

7.07 PNEUMOCOCCAL CONJUGATE VACCINE

13-Valent Adsorbed Pre-Filled Syringe, 0.5 mL

Prevenar 13®

Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 Listing on the National Immunisation Program (NIP) for 13-valent pneumococcal conjugate vaccine (13vPCV) for the prevention of pneumococcal disease (community acquired pneumonia [CAP] and invasive pneumococcal disease [IPD] in adults). At the July 2015 meeting, the PBAC recommended listing of 13vPCV on the basis of cost-minimisation to 23-valent pneumococcal polysaccharide vaccine (23vPPV). This application sought to demonstrate 13vPCV is cost-effective compared with 23vPPV.

2 Requested listing

- 2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	NIP price	Proprietary Name and Manufacturer
PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 13- VALENT ADSORBED Pre-filled syringe, 0.5 mL <u>NIP population:</u>	1	0	\$ [REDACTED]	Prevenar 13 Pfizer

- A single 13vPCV dose for pneumococcal vaccine naïve non-Indigenous adults aged 65 years and over
- A single 13vPCV dose for pneumococcal vaccine naïve Indigenous adults aged 50 years and over

- 2.2 The requested listing was the same as recommended by the PBAC at the July 2015 meeting.
- 2.3 The current submission requested a price of \$ [REDACTED] per dose of 13vPCV. By comparison, the requested prices in the March 2015 and July 2015 submissions were \$ [REDACTED] and \$ [REDACTED], respectively.
- 2.4 The submission did not discuss how the pneumococcal vaccination status of adults would be determined (i.e. whether naïve or not). The 2015-16 Commonwealth Budget included the expansion of the existing Australian Childhood Immunisation Register to the Australian Immunisation Register from September 2016. The Australian Immunisation Register will capture all vaccines administered throughout a person's life (birth to death), given through general practice and community clinics.
- 2.5 ATAGI considered it clinically appropriate for all adults previously vaccinated with 23vPPV to receive a single dose of 13vPCV because of the additional clinical benefits in terms of prevention of CAP (July 2016 ATAGI pre-submission advice). A listing for use in adults previously vaccinated with 23vPPV was not requested.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 **TGA status at time of PBAC consideration:** 13vPCV was registered on 28 October 2011 for adults aged 50 years and older.
- 3.2 The PBAC previously considered 13vPCV for adults in March 2015 and July 2015.
- At the March 2015 meeting, the PBAC rejected a major submission on the basis of uncertain cost-effectiveness. The PBAC considered that 13vPCV was likely to be superior to 23vPPV in terms of prevention of vaccine type (VT) CAP, but the submission did not provide sufficient evidence to allow the PBAC to be confident that 13vPCV would be cost effective (13vPCV PSD March 2015, paragraph 7.1).
 - At the July 2015 meeting, the PBAC recommended 13vPCV for listing on the NIP on the basis of cost-minimisation to 23vPPV. The PBAC considered the equi-effective doses to be 13vPCV 0.5 mL injection and 23vPPV 0.5 mL injection (13vPCV PSD July 2015, paragraphs 7.1 and 7.3).

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

- 4.1 Infections with *Streptococcus pneumoniae* can cause IPD such as meningitis, septicaemia and bacteraemic pneumonia, and other forms of disease such as non-bacteraemic CAP. The pneumococcal vaccine currently listed on the NIP for adults is a 23vPPV. 13vPCV is a 13-valent pneumococcal conjugate vaccine which covers 12 of the 23 serotypes covered by 23vPPV and one additional serotype. The claimed benefit for 13vPCV over 23vPPV is in the reduction of non-bacteraemic CAP (referred to here as CAP).
- 4.2 At the July 2015 meeting, the PBAC recommended that a single dose of 13vPCV be made available to pneumococcal vaccine naïve non-Indigenous adults aged 65 years and over and to pneumococcal vaccine naïve Indigenous adults aged 50 years and over. This dose of 13vPCV would replace the single dose (or the first dose for adults with risk factors) of 23vPPV that is currently provided to these populations (13vPCV PSD July 2015 paragraph 7.1). Individuals in specified at-risk groups would continue to receive 23vPPV five years following the primary dose of 13vPCV (13vPCV PSD July 2015 paragraph 7.2). ATAGI advised that "the recommended vaccine schedule for adults with risk factors, including the optimum interval between doses of 13vPCV and 23vPPV in a sequential dosing schedule, is still under deliberation by ATAGI (post-submission advice).

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated 23vPPV as the main comparator. The ESC noted that the PBAC considered this was the appropriate comparator for the March 2015 and July 2015 submissions.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described the debilitating symptoms of pneumonia. The PBAC noted the advice received from the Lung Foundation Australia clarifying the health burden of pneumonia and the need for further awareness of the benefit of pneumococcal vaccination in older Australians and other high risk populations.

Clinical trials

6.3 The key clinical evidence for 13vPCV and 23vPPV remained unchanged from that presented in the March 2015 and July 2015 submissions. The current submission was based on:

- One 13vPCV placebo-controlled efficacy trial (CAPiTA)
- A meta-analysis of 5 randomised efficacy trials of 23vPPV in adults reporting the incidence of CAP
- A meta-analysis of 12 non-randomised studies of 23vPPV in adults reporting the incidence of IPD (including Gutiérrez Rodríguez 2014 and Leventer Roberts 2015 not previously presented)
- 16 immunogenicity studies including 13vPCV (including studies B1851138 and B1851020 not previously presented).

6.4 Details of the additional studies and an additional reference for CAPiTA presented in the current submission are provided in Table 1 (refer to the March 2015 PSD for the remaining trials and associated reports).

Table 1: Additional trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Proposed vaccine: 13vPCV randomised trial		
CAPiTA	Final report: a phase 4, randomised, placebo-controlled clinical trial of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease.	22 May 2014
New reference	Bonten MJ, Huijts SM, Bolkenbaas M, <i>et al.</i> Polysaccharide conjugate vaccine pneumococcal pneumonia in adults.	N Engl J Med 2015; 372:1114-25.
Comparator vaccine: 23vPPV non-randomised studies		
Gutiérrez Rodríguez 2014	Gutiérrez Rodríguez MA, Ordobás Gavin MA, García-Comas L, <i>et al.</i> Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008-2011.	Euro Surveill 2014; 19:20922.

Public Summary Document – July 2016 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
Leventer-Roberts 2015	Leventer-Roberts M, Feldman BS, Brufman I, <i>et al.</i> Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged ≥65 years: a retrospective case-control study.	Clin Infect Dis 2015; 60:1472-80.
Immunogenicity studies		
B1851138	A phase 4, randomised, double-blind trial to evaluate the immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine when administered concomitantly with seasonal inactivate influenza vaccine in adults 50 years and older who received 1 or more doses of 23-valent pneumococcal polysaccharide vaccine prior to study enrolment.	December 2015
B1851020	Clinical study report (6115A1-3001; B1851020). Years 1 through 5 report: a phase 3, randomised, double-blind trial to evaluate the safety, tolerability and immunogenicity of a 13-valent pneumococcal conjugate vaccine when administered concomitantly with trivalent inactivated influenza vaccine in healthy adults 50-59 years of age who are naïve to 23-valent pneumococcal polysaccharide vaccine and to evaluate the immune response of a second dose of 13vPCV administered 5 years after initial 13vPCV vaccination.	December 2014

Source: Table 6, p30; Table 18, p50; Table 32, p69; Table 42, p83-85 of the submission

- 6.5 The key features of the 13vPCV and 23vPPV randomised efficacy trials, and the 23vPPV non-randomised study used in the economic evaluation, are summarised in Table 2. ESC noted that the primary outcome of the 23vPPV vs placebo or no vaccine studies was all-cause CAP instead of VT CAP.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation
13vPCV vs placebo						
CAPiTA	84,496	R, DB 4 years	Low	Aged ≥65 years	VT CAP	VE for VT CAP, VT IPD
23vPPV vs placebo or no vaccine						
Alfageme 2006	600	R, OL 2.7 years	Moderate	Mean age 68 years COPD	CAP of pneumococcal or unknown aetiology	VE for VT CAP
Furumoto 2008	191	R, OL 2 years	Moderate	Aged 40-80 years Chronic lung disease	CAP (all-cause)	VE for VT CAP
Kawakami 2010	786	R, OL 2 years	Moderate	Aged ≥65 years Immunised against influenza Treated by pulmonary physician	CAP (all-cause)	VE for VT CAP
Maruyama 2010	1,006	R, DB 2.3 years	Low	Mean age 85 years Nursing home residents	Pneumococcal CAP	VE for VT CAP
Örtqvist 1998	693	R, DB 2.5 years	Low	Aged 50-85 years Previously treated as inpatient for CAP	Pneumococcal CAP	VE for VT CAP
Meta-analyses	2,293- 3,246	Assessed CAP (all-cause), pneumococcal CAP, bacteraemic pneumococcal pneumonia				VE for VT CAP
23vPPV non-randomised study used in the economic evaluations						
Menzies 2014	900 IPD cases	Used screening method	High	IPD cases from NNDSS in adults ≥65 years	VT IPD	VE for VT IPD

CAP=community acquired pneumonia; COPD=chronic obstructive pulmonary disease; DB=double blind; IPD=invasive pneumococcal disease; OL=open label; mITT=modified intent to treat; NNDSS=National Notifiable Diseases Surveillance System; R=randomised; VE=vaccine efficacy; VT=vaccine type
Source: compiled during the evaluation of the March 2015 submission.

Comparative effectiveness

- 6.6 The results for the primary and key secondary outcomes for CAPiTA for the modified intention to treat (mITT) case population are presented in Table 3.

Table 3: Results of VT pneumonia and IPD outcome in CAPiTA (mITT population)

Outcome	13vPCV n with event/N (%)	PBO n with event/N (%)	RD (%) (95% CI)	VE ^a (%) (95.2% CI ^b)	NNV ^c
VT pneumonia	66/42,240 (0.156)	106/42,256 (0.251)	-0.09 (-0.16, -0.03)	37.7 (14.3, 55.1)	1,057
NB/NI VT pneumonia	43/42,240 (0.102)	73/42,256 (0.173)	-0.07 (-0.12, -0.02)	41.1 (12.7, 60.7)	1,409
VT IPD	8/42,240 (0.019)	33/42,256 (0.078)	-0.06 (-0.09, -0.03)	75.8 (46.5, 90.3)	1,690

Source: Tables 11 and 12 p40-41 of the submission; and calculated during the evaluation of the March 2015 submission.

PBO=placebo; IPD=invasive pneumococcal disease; NB/NI=non-bacteraemic/non-invasive; NNV=number needed to vaccinate; RD=risk difference; VE=vaccine efficacy; VT=vaccine type

^a VE = (1-RR) x 100

^b O'Brien-Fleming adjustment for 1 interim analysis

^c number needed to vaccinate = 1/RD

- 6.7 The pooled results for the 23vPPV randomised efficacy trials, and the matching exploratory outcomes from CAPiTA, are presented in Table 4. On the basis of a statistically significant reduction in CAP outcomes not being observed in the meta-analysis of 23vPPV randomised trials, the submission assumed that 23vPPV is ineffective against VT CAP. The ESC considered that a lack of statistical significance does not necessarily imply a zero treatment effect. The ESC further noted that the meta-analysis was underpowered for these outcomes. The PSCR argued the assumption that 23vPPV is not effective against VT-CAP was based on ATAGI advice. Assuming a zero protective benefit with 23vPPV resulted in the incremental benefit with 13vPCV being maximised. The ESC noted that the vaccine effectiveness of 13vPCV against VT CAP could be as low as 14.3% (lower limit of the 95% confidence interval), which was roughly the same as the ATAGI recommended upper limit of 23vPPV vaccine effectiveness against pneumococcal CAP (of 14%).
- 6.8 Twelve non-randomised studies assessing the efficacy of 23vPPV against IPD were included in the submission. Consistent with the March 2015 and July 2015 submissions, the economic evaluation only used the results of Menzies 2014 (VE=61%, 95%CI 55%, 67%). This compared with VE of 75.8% for 13vPCV (Table 3).

Comparative harms

- 6.9 The harms data were the same as presented in the July 2015 and March 2015 submissions. No safety concerns were previously raised by the PBAC.

Benefits/harms

- 6.10 A summary of the comparative benefits and harms for 13vPCV versus 23vPPV is presented in Table 4.

Table 4: Summary of comparative benefits and harms for 13vPCV and 23vPPV

Trial	13vPCV	23vPPV/PBO	RR (95% CI)	Event rate/100 patients*			RD (95% CI)	
				13vPCV	23vPPV/PBO			
Benefits								
VT pneumococcal CAP								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	13vPCV	PBO ^a	23vPPV	RD (95% CI)
CAPiTA	66/ 42,240	106/ 42,256	-	0.62 (0.45, 0.86)	0.16	0.25	-	-0.0009 (-0.0016, -0.0003)
23vPPV	No 23vPPV studies available assessing VT CAP							
Pneumococcal CAP								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	13vPCV	PBO ^a	23vPPV	RD (95% CI)
CAPiTA	135/ 42,240	174/ 42,256	-	0.78 (0.62, 0.98)	0.3	0.4	-	-0.0009 (-0.0017, -0.0001)
23vPPV RCTs pooled, 3 trials	-	58/ 1,154	33/ 1,139	0.54 (0.18, 1.65) Heterogeneity p- value=0.01	-	5.0	2.9	-0.02 (-0.05, 0.01) Heterogeneity p- value=0.03
CAP (all-cause)								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	13vPCV	PBO ^a	23vPPV	RD (95% CI)
CAPiTA	747/ 42,240	787/ 42,256	-	0.95 (0.86, 1.05)	1.8	1.9	-	-0.0009 (-0.0027, 0.0009)
23vPPV RCTs pooled, 5 trials	-	260/ 1,626	226/ 1,620	0.91 (0.69, 1.20) Heterogeneity p- value=0.04	-	16.0	14.0	-0.01 (-0.06, 0.03) Heterogeneity p- value=0.03
VT IPD								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	13vPCV	PBO ^a	23vPPV	RD (95% CI)
CAPiTA	8/ 42,240	33/ 42,256	-	0.24 (0.10, 0.54)	0.019	0.078	-	-0.0006 (-0.0009, -0.0003)
Menzies 2014	Non-randomised study using screening method, RR=0.39 (0.33, 0.45)							
Harms								
	13vPCV	23vPPV	RR (95% CI)	13vPCV	23vPPV	RD (95% CI)		
Pain at injection site								
004	265/331	221/301	0.92 (0.84, 1.00)	80.1	73.4	0.066 (-0.00, 0.13)		
3010	256/370	102/175	0.84 (0.73, 0.97)	69.2	58.3	0.109 (0.02, 0.20)		

* Mean duration of follow-up: CAPiTA=3.97 years; Alfageme 2006=2.7 years; Furumoto 2008=2 years; Kawakami 2010=2 years; Maruyama 2010=2.28 years; Örtqvist 1998=2.4 years; 004=14 days; 3010=14 days

^a No vaccine for Alfageme 2006, Furumoto 2008, Kawakami 2010

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio

Source: 13vPCV PSD March 2015, table in paragraph 6.17.

- 6.11 Based on the qualitative indirect comparison using placebo/no vaccine as the common comparator, it was not clear whether 13vPCV is worse or better than 23vPPV in the prevention of invasive pneumococcal disease.
- 6.12 On the basis of a trial comparing 13vPCV with placebo conducted in a population with a 7vPCV infant vaccine program, 1,057 adults aged ≥65 years would need to be vaccinated with 13vPCV to prevent one case of vaccine type pneumonia. Clinical trial data assessing the effect of 23vPPV in the prevention of vaccine type pneumonia were not available.

- 6.13 On the basis of the head to head immunogenicity trials and the indirect comparison presented, in subjects naïve to 23vPPV the frequency of adverse effects is comparable.

Clinical claim

- 6.14 The submission described 13vPCV as:
- superior in terms of comparative effectiveness for the prevention of VT-CAP over 23vPPV;
 - equivalent to 23vPPV in terms of comparative effectiveness for the prevention of IPD; and
 - equivalent to 23vPPV in terms of comparative safety.
- 6.15 At the March 2015 meeting, while noting the limitations in the available evidence for 23vPPV, the PBAC considered that 13vPCV is likely to be superior to 23vPPV in terms of prevention of VT CAP, although the magnitude of superiority was unclear. At the July 2015 meeting, the PBAC did not consider that the minor re-submission adequately addressed the uncertainty regarding the sponsor's claim of superiority in prevention of VT CAP (13vPCV PSD July 2015 paragraph 7.7). No new data were presented in the current submission assessing the efficacy of 13vPCV or 23vPPV against VT CAP. The PSCR argued that the magnitude of superiority is clear based on the CAPiTA study for 13vPCV and ATAGI advice for 23vPPV. The ESC considered that in the absence of any new clinical data to support this claim, the magnitude of superiority continued to remain highly uncertain.
- 6.16 The ESC noted vaccine effectiveness estimates against IPD used in the economic model, of 61% for 23vPPV and 75.8% for 13vPCV, contradicted the claim of equivalent comparative effectiveness for the prevention of IPD. In addition, the submission assumed a longer duration of efficacy for 13vPCV, compared with 23vPPV. Accordingly, despite the claim of equivalent comparative effectiveness and the reduced serotype coverage, 13vPCV prevented more cases of IPD in the economic model than 23vPPV. The pre-PBAC response accepted that VE for IPD should be equivalent for 13vPCV and 23vPPV and used the 61% estimate for both 13vPCV and 23vPPV in a revised model.
- 6.17 The PBAC considered that because of the reduced serotype coverage of 13vPCV compared with 23vPPV, the claim of equivalent effectiveness for prevention of IPD was highly uncertain, and dependent not only on assumptions regarding the height and duration of protection against VT IPD for each vaccine, but also on the relative contribution of 23vPPV/non13vPCV serotypes to IPD over time. If 13vPCV serotypes are eventually eliminated as a result of the infant program, 13vPCV will become inferior to 23vPPV for IPD.
- 6.18 In line with previous considerations, the PBAC considered that 13vPCV is likely to be superior to 23vPPV in terms of prevention of VT CAP.
- 6.19 The PBAC considered that the claim of equivalent comparative safety was reasonable.

Economic analysis

6.20 The model structure was the same as that presented in the July 2015 submission. The key inputs that were changed were 13vPCV cost (reduced), CAP incidence (reduced), proportion of CAP due to 13vPCV serotypes (reduced) and duration of protection with 23vPPV (reduced).

Table 5: Summary of model structure and rationale

Time horizon	Average follow-up is 12.1 years versus 2-4 years in the trials.
Outcome	LY and QALY gained
Methods used to generate results	Cohort expected value analysis
Health states (for base case)	Alive, Dead
Events modelled	IPD (bacteraemia; meningitis), Hospital treated CAP, GP treated CAP
Cycle length	1 year, half cycle correction applied
Transition probabilities	Transition to 'Dead': Australian population death rates if no event or GP treated CAP; 12.5% for IPD; 10.0% for hospitalised CAP

Source: compiled during the evaluation

6.21 The key model drivers are summarised in Table 6.

Table 6: Key drivers of the model

Description	Method/Value	Impact
13vPCV efficacy for hospitalised CAP	Sourced from CAPiTA trial (37.7%), a RCT in 84,496 subjects	High
23vPPV efficacy for hospitalised CAP	Zero protective benefit assumed based on 5 underpowered RCTs in a total of 3,246 subjects	High, favours 13vPCV
Time horizon/duration of protection	Time horizon: up to 18 years assumed from 2-4 year trial duration Duration of protection: • 13vPCV: constant for 5 years, then declines over model duration • 23vPPV: constant for 2 years, then declines to 0 by 5 years	High, favours 13vPCV
Incidence of VT hospitalised CAP	• Australian hospital admissions in 2010/2011 for pneumonia: 1,364/100,000 person years • 20.6% due to pneumococci (ATAGI; hospital admissions coded as pneumococcal) • 30.6% due to 13vPCV serotypes (ATAGI; 2014 IPD serotype data) • VT CAP reduced over 8 years by up to 90% to account for herd immunity from infant program	High
Distribution across the age cohorts	Based on distribution of Australian population	High

Source: compiled during the evaluation

6.22 Compared with the July 2015 re-submission, the following model inputs were changed in the base case analysis:

- The cost of a dose of 13vPCV was reduced to \$ [REDACTED] from \$ [REDACTED] in the March 2015 submission and \$ [REDACTED] in the July 2015 resubmission.
- Duration of protection:
 - 13vPCV VE protection against IPD: efficacy was assumed to wane over 18 years in an increasing stepwise manner instead of linearly. This had minimal impact on the results. The submission concluded 13vPCV is effective for at least 5 years, based on immunogenicity trial B1851020, however neither

- clinical or immunogenicity data were available to support a duration of protection of longer than 5 years.
- 13vPCV VE protection against CAP: VE was assumed to wane over 18 years in a similar fashion to IPD. The evaluation considered that the assumed duration of benefit with 13vPCV (up to 18 years) appeared inconsistent with the recommendation to revaccinate high-risk individuals after 5 years with 23vPPV. However, ATAGI advised that the primary expected benefit of recommending a dose of 23vPPV following 13vPCV for high risk individuals is for protection against pneumococcal disease due to the additional (23v-non-13v) serotypes, rather than boosting of effects against the common serotypes (post-submission advice). The ESC noted that the economic analysis only modelled the single dose of 13vPCV and not the impact on the effectiveness of the subsequent doses of 23vPPV.
 - 23vPPV VE protection against IPD: no efficacy assumed after 5 years. The efficacy of 23vPPV was assumed to be constant for the first two years, and then linearly decreased to zero from Years 2 to 5. In the previous submission a linear decline over 18 years was assumed. The assumed differential waning rates between 23vPPV and 13vPCV resulted in 13vPCV preventing more cases of IPD despite the reduced serotype coverage (bacteraemia and meningitis in Table 7). This is inconsistent with the claim of equivalent effectiveness for the prevention of IPD. By comparison, the July 2015 model estimated an increase in IPD due to the reduced serotype coverage with 13vPCV.
 - The incidence of VT-CAP was reduced over time to account for herd effects from the 13vPCV infant program. The evaluation considered that this was implemented incorrectly in the model because:
 - The reduction was applied to all 13vPCV serotypes rather than only the 13v-non7vPCV serotypes. The impact of the 7vPCV infant program (which was introduced in 2005) on the incidence of CAP in adults is expected to have already reached its maximal effect and hence no further reductions in the incidence of disease due to the 7vPCV serotypes is expected;
 - CAP incidence data from 2012 are combined with serotype data from 2014; and
 - The proportion of pneumococcal CAP due to 13vPCV serotypes was not reduced sufficiently in future years to account for the impact of the herd immunity. The proportion was reduced from 35.1% in the July 2015 model to 30.6% based on 2014 serotype data, however further reductions are expected beyond 2014 as the 13vPCV infant program was only introduced in 2011.
 - The PSCR disagreed that the impact of the herd immunity from the 13vPCV infant program was underestimated. The PSCR stated that herd effects were calculated using the same methodology as that used to estimate IPD herd effects.
 - The ESC agreed with the evaluation, noting that the reduction in the incidence of pneumococcal CAP was calculated by reducing the incidence of all 13vPCV serotypes whereas, consistent with the approach used for IPD in the March 2015/July 2015 model, the reduction should have only been applied to 13v-non7vPCV serotypes.
 - In this regard, the ESC noted that ATAGI (post-submission advice) considered it reasonable to assume that:

- any further reductions in the incidence of CAP would occur in the proportion attributable to 13v-non7vPCV only. From 2011, 7vPCV-type IPD incidence rates have reached a steady state in the presence of the ongoing childhood 13vPCV program, and a further reduction in incidence of IPD arising from the herd effect of the childhood program would occur almost entirely in the 13v-non7vPCV component; and
- the proportion of adult CAP due to 13v-non7vPCV serotypes would progressively decline with each consecutive year of 13vPCV use in children. The estimate of 6.3% as suggested for 2014 for 13vPCV serotype CAP should be reduced in 2015 and beyond.
- o The pre-PBAC response accepted the revised methodology for accounting for herd immunity.

6.23 A comparison of the number of events avoided with 13vPCV compared with 23vPPV in the July 2015 model and the current submission's model is presented in Table 7.

Table 7: Number of events avoided with 13vPCV compared with 23vPPV (per 1,000 population)

Event	July 2015 re-submission	Current submission	Calculated during the evaluation*
Bacteraemia	-0.024	0.134	0.134
Meningitis without complication	-0.001	0.007	0.007
Meningitis with complication	-0.001	0.003	0.003
CAP hospitalisations	2.458	1.387	0.769
GP treated CAP	1.360	0.735	0.407
Total pneumococcal events	3.792	2.266	1.319
Deaths	0.152	0.097	0.059

Source: Table 94 p182 of the submission; compiled during the evaluation using '13vPCV' and '23vPPV' worksheets, Section D Non-Indigenous (65-84 y).xls and adaptations to model in Attachment D; 7.08 PBAC Public Summary Document Table 4 paragraph 6.17.

*The pre-PBAC response revised the model so that 23vPPV and 13vPCV had equivalent VE for IPD. This change has not been taken account of in these estimates.

6.24 In the base case analysis presented in the submission 13vPCV was dominant over 23vPPV (see Table 8). After the evaluation revised the calculation for the herd immunity, the cost/QALY gained increased to less than \$15,000 per QALY. This compared with \$15,000 - \$45,000/QALY gained in the July 2015 submission.

Table 8: Results of the economic evaluation (per 1,000 population)

Step and component	13vPCV	23vPPV	Increment
July 2015 submission			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	7,462.959	7,461.768	1.191
Incremental cost/extra LY gained			\$ [REDACTED]
QALY gained	0.878	5,499.323	0.878
Incremental cost/extra QALY gained			\$ [REDACTED]
Non-Indigenous adults (65-84y) model (corrected during the evaluation)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
QALY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Indigenous adults (50-69y) model (not corrected during the evaluation)			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
LY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained (as presented in submission)			Dominant
QALY gained	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained (as presented in submission)			Dominant

Source: Table 95 p183 of the submission and calculated during the evaluation; values in italics calculated during the evaluation.

- 6.25 Of the model inputs that were revised, the 13vPCV price and the inclusion of the herd immunity had the largest impact. The price reduction (\$ [REDACTED] to \$ [REDACTED]) alone (without the herd immunity) resulted in 13vPCV being dominant in the submission. Including the herd immunity only (using the revised methodology and without the price reduction) increased the ICER from \$15,000 - \$45,000/QALY gained to \$75,000 - \$105,000/QALY gained.

- 6.26 As with the July 2015 model, the results were sensitive to the assumed duration of protection with 13vPCV. In the base case analysis 13vPCV efficacy for hospitalised CAP was reduced from 37.7% (assumed for the first 5 years) to 27.7% at year 10 and 18.4% at year 18 (model end). Clinical data (CAPiTA) support a duration of protection of at least 4 years. Immunogenicity data support a duration of protection of 5 years for most serotypes, but not serotype 3 which is relatively common. The evaluation considered that assuming substantial protection beyond 5 years appeared inconsistent with the recommendation to vaccinate at-risk groups with 23vPPV five years following the primary dose of 13vPCV. However, the ESC noted ATAGI's view that the primary expected benefit of recommending a dose of 23vPPV following 13vPCV is for protection against pneumococcal disease due to the additional (23v-non-13v) serotypes, rather than boosting of effects against the common serotypes. In the March 2015 submission it was estimated that more than half (52.4%) of people aged 65 years and above are classified as "at risk" and hence would be eligible for re-vaccination after 5 years.
- The PSCR argued that it is not reasonable to assume the duration of protection of 13vPCV would be limited to 5 years, stating that efficacy of 13vPCV was sustained for the 5-year duration of the CAPiTA trial. The PSCR referred to a new publication of CAPiTA which has recently become available (Patterson et al 2016)¹. The PSCR stated that if duration of protection was limited to 5 years, waning would have been seen within the 5-year duration of the trial, as reported for 23vPPV.
 - The ESC noted that Patterson et al 2016 reported a post-hoc analysis of the CAPiTA study which should be interpreted with caution. The publication concluded 13vPCV was protective with no waning of efficacy observed during the mean follow-up time of approximately 4 years. The publication did not report the vaccine efficacy of 13vPCV beyond a 5-year period.
 - ATAGI advised that while the exact rate of waning of 13vPCV-induced protection is uncertain, the proposed base case waning profile was acceptable. However, ATAGI advised that inclusion in sensitivity analysis of the scenario of a shorter duration of protection with zero efficacy from 10 years after vaccination was appropriate (post-submission advice).
 - The PBAC noted that the sensitivity analysis for the 10 year scenario was informative.
- 6.27 As per paragraph 6.16, the pre-PBAC response agreed with the ESC that VE for IPD should be equivalent for 13vPCV and 23vPPV and provided a revised ICER with this change of less than \$15,000 per QALY.
- 6.28 The ESC Advice included a multivariate sensitivity analysis investigating the effect of the assumed efficacy for 23vPPV and duration of protection with 13vPCV on the cost effectiveness of 13vPCV. Table 9 provides corrected univariate and multivariate sensitivity analysis as presented in the pre-PBAC response and confirmed by the evaluator.
- In the base case 0% efficacy was assumed. ATAGI considered that this estimate was appropriate but noted that a non-zero efficacy of 14% is plausible (revised from 46% for the March 2015 submission) as an informative sensitivity analyses (pre-submission advice). This increased the ICER from less than \$15,000 per

¹ Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). *Trials in Vaccinology* 2016; 5:92–6.

- QALY gained to less than \$15,000 per QALY gained.
- The assumed duration of protection was only up to 5 years for 23vPPV (declining from 2 years) compared with up to 18 years for 13vPCV. Reducing the duration of protection with 13vPCV to 10 years increased the ICER from less than \$15,000 per QALY to \$15,000/QALY - \$45,000/QALY.
 - Assuming 14% efficacy for 23vPPV and 10 years of protection with 13vPCV increased the ICER to \$15,000/QALY - \$45,000/QALY gained.

Table 9: Revised base case and sensitivity analyses (non-Indigenous adults 65-84y)

Scenario	\$/LYG	\$/QALY
Evaluation base case	\$ [REDACTED]	\$ [REDACTED]
Pre-PBAC response base case (equivalent IPD VE)	\$ [REDACTED]	\$ [REDACTED]
Univariate sensitivity analyses on pre-PBAC response base case		
23vPPV VE for CAP, Upper limit: 0%→14% (CAP hospitalisations) or 5.3% (CAP GP visits) and effective for additional serotypes of pneumococcal CAP (22.1% for 65-74 years cohort and 19.0% for 75-84 years cohort)	\$ [REDACTED]	\$ [REDACTED]
13vPCV VE zero beyond 10 years	\$ [REDACTED]	\$ [REDACTED]
Multivariate analysis on pre-PBAC response base case		
Both of the above univariate analysis scenarios	\$ [REDACTED]	\$ [REDACTED]

Source: Pre-PBAC response

- 6.29 A sensitivity analyses was presented in the submission assessing the impact of serotype replacement (an increase in pneumococcal disease due to non-VT serotypes) due to the replacement of 23vPPV with 13vPCV. Consistent with the assumption that 23vPPV is only effective against IPD, an increase (33%) in the incidence of IPD only was assumed. The ICER for the non-Indigenous (65-85 years) model (corrected during the evaluation) increased to less than \$15,000 per QALY (compared with less than \$15,000 per QALY).
- 6.30 For the Indigenous population, 13vPCV was dominant over 23vPPV (Table 8). The calculations for the herd protection were not corrected during the evaluation as data on serotype distribution over time for the Indigenous population were not provided. The key inputs changed for the Indigenous population were the baseline incidence of IPD and CAP (increased from 13/100,000 to 90/100,000 for IPD and from 281/100,000 to 824/100,000 for hospitalised pneumococcal CAP) and the proportion of pneumococcal disease due to 13vPCV serotypes (decreased from 30.6% to 14.3%). Overall, 13vPCV is likely to be more cost-effective in the Indigenous population, compared with the non-Indigenous population, due to the increased disease incidence (although there are limited Indigenous specific data informing this conclusion).
- 6.31 The initial distribution across the age cohorts was not tested in the submission's sensitivity analyses. 13vPCV is less cost-effective in older individuals because they have fewer years to benefit from the vaccine. The average age at vaccination in the base case was 73 years.

Drug cost/patient/dose: \$ [REDACTED]

- 6.32 The 13vPCV cost per dose in the submission was \$ [REDACTED]. The 23vPPV cost per dose in the submission was \$35.12.

Estimated PBS usage & financial implications

6.33 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the extent of use of 13vPCV. The estimates were based on the projected Australian population and assumed uptake. The approach is the same as used in the July 2015 submission. At year 5, the estimated number of patients would be over 200,000 per year and the net cost to the NIP would be less than \$10 million per year.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Non-Indigenous population aged 65 yrs Uptake	%	%	%	%	%
Non-Indigenous population aged 66-84 yrs ^a Uptake	%	%	%	%	%
Indigenous population aged 50 yrs Uptake	%	%	%	%	%
Indigenous population aged ≥51 yrs ^a Uptake	%	%	%	%	%
Total 13vPCV doses (current submission)					
Total 13vPCV doses (July 2015)					
Estimated net cost to NIP					
Total 13vPCV cost, including 5% wastage	\$	\$	\$	\$	\$
Cost of substituted 23vPPV ^b	\$	\$	\$	\$	\$
Net cost to NIP (current submission)	\$	\$	\$	\$	\$
Net cost to NIP (July 2015)	\$	\$	\$	\$	\$

^a individuals previously vaccinated with 23vPPV or 13vPCV removed from population

^b assumes 75% of 13vPCV doses replace 23vPPV doses

Source: Tables 101, 102 and 103 p189 and 190 of the submission; Tables 7, 8 and 9 p10-11 of the July 2015 submission; 7.08 PBAC Public Summary Document Table 6 paragraph 6.26.

6.34 The July 2015 submission estimated that 65.5% of 13vPCV doses would replace a dose of 23vPPV although the source for this estimate was not clear. In the current submission it was estimated that 75% of 13vPCV doses would replace a dose of 23vPPV based on the estimate included in the March 2015 Public Summary Document.

6.35 For the 25% of 13vPCV doses that do not replace 23vPPV, there may be an additional administration cost. Assuming 25% of patients require an additional GP visit for vaccine administration, the MBS cost (based on a level A consult) over the 5 years would be less than \$10 million. The PSCR argued that ATAGI's understanding is that 100% of projected 13vPCV doses would serve as replacement doses of 23vPPV as used in the current program and therefore there are no additional administration costs. However, despite this advice from ATAGI, the ESC noted that the submission assumed that only 75% of 13vPCV doses would replace a dose of 23vPPV.

6.36 The submission did not consider the risk of adults previously vaccinated with 23vPPV being vaccinated with 13vPCV. The proposed listing is for a single dose of 13vPCV

for pneumococcal vaccine naïve adults; however, ATAGI considered that it is clinically appropriate for all adults previously vaccinated with 23vPPV to receive a single dose of 13vPCV (ATAGI pre-submission advice). The PSCR stated that a catch-up program for adults previously vaccinated with 23vPPV has not been requested and indicated that the sponsor would seek assistance from the National Prescribing Service to ensure usage of 13vPCV is consistent with the NIP listing.

- 6.37 The submission did not consider the risk of adults being vaccinated with both 13vPCV and 23vPPV. Given the reduced serotype coverage with 13vPCV compared with 23vPPV there is the potential for vaccination with both 13vPCV and 23vPPV, especially in adults with risk factors for pneumococcal infections. In the March 2015 submission it was estimated that more than half (52.4%) of people aged 65 years and above are classified as “at risk” and hence would be eligible for re-vaccination after 5 years. The PSCR noted that if 13vPCV was included on the NIP for adults, then individuals in specified at-risk groups would continue to receive a 23vPPV dose 5 years following 13vPCV (with 13vPCV only replacing the initial 23vPPV dose). The ESC noted that ATAGI stated that the interval between 13vPCV and a subsequent 23vPPV dose may be shorter than 5 years but the exact interval is under deliberation (post-submission advice).
- 6.38 The uptake in adults not vaccinated with 13vPCV in their 65th year is ■■■% for each future year. Thus over time uptake approaches ■■■%. Assuming adults not vaccinated in their 65th are not vaccinated in subsequent years decreases the NIP cost from \$30 - \$60 million to \$30 - \$60 million over 5 years.

Quality Use of Medicines

- 6.39 The Sponsor proposed to provide education to healthcare professionals and information for patients to help ensure appropriate use of 13vPCV.

Financial Management – Risk Sharing Arrangements

- 6.40 The submission acknowledged that a Risk Share Arrangement may be required; however, no specific details were provided.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended a change to the circumstances under which 13vPCV is made available as a designated vaccine for the NIP for the prevention of pneumococcal pneumonia and IPD in adults on the basis of cost-effectiveness compared with 23vPPV.
- 7.2 The PBAC recalled that it previously recommended 13vPCV on a cost minimisation basis to 23vPPV. At that time it recommended that a single dose of 13vPCV be made available to pneumococcal vaccine naïve non-Indigenous adults aged 65 years and over and to pneumococcal vaccine naïve Indigenous adults aged 50 years and over. The PBAC recommended that this dose of 13vPCV should replace the single dose (or the first dose for those adults with risk factors) of 23vPPV that is currently

provided to these populations. The PBAC noted that if 13vPCV was included on the NIP for adults, then individuals in specified at-risk groups would continue to receive 23vPPV five years following the primary dose of 13vPCV.

- 7.3 The PBAC recalled that it previously accepted that 23vPPV was the appropriate comparator.
- 7.4 The PBAC recalled it previously noted that the evidence for 13vPCV over no vaccination was of higher quality than for 23vPPV over no vaccination. In the absence of direct comparative evidence between 13vPCV and 23vPPV, the PBAC accepted that the effectiveness of 13vPCV against CAP is likely to be superior to that of 23vPPV, whereas effectiveness against IPD was likely to be at least equivalent to that of 23vPPV where IPD was caused by serotypes common to both vaccines, but not where IPD was caused by serotypes contained only within 23vPPV. Although the PBAC considered that 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT pneumonia, the PBAC previously considered that the submission had not provided sufficient evidence to allow the PBAC to be confident that recommending 13vPCV at the requested price would be cost effective.
- 7.5 In its consideration of the current submission, the PBAC noted that no new evidence on the comparative effectiveness of 13vPCV and 23vPPV was presented and did not change its previous consideration of the clinical claims.
- 7.6 The PBAC recalled that in July 2015 it rejected the minor re-submission's assumption that there would be no additional herd immunity from the 13vPCV infant programme for pneumococcal CAP. The PBAC recalled that a 13vPCV infant program was only introduced in Australia in 2011, and considered that further reductions in the prevalence of the 13 serotypes in age groups other than those vaccinated (including the ≥65 year old population) would be likely to occur. The PBAC noted that the current submission included a reduction in the incidence of VT-CAP over time to account for herd effects from the 13vPCV infant program (the methodology for which was corrected during the evaluation and accepted by the sponsor in the pre-PBAC response).
- 7.7 The PBAC accepted the base case for the economic model in the pre-PBAC response which resulted in an ICER of less than \$15,000/QALY and noted that the ICER remained between \$15,000/QALY - \$45,000/QALY under a range of scenarios. The PBAC considered that the revised model, and the [REDACTED] price reduction offered in the submission, enabled it to have greater confidence that the requested listing of would be cost effective compared with 23vPPV.
- 7.8 The PBAC noted that the cost-effectiveness of 23vPPV had not been previously reviewed. It was further noted that the information provided in the 13vPCV submission suggested that 23vPPV is unlikely to prevent CAP, and the impact on the incidence of IPD may be minimal because of the short duration of protection and the reduction in 13vPCV-serotypes due to the infant programme. The PBAC requested advice from ATAGI on the clinical place and effectiveness of 23vPPV on the NIP with a view to potentially informing a review of the cost-effectiveness of 23vPPV compared with no vaccine. The PBAC noted that any outcomes of the review of 23vPPV may have implications for the 13vPCV listing. This review should include the use of 23vPPV as currently specified in the NIP schedule (i.e. in children and

Aboriginal and Torres Strait Islander adolescents medically at risk and in adults with and without risk factors).

- 7.9 The financial estimates assumed that 13vPCV will replace 23vPPV in pneumococcal naïve adults (or the first dose of 23vPPV in high risk individuals), as per the requested listing. The PBAC noted that the sponsor proposed to provide education to healthcare professionals and information for patients to help ensure appropriate use of 13vPCV. The PBAC further noted that from September 2016, the Australian Immunisation Register will capture all vaccines administered throughout a person's life given through general practice and community clinics. Accordingly, the PBAC accepted the utilisation and financial estimates.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new indication as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 13-VALENT ADSORBED Pre-filled syringe, 0.5 mL	1	0	Prevenar 13	Pfizer

National Immunisation Program

- A single 13vPCV dose for pneumococcal vaccine naïve non-Indigenous adults aged 65 years and over
- A single 13vPCV dose for pneumococcal vaccine naïve Indigenous adults aged 50 years and over

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Pfizer Australia is pleased that the PBAC recognise the cost effectiveness of Prevenar 13 for the prevention of pneumococcal pneumonia and invasive pneumococcal disease in adults compared with Pneumovax. Pfizer is committed to working with the PBAC and the Office of Health Protection to ensure the timely and equitable access of Prevenar 13 to adults given the significant burden of pneumococcal pneumonia in older Australians.