1135.4)	1062	(870.6, 1294.9)
9V	35	(24.8, 49.7)	416	(298.7, 578.9)	693	(517.4, 927.7)	880	(663.9, 1167.1)
14	197	(148.3, 262.4)	651	(523.0, 810.3)	700	(580.5, 844.3)	812	(682.4, 965.4)
18C	33	(23.5, 44.9)	453	(326.0, 630.2)	541	(405.3, 721.5)	705	(529.7, 938.3)
19A	34	(27.1, 43.5)	282	(225.9, 351.0)	387	(330.4, 453.6)	415	(356.3, 484.3)
19F	13	(10.0, 16.3)	123	(89.0, 170.4)	253	(194.1, 328.8)	242	(183.8, 318.9)
23F	8	(6.4, 9.2)	93	(67.4, 128.3)	281	(211.8, 373.0)	400	(304.5, 526.4)

a. Protocol-specified timing for blood sample.
b. N = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

INDICATIONS

Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age.

The use of Prevenar 13 should be guided by official recommendations.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid
- Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent).

PRECAUTIONS

Do not administer Prevenar 13 intravenously. Do not administer Prevenar 13 intravascularly. Take care to avoid injecting into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area (see Dosage and Administration).

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

As with other vaccines, the administration of Prevenar 13 should be postponed in individuals suffering from acute moderate or severe febrile illness.

Effects on fertility

Prevenar 13 showed no adverse effects on mating or fertility in a combined fertility and embryofoetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24 (see also Use in pregnancy).

Use in pregnancy

Category B2

Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans.

Prevenar 13 showed no treatment-related effects on mating, fertility, pregnancy, parturition, foetal gross, external, soft tissue and skeletal alternations, and pup survival and growth in a combined fertility and embryofoetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24. Serotype-specific antibodies against each of the 13 vaccine serotypes were detected in does, foetuses, and pups.

Use in lactation

Safety during lactation has not been established. It is not known whether vaccine antigens or antibodies are excreted in breast milk.

In a female rabbit fertility and embryofoetal development study, serotype–specific antibodies against each of the 13 vaccine serotypes were detected in the pups of does administered the vaccine prior to mating and during gestation. There were no adverse findings in these pups.

Use in the elderly

Prevenar 13 has been shown to be safe and immunogenic in the geriatric population. Of the 5,667 adults in the 6 studies of the clinical development program who received Prevenar 13, 1,785 (31.5%) were 65 to 74 years of age, and 1,266 (22.3%) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65 to 74 year-old individuals and greater than 75 year-old individuals.

Genotoxicity

Prevenar 13 has not been tested for genotoxic potential.

Carcinogenicity

Prevenar 13 has not been tested for carcinogenic potential.

Disease coverage

Prevenar 13 will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other micro-organisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

Blood disorders

As with other vaccines administered intramuscularly, this vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Impaired immune response

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Vaccination in high risk groups

Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and adults with HIV infection (see Special Populations). Data are not currently available for individuals in other immunocompromised groups (e.g., malignancy, haematopoietic stem cell transplant, nephrotic syndrome) and vaccination should be considered on an individual basis.

Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 24 months of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Prevenar 13 should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the 13-valent pneumococcal conjugate vaccine (Prevenar 13) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of 23-valent pneumococcal polysaccharide vaccine to unprimed children or to children primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

Risk of apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born £

28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Prophylactic antipyretics

Antipyretic treatment should be initiated according to local treatment guidelines.

Prophylactic antipyretic medication is recommended:

- for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions
- for children with seizure disorders or with a prior history of febrile seizures.

Effects on ability to drive and operate machinery

Not relevant.

INTERACTIONS WITH OTHER MEDICINES

Different injectable vaccines should always be given at different injection sites.

Infants and children aged 6 weeks to 5 years

Prevenar 13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical trials demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Data from a postmarketing clinical study evaluating the impact of prophylactic use of antipyretics on the immune response to Prevenar 13 suggest that concomitant administration of paracetamol may reduce the immune response to Prevenar 13 after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Previously, trials with Prevenar (7-valent) and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in Prevenar (7-valent) and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed if Prevenar 13 is used. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed.

When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see Adverse Effects - Infants and children aged 6 weeks to 5 years).

Children 6 to 17 years of age

No data are currently available regarding concomitant use with other vaccines.

Adults aged 18 to 49 years

No data are available regarding concomitant use with other vaccines.

Adults aged 50 years and older

Prevenar 13 may be administered concomitantly with the seasonal trivalent inactivated influenza vaccine (TIV) with no interference with the immune responses to TIV. Concomitant use with other vaccines has not been investigated.

Prevenar 13 is not contraindicated in people who have previously been vaccinated with 23vPPV. Clinical studies have demonstrated Prevenar 13 can be safely given one year after 23vPPV. However, when Prevenar 13 was given 1 year after 23vPPV the immune responses were lower for all serotypes compared to when Prevenar 13 was given to subjects not previously immunised with 23vPPV. The clinical significance of this is unknown (see also Dosage and Administration - Adults).

Studies in which Prevenar 13 was given to subjects who had 23vPPV at least one year prior have not found an increased incidence of local or systemic side effects.

ADVERSE EFFECTS

Adverse reaction frequencies are listed below in CIOMS frequency categories:

Very common: ³ 10%
Common: ³ 1% and < 10%
Uncommon: ³ 0.1% and < 1%
Rare: ³ 0.01% and < 0.1%
Very rare: < 0.01%

Children

These data are from clinical trials in which Prevenar 13 was administered to children simultaneously with other routine childhood vaccines.

Body as a whole	
Very common:	Fever; any injection-site erythema, induration/swelling or pain/tenderness; Injection-site erythema or induration/swelling 2.5 cm –7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39ºC; injection-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm
Gastrointestinal disorders	
Common:	Diarrhoea; vomiting
Immune system disorders	
Rare:	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Metabolic and nutritional disorders	
Very common:	Decreased appetite
Nervous system disorders	
Very common:	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon:	Seizures (including febrile seizures)
Rare:	Hypotonic-hyporesponsive episode
Skin and appendages	
Common:	Rash
Uncommon:	Urticaria or urticaria-like rash
Psychiatric disorders	
Very common:	Irritability
Uncommon:	Crying

Table 12: Percentage of infant and toddler subjects reporting solicited local reactions at the Prevenar 13 or Prevenar (7-valent) injection sites

	Dose 1[a]		Dose 2[a]		Dose 3[a]		Dose 4[b]	
Graded Local Reaction	**Prevenar 13** (N^c=3601-3878)	**Prevenar 7** (N^c=2025-2148)	**Prevenar 13** (N^c=3087-3388)	**Prevenar 7** (N^c=1699-1824)	**Prevenar 13** (N^c=2603-2809)	**Prevenar 7** (N^c=1245-1364	**Prevenar 13** (N^c=1049-1198)	**Prevenar 7** (N^c=654-791)
Tenderness								
Any	46.8	44.9	44.7	43.9	41.0	39.5	52.1	56.0
Significant[d]	8.3	9.3	6.3	8.6*	6.0	5.9	6.2	8.1
Induration								
Any	23.0	21.9	28.0	28.9	30.1	30.3	32.6	33.5
Mild[e]	19.8	20.0	25.6	26.5	27.6	27.9	29.8	29.4
Moderate[e]	6.9*	4.7	7.0	6.1	8.0	7.2	12.0	10.5
Severe[e]	0	0	0.1	0	0	0	0	0
Erythema								
Any	26.3	27.8	35.3	35.1	38.3	37.0	43.6	43.7
Mild[e]	24.7	26.8	33.9	33.9	36.5	35.3	39. 4	40.0
Moderate[e]	2.7*	1.8	3.0	3.1	5.0	5.3	11.8	11.7
Severe[e]	0	0	0.1	0	0	0	0.1	0.2

* Statistically significant difference $p < 0.05$
Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.
b. Toddler dose data are included for the 6 infant studies with toddler dose data.
c. Number of subjects reporting Yes for at least 1 day or No for all days.
d. Significant = present and interfered with limb movement.
e. Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

Table 13: Percentage of infant and toddler subjects reporting solicited systemic adverse reactions, fever and antipyretic medications after each vaccination

	Dose 1a		Dose 2a		Dose 3a		Dose 4b	
Graded Systemic Events	**Prevenar 13 (N^c=3594-4022)**	**Prevenar 7 (N^c=1998-2215)**	**Prevenar 13 (N^c=3110-3606)**	**Prevenar 7 (N^c=1718-1969)**	**Prevenar 13 (N^c=2580-3024)**	**Prevenar 7 (N^c=1253-1480)**	**Prevenar 13 (N^c=1073-1283)**	**Prevenar 7 (N^c=666-873)**
Decreased Appetite	38.4	37.2	37.8	41.0	36.6	38.1	42.2	50.2
Irritability	69.2	63.9	68.8	68.1	61.9	60.6	63.4	69.6
Increased Sleep	59.0	57.4	50.9	51.1	41.2	40.7	42.7	52.3
Decreased Sleep	36.4*	33.5	35.3	34.9	34.0	32.8	30.1	33.2
Fever[d]								
Any	25.0*	24.4	32.2	38.4	27.8	32.4	43.0	49.8
Mild	24.1*	23.5	30.7	37.3	26.8	31.3	41.1	48.2
Moderate	1.5	1.2	3.0	2.9	2.9	2.6	6.6	8.3
Severe	0.0	0.2*	0.1	0.1	0.2	0.2	0.3	0.2
Antipyretic Medications								
Treat	45.9	45.9	49.8	55.3	46.1	51.9	43.0	50.4
Prevent	46.5	46.0	48.9	50.9	47.1	51.1	36.1	46.5

* Statistically significant difference $p < 0.05$
Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.
b. Toddler dose data are included for the 6 infant studies with toddler dose data.
c. Number of subjects reporting Yes for at least 1 day or No for all days.
d. "Any" fever = subjects with any temperature ≥38°C; for subcategories of fever by grading, subjects may be included in more than 1 row. Fever grading: mild ≥38°C but ≤39°C, moderate >39°C but ≤40°C, severe >40°C.

Children and adolescents aged 5 to 17 years of age

Safety was evaluated in 592 children aged 5 to 17 years of age, 294 children aged 5 to 10 years previously immunised with at least one dose of Prevenar and 298 children aged 10 to 17 years who had not received a pneumococcal vaccine.

The most common adverse events in children and adolescents 5 to 17 years of age were:

General disorders and administration site conditions Very common: Common:	 Irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; somnolence; poor quality sleep; vaccination-site tenderness (including impaired movement) Pyrexia
Gastrointestinal disorders Very common: Common:	 Decreased appetite Vomiting; diarrhoea
Nervous system disorders Common:	 Headaches
Skin subcutaneous tissue disorders Common:	 Rash; urticaria or urticaria-like rash

Other adverse events previously observed in infants and children 6 weeks to 5 years of age may also be applicable to this age group but were not seen in this study possibly due to the small sample size.

Infants and children aged 6 weeks to 5 years

In a clinical study (0887X-100811) with Prevenar (7-valent) in infants vaccinated at 2, 3, and 4 months of age, fever ≥ 38°C was reported at higher rates among infants who received Prevenar (7-valent) concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12 to 15 months of age, the rate of fever ≥ 38°C was 50.0% in infants who received Prevenar (7-valent) and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient.

In clinical studies with Prevenar 13, reports of mild fever (≥38.0°C but ≤39.0°C) ranged from 20.9% to 55.5% (across the 3 infant doses) and 31.4% to 63.7% (after toddler dose) when co-administered with Infanrix hexa. Moderate fever (39.0°C but ≤40.0°C) ranged from 0.8% to 8.8% in infants and 4.5% to 12.6% after the toddler dose, when co-administered with Infanrix hexa. The incidence of severe fever (>40.0°C) across all studies was ≤1.1%. When fever was present, it was most commonly observed in the first 2 days after vaccination.

Adults

Safety was assessed in 6 clinical studies including 7,097 adults ranging in ages from 18 to 95 years, of which 5,667 received Prevenar 13. There were 2,616 adults aged 50 to 64 years and 3,051 adults 65 years and older. Of the Prevenar 13 recipients, 1,916 adults were previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine more than 3 years prior.

One of the six studies included a group of adults (n=899) ranging from 18 to 49 years who received Prevenar 13 and who were not previously vaccinated with 23vPPV.

A trend to lower frequency of adverse reactions was associated with greater age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in the youngest adults, 18 to 29 years of age. Overall, the frequency categories were similar for all age groups, with the exception of vomiting which was very common (³ 1/10) in adults aged 18 to 49 years and common (³ 1/100 to < 1/10) in all other age groups.

Adverse reactions from clinical studies
The following frequencies are based on adverse reactions assessed as related to vaccination with Prevenar 13 in adults:

Gastrointestinal disorders: Very common: Common: Uncommon:	 Diarrhoea, vomiting (in adults aged 18 to 49 years) Vomiting (in adults aged 50 years and over) Nausea
General disorders and administration site conditions Very common**:** Common: Uncommon:	 Chills; fatigue; injection site erythema; injection site induration /swelling; injection site pain/tenderness; limitation of arm movement Fever Lymphadenopathy localized to the region of the injection site
Immune system disorders Uncommon:	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Musculoskeletal and connective tissue disorders Very common	New joint pain/aggravated joint pain; new muscle pain/aggravated muscle pain
Metabolic and nutritional disorders Very common:	Decreased appetite
Nervous system disorders Very common:	Headaches
Skin and subcutaneous tissue disorders Very common:	 Rash

Overall, no significant differences in frequencies of adverse reactions were seen when Prevenar 13 was given to adults previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine or adults not vaccinated with 23-valent pneumococcal polysaccharide vaccine.

Solicited adverse reactions in adult studies with Prevenar 13

The proportion of adults reporting local and systemic adverse reactions within 14 days of vaccination with Prevenar 13 are listed below in tables 14 and 15, respectively.

Table 14: Percentage of adults reporting solicited local reactions at Prevenar 13 injection site within 14 days after vaccination

	- Naïve to 23vPPV -				Pre-immunised with 23vPPV
	Age (years) Number of Subjects				
Local Reaction	**18-49** 209-787	**50-59** 136 - 322	**60-64** 178 - 331	**≥65** 848 - 950	**≥70** 297 - 362
Redness[a]					
Any	30.5	15.8	20.2	14.4	10.8
Mild	26.4	15.2	15.9	12.1	9.5
Moderate	11.9	5	8.6	6.1	4.7
Severe	2.8	0.7	1.7	0.8	1.7
Swelling[a]					
Any	39.4	21.7	19.3	12	10.4
Mild	37.2	20.6	15.6	10	8.9
Moderate	15.1	4.3	8.2	4.6	4
Severe	1.4	0	0.6	0.1	0
Pain[b]					
Any	96.7	88.8	80.1	41.7	51.7
Mild	93.2	85.9	78.6	36.1	50.1
Moderate	77.1	39.5	23.3	17.2	7.5
Severe	16.0	3.6	1.7	2	1.3
Limitation of arm movement[c]					
Any	75.2	40.7	28.5	14.4	10.5
Mild	71.5	38.6	26.9	13.2	10.3
Moderate	18.5	2.9	2.2	1.2	0.3
Severe	15.6	2.9	1.7	1.6	0.7

a. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
b. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
c. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Table 15: Percentage of adults reporting solicited systemic adverse reactions, use of medication to treat pain and fever within 14 days after vaccination with Prevenar 13

	- Naïve to 23vPPV -				Pre-immunised with 23vPPV
	Age (years) Number of Subjects				
Systemic Event	**18-49** 208-561	**50-59** 136 - 248	**60-64** 177 - 277	**≥65** 420 - 456	**≥70** 297 - 350
Fever					
-Any (≥38°C)	7.2	1.5	7.7	4.2	1.0
-Mild (≥38°C but <38.5°C)	4.2	1.5	3.9	3.1	1.0
-Moderate (≥38.5°C but <39°C)	1.9	0.0	0.6	1.0	0.0
-Severe (≥39°C but ≤40°C)	1.4	0.0	0.0	0.0	0.0
-Potentially life threatening (>40°C)	0.5	0.0	0.0	0.0	0.0
Fatigue	80.5	63.3	63.2	28.5	34.0
Headache	81.4	65.9	54.0	24.7	23.7
Chills	38.1	19.6	23.5	9.1	7.9
Rash	21.3	14.2	16.5	6.8	7.3
Vomiting	15.0	6.9	3.9	1.7	1.7
Diarrhoea	N/A	N/A	N/A	N/A	N/A
Decreased appetite	55.6	25.3	21.3	11.3	10.4
New muscle pain	82.0	61.8	56.2	23.4	36.8
Aggravated muscle pain	55.9	39.9	32.6	15.0	20.6
New joint pain	41.7	31.5	24.4	11.5	12.6
Aggravated joint pain	28.6	25.6	24.9	8.6	11.6
Use of medication to treat pain	N/A	N/A	N/A	9.9	22.0
Use of medication to treat fever	N/A	N/A	N/A	5.4	3.0
Abbreviation: N/A = not applicable					

Solicited adverse reactions in adult studies with Prevenar 13 and TIV

The safety of concomitant administration of Prevenar 13 with Trivalent Inactivated Influenza Vaccine (TIV) was assessed in two studies in 23vPPV unvaccinated adults. Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥ 65 years were similar after Prevenar 13 was administered with TIV compared to Prevenar 13 administered alone.

Higher frequency of some solicited systemic reactions was observed when Prevenar 13 was administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or Prevenar 13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Additional information in special populations

Adults with HIV previously vaccinated with the pneumococcal polysaccharide vaccine, have similar frequencies of adverse reactions, except that vomiting was very common and nausea was common.

Adverse reactions from Prevenar 13 postmarketing experience

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for Prevenar 13 as they were reported in the postmarketing

experience. Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

General disorders and administration site conditions	Injection-site dermatitis; injection-site urticaria, injection-site pruritus, flushing
Blood and lymphatic system disorders	Lymphadenopathy localised to the region of the injection-site
Immune system disorders	Anaphylactic/anaphylactoid reaction including shock, angioedema
Skin and subcutaneous tissue disorders	Erythema multiforme

Analysis of post-marketing reporting rates suggests a potential increased risk of convulsions, with or without fever, and HHE (hypotonic-hyporesponsive episode) when comparing groups which reported use of Prevenar 13 with Infanrix hexa to those which reported use of Prevenar 13 alone. These events were reported in infants less than 2 years of age.

DOSAGE AND ADMINISTRATION

The dose of Prevenar 13 is 0.5 mL given intramuscularly only, with care to avoid injection into or near nerves and blood vessels. The preferred sites are anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in children and adults.

Do not administer Prevenar 13 intravascularly or into the gluteal area. Do not administer Prevenar 13 intravenously, subcutaneously or intradermally, since the safety and immunogenicity of these routes have not been evaluated.

Upon storage, a white deposit and clear supernatant can be observed. The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. Prevenar 13 is a suspension containing an adjuvant. The vaccine must not be used if it cannot be uniformly suspended.

Prevenar 13 is not to be mixed with other vaccines or products in the same syringe. Prevenar 13 is for single-use in one patient only. The suspension contains no antimicrobial agent. Discard any residue.

Immunisation schedules

Data on the interchangeability of Prevenar (7-valent) or Prevenar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

It is recommended that infants who receive a first dose of Prevenar 13 complete the vaccination course with Prevenar 13.

The immunisation schedules for Prevenar 13 should be based on official recommendations.

Infants aged 6 weeks - 6 months

The primary infant series consists of three doses, each of 0.5 mL, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose.

Routine vaccination schedule for infants (6 weeks – 6 months of age)				
Dose:	Dose 1	Dose 2	Dose 3	Dose 4
Age at Dose:	2 months	4 months	6 months	12-15 months

Preterm infants (< 37 weeks gestation)

In preterm infants, the primary infant series consists of three doses, each of 0.5 mL, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first may be given as early as six weeks of age. A fourth (booster) dose is recommended between 11 and 15 months of age (see Pharmacology and Precautions).

Unvaccinated infants and children 7 months – 17 years of age

Vaccination schedule for previously unvaccinated children ³ 7 months of age		
Age at first dose	**Total number of 0.5 mL doses**	**Duration between doses**
7-11 months of age	3	Between dose 1 and 2: At least 1 month Between dose 2 and 3: At least 2 months (3rd dose after 12 months of age)
12-23 months of age	2	At least 2 months
24 months to 17 yrs of age	1	N/A

Infants and children previously vaccinated with Prevenar (7-valent)

Prevenar 13 contains the same 7 serotypes contained in Prevenar (7-valent) and is manufactured based on the same conjugate technology using the same carrier protein CRM_{197}.

Infants and children who have begun immunisation with Prevenar (7-valent) may complete immunisation by switching to Prevenar 13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable.

Young Children (12 – 59 months) completely immunised with Prevenar (7-valent)

Children aged 12 months to 5 years of age who have completed primary infant immunisation with Prevenar (7-valent) may receive one dose of Prevenar 13 to elicit immune responses to the six additional serotypes. This catch-up (supplemental) dose of Prevenar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevenar (7-valent).

Children 6 –17 years (prior to 18th birthday) previously immunised with Prevenar (7-valent)

Children 6 to 17 years of age may receive a single dose of Prevenar 13 if they have been previously vaccinated with one or more doses of Prevenar (7-valent). This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of Prevenar (7-valent).

Adults

One single dose in adults, including those previously vaccinated with pneumococcal polysaccharide vaccine.

The need for revaccination with a subsequent dose of Prevenar 13 has not been established. Refer to local recommendations.

If sequential administration of Prevenar 13 and 23vPPV is considered, Prevenar 13 should be given first for maximal efficacy and to avoid blunting of the immune response by 23vPPV.

Special populations

Individuals who may be at higher risk of pneumococcal infection (such as sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13. Subsequent doses of Prevenar 13 produce immune responses that are comparable or higher than those after the first dose and therefore may be of benefit in certain individuals. The dosing schedule of Prevenar 13 in special populations should be guided by official recommendations (see also Clinical Trials – Immune responses in special populations).

Influence of foods, compatibility with drugs/fluids

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children, there have been reports of overdose with Prevenar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended paediatric schedules of Prevenar 13.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Prevenar 13 is presented as a suspension in 0.5 mL pre-filled syringes (Type I glass) in packs of 1 and 10. All syringe components are latex-free.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if the vaccine has been frozen. Prevenar 13 is stable at temperatures up to 25°C for four days. At the end of this period, Prevenar 13 should be used or discarded. These data are intended to guide health care professionals in case of temporary temperature excursions.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

29 March 2010

DATE OF MOST RECENT AMENDMENT

27 May 2014

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