

6.06 PNEUMOCOCCAL CONJUGATE VACCINE 13-valent adsorbed pre-filled syringe, 0.5 mL Prevenar 13[®], Pfizer

1 Purpose of Application

- 1.1 The major submission sought National Immunisation Program (NIP) listing for 13-valent pneumococcal conjugate vaccine (13vPCV) for prevention of pneumococcal pneumonia and invasive pneumococcal disease in adults.

2 Requested listing

- 2.1 The submission sought the following listing:

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

Primary program: A single dose for non-Indigenous adults at age 65 years and Indigenous people at age 50 years

Catch-up program: A single dose for non-Indigenous adults aged 70-84 years and Indigenous people aged 55 years and older in a 5 year catch-up program

- 2.2 Listing was requested based on cost-effectiveness compared with 23-valent pneumococcal polysaccharide vaccine (23vPPV) for the primary program and cost-effectiveness compared with no vaccine for the catch-up program.
- 2.3 The ESC noted that the requested listing was only for a specific year of age and may result in confusion and some adults missing the chance to receive the 13vPCV. For example, a non-Indigenous adult without risk factors who did not receive the 13vPCV at age 65 would be ineligible to receive the 13vPCV at age 66. ATAGI 'recommended that, in the primary program, a single dose of 13vPCV is offered for non-Indigenous adults from their 65th birthday and for Indigenous adults from their 50th birthday. Rather than single year of age target cohorts (non-Indigenous adults to their 66th birthday and Indigenous adults to their 51st birthday), ATAGI recommended that persons who become age-eligible under the primary program have continued eligibility for a single 13vPCV dose until they reach their 85th birthday, which is the current upper age limit of evidence of efficacy from the CAPiTA trial. This continued eligibility for a first dose of 23vPPV is consistent with the current NIP program eligibility.' (ATAGI post submission advice)
- 2.4 The Pre-Sub-Committee Response (PSCR) proposed a revised five year catch-up program for adults aged 66-74 years or 70-74 years in response to the cost-effectiveness of the program being found to be higher than indicated in the submission during the evaluation. The ATAGI post submission advice '...recommended that those adults who had attained their 65th birthday (or 50th for Indigenous adults) prior to the commencement date of any primary 13vPCV NIP program receive a single dose of 13vPCV through the proposed 5-year catch-up program regardless of their previous 23vPPV vaccination history. ATAGI noted the

revised proposal of Pfizer to consider limiting the eligible age window for the 5 year catch-up program to 70–74 years and supported this proposal from the perspective of program implementation’.

- 2.5 The 13vPCV listing proposed in the submission would result in two different vaccine formulations being used for the prevention of the same disease. For the catch-up program this may result in adults without risk factors receiving 23vPPV and 13vPCV sequentially (compared with a single dose of 23vPPV currently) and adults with risk factors receiving 13vPCV instead of a second dose of 23vPPV. For both programs, given the reduced serotype coverage with 13vPCV, adults may receive concomitant vaccination with 13vPCV and 23vPPV, especially adults with risk factors. These scenarios are not considered in the submission. The PSCR argued that these scenarios are unlikely but indicated the sponsor’s willingness to work with ATAGI and the PBAC to work through issues with the implementation of the catch-up program. The ATAGI post-PBAC submission Advice recommended that the 13vPCV dose provided through the catch-up program for those with risk factors should replace the recommended second dose of 23vPPV in those who have already received their first dose of 23vPPV under the existing program. This recommendation was based on the lack of clear evidence of benefit of an additional dose of 23vPPV following 13vPCV, and simplicity of program implementation.

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

3 Background

- 3.1 TGA status: 13vPCV was TGA registered on 28 October 2011 for adults aged 50 years and older. The approval was based on immunogenicity studies.
- 3.2 13vPCV for adults has not been considered by the PBAC previously.
- 3.3 In July 2010 the PBAC recommended listing 13vPCV (Prevenar 13) on the NIP for children under the same circumstances of use as the existing NIP listed pneumococcal 7-valent vaccine (Prevenar). The PBAC further recommended that Prevenar 13 pre-filled syringes should be priced to achieve parity between a complete course of Prevenar 13 and a complete course of the 10-valent vaccine (Synflorix) taking into account the proportion of the Prevenar 13 targeted population who will require a fourth dose and including the \$7 cost of administering this dose at an existing vaccination point (Public Summary Document, July 2010). It should be noted that the 7-valent vaccine had not been considered by the PBAC as its listing pre-dated the requirement for a PBAC recommendation for vaccines to be funded under the NIP. The 10-valent vaccine was considered at the July 2009 PBAC meeting.
- 3.4 In November 2010, ‘the PBAC recommended extension of the recommended listing, in the NIP, of 13vPCV to include a single supplementary (catch-up) dose of 13vPCV for children aged between 12 and 23 months who have completed primary vaccination with 3 doses of 7vPCV, assuming that the catch-up program commences at around the same time as any switch from 7vPCV to 13vPCV on the NIP. Although noting that some uncertainty remained about the duration of direct benefits and the extrapolation of the surrogate immunogenicity data provided into clinical benefits, the

Committee considered that the ICER of between \$15,000 - \$45,000 per quality adjusted life-year (QALY) using the QALY weights proposed during the evaluation, including direct and indirect effects and the current price of 13vPCV, represented acceptable cost-effectiveness in this context.' (Public Summary Document, November 2010).

- 3.5 Vaccination using 23vPPV (comparator) was introduced in 1999 for all Indigenous adults aged ≥50 years and younger Indigenous adults with risk factors. Since January 2005, 23vPPV has also been funded under the NIP for non-Indigenous adults aged ≥65 years. Persons aged <65 years with a condition(s) associated with an increased risk of invasive pneumococcal diseases (IPD) can access 23vPPV through the Pharmaceutical Benefits Scheme. (Australian Immunisation Handbook 10th Edition p.319)

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 pneumonia. 13vPCV is a 13-valent pneumococcal conjugate vaccine. The pneumococcal vaccine currently listed on the NIP for adults is a 23-valent capsular polysaccharide vaccine. 13vPCV covers 12 of the 23 serotypes covered by 23vPPV and one additional serotype.
- 4.2 Primary program: for adults without at-risk conditions, a single dose of 13vPCV is to replace the single dose of 23vPPV. For adults with an at-risk condition, a single dose of 13vPCV is to replace the initial dose of two or three dose of 23vPPV, noting that a dose of 23vPPV will still be required 5 years later.
Catch-up program: a single dose of 13vPCV for adults 66-74 or 70-74 years of age over five years to increase vaccination coverage.
- 4.3 The following table shows the proposed listing for the primary program compared with the current schedule.

13vPCV proposed listing compared with current 23vPPV

		Current schedule	Proposed schedule
Non-Indigenous	Without at-risk conditions	23vPPV at ≥65 years	13vPCV at 65 years
	With at-risk conditions	23vPPV at ≥65 years with a subsequent dose ≥5 years after the first dose	13vPCV at 65 years and 23vPPV ≥5 years after the first dose
Indigenous	Without at-risk conditions	23vPPV at ≥50 years	13vPCV at 50 years
	With at-risk conditions	23vPPV at ≥50 years with a subsequent dose ≥5 years after the first dose	13vPCV at 50 years and 23vPPV ≥5 years after the first dose

Source: Australian Immunisation Handbook 10th Edition p.332-3

- 4.4 The ESC noted that if the ages remain at 65 years and 50 years for non-Indigenous and Indigenous adults respectively, as opposed to ≥65 years and ≥50 years, the

listing will mean that if an adult does not receive the 13vPCV before turning 66 years of age, they will no longer be eligible for 13vPCV. The Pre-PBAC response indicated that the sponsor would be willing to discuss the approach recommended by ATAGI.

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

5 Comparator

- 5.1 The submission nominated 23vPPV for the primary program. This was the appropriate comparator.
- 5.2 The submission nominated no vaccine for the catch-up program. This was the appropriate comparator for adults without risk factors for pneumococcal disease. For adults with risk factors the 13vPCV dose may have replaced the second dose of 23vPPV. The PSCR argued that this scenario was unlikely. The ATAGI post-PBAC submission advice recommended that the 13vPCV dose provided through the catch-up program for those with risk factors should replace the recommended second dose of 23vPPV in those who have already received their first dose of 23vPPV under the existing program. This recommendation was based on the lack of clear evidence of benefit of an additional dose of 23vPPV following 13vPCV, and simplicity of program implementation.

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 that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on:
 - One 13vPCV placebo-controlled efficacy trial (CAPiTA)
 - A meta-analysis of six randomised efficacy trials of 23vPPV in adults reporting the incidence of pneumonia
 - A meta-analysis of 17 non-randomised studies of 23vPPV in adults reporting the incidence of IPD
 - 14 immunogenicity studies including 13vPCV
- 6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID/ First Author	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
Comparator vaccine: 23vPPV randomised trials		
Alfageme	Clinical efficacy of anti-pneumococcal vaccination in patients with COPD.	<i>Thorax</i> 2006; 61:189–95
Furumoto	Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease.	<i>Vaccine</i> 2008; 26:4284–9
Kawakami	Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan.	<i>Vaccine</i> 2010; 28:7063–9
Maruyama	Efficacy of 23-valent pneumococcal conjugate vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial.	<i>BMJ</i> 2010; 340:C1004
Örtqvist	Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group.	<i>Lancet</i> 1998; 351:399–403
Teramoto	Clinical efficacy of anti-pneumococcal vaccination in elderly patients with COPD (Abstract only)	American Thoracic Society International Conference. San Francisco, CA, USA, 18–23 May 2007
Comparator vaccine: 23vPPV non-randomised studies		
Andrews	Effectiveness of a publicly funded pneumococcal vaccination program against invasive pneumococcal disease among the elderly in Victoria, Australia.	<i>Vaccine</i> 2004; 23:132–8
Andrews	Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales.	<i>Vaccine</i> 2012; 30:6802-8
Christenson	Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study.	<i>Lancet</i> 2001; 357:1008–11
Christenson	Additive preventive effect of influenza and pneumococcal vaccines in elderly persons.	<i>Eur Respir J</i> 2004; 23:363–8
Christenson	Effect of influenza and pneumococcal vaccines in elderly persons in years of low influenza activity.	<i>Virology</i> 2008; 5:52
Dominguez	Effectiveness of pneumococcal vaccination for elderly people in Catalonia, Spain: a case-control study.	<i>Clin Infect Dis</i> 2005; 40:1250–7
Hedlund	Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up.	<i>Vaccine</i> 2003; 21:3906-11
Honkanen	Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older.	<i>Vaccine</i> 1999; 17:2493–500
Jackson	Effectiveness of pneumococcal polysaccharide vaccine in older adults.	<i>N Engl J Med</i> 2003; 348:1747–55
Johnstone	Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia.	<i>Arch Intern Med</i> 2007; 167:1938-43
Menzies	Impact of pneumococcal polysaccharide vaccine in people aged 65 years or older.	<i>Med J Aust</i> 2014; 200:112–5

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Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Mooney	The impact and effectiveness of pneumococcal vaccination in Scotland for those aged 65 and over during winter 2003/2004.	<i>BMC Infect Dis</i> 2008; 8:53
Musher	Effect of pneumococcal vaccination: a comparison of vaccination rates in patients with bacteremic and nonbacteremic pneumococcal pneumonia.	<i>Clin Infect Dis</i> 2006; 43:1004–8
Mykietiuik	Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia.	<i>Eur J Clin Microbiol Infect Dis</i> 2006; 25:457-62
Vila-Corcoles	Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the Evan-65 study.	<i>Clin Infect Dis</i> 2006; 43:860–8
Vila-Corcoles	Effectiveness of the 23-valent polysaccharide pneumococcal vaccine against invasive pneumococcal disease in people 60 years or older.	<i>BMC Infect Dis</i> 2010; 10:73
Wright	Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in people aged 65 years and over in the North East of England, April 2006-July 2012.	<i>Trials Vaccinol</i> 2013; 2:45-8.
Immunogenicity studies		
B1851088	A phase 3, randomised, modified double-blind, active controlled trial evaluating the safety, tolerability and immunogenicity of a 13-valent pneumococcal conjugate vaccine (13vPCV) in Japanese elderly adults aged 65+ years who are naïve to pneumococcal vaccine.	April 2013
004	A phase 3, randomised active-controlled, modified double-blind trial evaluating the safety, tolerability and immunogenicity of a 13-valent pneumococcal conjugate vaccine (13vPCV) compared to a 23-valent pneumococcal polysaccharide vaccine (23vPPV) in adults 60 to 64 years old who are naïve to 23vPPV and the safety, tolerability and immunogenicity of 13vPCV in adults 18 to 59 years old who are naïve to 23vPPV. Jackson LA, Gurtman LA, van Cleeff A, <i>et al.</i> Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults.	August 2010 <i>Vaccine</i> 2013; 31:3577-584
3001 Frenck	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. Randomised, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults.	November 2009 <i>Clin Vaccine Immunol</i> 2012; 19:1296
3004	A phase 3, open-label trial to evaluate the safety, tolerability, and immunogenicity of a 13-valent pneumococcal conjugate vaccine when administered to healthy Japanese adults aged ≥65 years and 50 to 64 years in Japan who have not received a previous dose of 23-valent pneumococcal polysaccharide vaccine.	July 2011
3008	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 65 years of age or older who are naïve to 23-valent pneumococcal polysaccharide vaccine.	August 2010

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Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Schwartz	A randomised, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged ≥65 years.	<i>Vaccine</i> 2011; 29:5195-202
3020	A phase 3, open label, single arm, multicentre, trial to assess the safety, tolerability and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy adults aged ≥50 years of age who are naïve to 23-valent pneumococcal polysaccharide vaccine in Mexico.	November 2010
CAPiTA	Immunogenicity supplement to final report (Supplemental clinical study report 2): a phase 4, randomized, placebo-controlled clinical trial of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease.	October 2014
Jackson	Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older.	<i>Vaccine</i> 2013; 31:3594-602
500	A randomised, open-label, controlled phase II study to evaluate the safety, tolerability and immunogenicity after two different 13-valent pneumococcal conjugate vaccine formulations with or without aluminium phosphate as adjuvant, and after 23-valent pneumococcal polysaccharide vaccine in ambulatory elderly persons aged 65 years and older who are naïve to previous 23vPPV immunisation.	October 2010
3005 Jackson	A phase 3, randomised, active-controlled, modified double-blind trial, evaluating the safety, tolerability and immunogenicity of a 13-valent pneumococcal conjugate vaccine (13vPCV) compared to a 23-valent pneumococcal polysaccharide (23vPPV) vaccine in ambulatory elderly individuals aged 70 years and older who received 1 dose of 23vPPV at least 5 years before study enrolment. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine.	October 2010 <i>Vaccine</i> 2013; 31:3585-593
3009	A phase 3, open-label, single-arm trial evaluating the safety, tolerability and immunogenicity of a subsequent dose of 13-valent pneumococcal conjugate vaccine (13vPCV) administration to individuals who participated in study 6115A1-500 and received in this study 13vPCV with aluminium phosphate followed by 23-valent pneumococcal polysaccharide vaccine 1 year later.	August 2010
3010 Greenberg	A phase 3, randomised, active-controlled, modified, double-blind trial to evaluate the safety, tolerability and immunogenicity of 13-valent pneumococcal conjugate vaccine (13vPCV) when administered over 12 months either as a 2-dose regimen or with 23-valent pneumococcal polysaccharide (23vPPV) in healthy adults 60 to 64 years of age who are naïve to 23vPPV. Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adult's 60-64 years of age.	August 2010 <i>Vaccine</i> 2014; 32:2364-374
3018	A study to evaluate the persistence of the antibody response elicited by 13-valent pneumococcal conjugate vaccine (13vPCV) in healthy adults who have previously been vaccinated with either 2 doses of 13vPCV or 13vPCV and 23-valent pneumococcal polysaccharide vaccine in different sequential order in study 6115A1-3010 or 6115A1-3005.	May 2012

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Trial ID/ First Author	Protocol title/ Publication title	Publication citation
3000	A phase-3, open-label single-arm trial evaluating the safety, tolerability and reactogenicity of a 13-valent pneumococcal conjugate vaccine in ambulatory elderly adults aged 68 years and older who received one or more doses of 23-valent pneumococcal polysaccharide vaccine at least 3 years prior to study enrolment.	February 2010

Source: Table 5, p B.14; Table 17, pB.34; Table 30, B.55; Table 40, p B.73 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 the table below. CAPiTA was designed to detect differences across treatment groups with respect to more specific outcomes (vaccine type (VT) pneumonia and VT IPD) in a population with less risk factors for pneumonia. An indirect statistical comparison of 13vPCV and 23vPPV was not presented in the submission. This was reasonable given the substantial differences across the 13vPCV and 23vPPV trials with respect to inclusion criteria, incidence of pneumonia in the control groups and outcomes assessed. As a result, however, a reliable estimate of the incremental efficacy was not available.
- 6.6 CAPiTA excluded nursing home residents and immunocompromised subjects. For subjects who became immune deficient or suppressed during the CAPiTA follow-up period, 13vPCV vaccine efficacy estimates were lower. Thus the efficacy of 13vPCV may be reduced in the NIP population, which includes immunocompromised subjects, compared with the CAPiTA population.
- 6.7 The ESC also noted that in the Netherlands, where the CAPiTA trial took place, 23vPPV is not routinely administered in the older generations. Using a placebo in the control group may not be appropriate to compare to the Australian population due to the current use of 23vPPV.
- 6.8 As CAPiTA was hospital based, patients in the trial may have been at the severe end of the disease spectrum. Results from CAPiTA may therefore appear more effective than they would in the Australian target population.

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, BD 4 years	Low	Aged ≥65 years	VT CAP (VT pneumonia in mITT population)	VE for VT pneumonia and 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 pneumonia
Furumoto 2008	191	R, OL 2 years	Moderate	Aged 40-80 years Chronic lung disease	Pneumonia (all- cause)	VE for VT pneumonia
Kawakami 2010	786	R, OL 2 years	Moderate	Aged ≥65 years Immunised against influenza Treated by pulmonary physician	Pneumonia (all- cause)	VE for VT pneumonia
Maruyama 2010	1,006	R, DB 2.3 years	Low	Mean age 85 years Nursing home residents	Pneumococcal pneumonia	VE for VT pneumonia
Örtqvist 1998	693	R, DB 2.5 years	Low	Aged 50-85 years Previously treated as inpatient for CAP	Pneumococcal pneumonia	VE for VT pneumonia
Teramoto 2007 (abstract only)	196	R, OL Not reported	Unclear	COPD	CAP of pneumococcal or unknown aetiology	VE for VT pneumonia
Meta-analyses	2,293- 3,246	Included all studies except Teramoto; assessed pneumonia (all-cause), pneumococcal pneumonia, bacteraemic pneumococcal pneumonia				VE for VT pneumonia
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

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

Comparative effectiveness

- 6.9 The results for the primary and key secondary outcomes for CAPiTA for the modified intention to treat (mITT) case population are presented in the table below. CAPiTA was not powered to detect serotype-specific vaccine efficacy.

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: Table 10, p B.25; Table 11, p B.26 of the submission; values in italics calculated during evaluation

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

- 6.10 The ESC noted that although the CAPiTA trial was a well conducted trial, comparative effectiveness and cost effectiveness was difficult to establish against 23vPPV.
- 6.11 The pooled results for the 23vPPV randomised efficacy trials, and the matching exploratory outcomes from CAPiTA, are presented in the table of comparative benefits and harms.
- 6.12 Nine of the 17 non-randomised studies included in the submission met the submission's selection criteria. These nine studies are likely to be subject to less bias. The economic evaluation used the results of Menzies 2014 only. Menzies 2014 estimated vaccine efficacy for VT IPD using the screening method. Of 900 IPD cases in the Australian National Notifiable Diseases Surveillance System (NNDSS) for the years 2004, 2006 and 2009, 328 (36.4%) were in individuals vaccinated with 23vPPV in the previous 5 years. The proportion of the population vaccinated ranged from 51.1% to 62.2%, and the vaccine efficacy was calculated to be 61.1% (95% CI 55.1, 66.9).

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

Comparative harms

- 6.13 Three immunogenicity RCTs provided comparative safety data for 13vPCV and 23vPPV. In these three studies there were no significant differences between the 13vPCV and 23vPPV groups in the incidence of unsolicited adverse events or serious adverse events within one or six months of vaccination. Pain was more frequent after 13vPCV compared with 23vPPV in subjects naïve to 23vPPV (Study 004: 80.1% vs 73.4%; Study 3010: 69.2% vs 58.3%). Redness (10.8% vs 22.2%), swelling (10.4% vs 23.1%), pain (51.7% vs 58.5%) and limitation of arm movement (10.5% vs 27.6%) were more frequent after 23vPPV compared with 13vPCV in subjects who had received 23vPPV at least five years previously (Study 3005).
- 6.14 In CAPiTA, no serious adverse events occurred in $\geq 1\%$ of subjects in either the 13vPCV or placebo group. The incidence of general disorders and administration site conditions was significantly higher for the 13vPCV group compared with the placebo group (23/42,237 [0.1%] vs 7/42,255 [$<0.1\%$]). Of the 30 subjects who had these serious adverse events, 14 had events of non-cardiac chest pain (12 in the 13vPCV group vs two in the placebo group), and 6 had events of chest pain (5 vs 1).

- 6.15 None of these events occurred within two days after vaccination. Mild and moderate, but not severe, local reactions were significantly more frequent in the 13vPCV group than in the placebo group.
- 6.16 In 2011, the increase in adverse events with a second dose of 23vPPV led to ATAGI recommending a single dose in adults without risk factors. ATAGI noted that for subjects pre-immunised with 23vPPV, vaccination with 13vPCV had a better safety profile than revaccination with 23vPPV (ATAGI Pre-Submission Advice). The proposed listing is for 13vPCV to replace the initial dose of 23vPPV, and therefore the majority of subjects should be naïve to 23vPPV.

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

Benefits/harms

- 6.17 A summary of the comparative benefits and harms for 13vPCV versus 23vPPV is presented in the following table. The sample size for CAPiTA was substantially larger than for the 23vPPV trials, even when pooled. The 23vPPV trials aimed to assess the impact of the vaccine on broad outcomes (e.g. all-cause pneumonia) in high risk patients. With the broad outcomes the effect of the vaccine is diluted as the vaccine is effective against only a proportion of the events (based on the placebo arm of CAPiTA, only 13% (106/787) of pneumonia cases were due to VT pneumonia). The 23vPPV trials were substantially underpowered to detect differences in specific outcomes for which the vaccine would be expected to be effective against. On the basis of a statistically significant reduction in pneumonia outcomes not being observed in the 23vPPV randomised trials, it is assumed in the economic evaluation that 23vPPV is ineffective against VT non-bacteraemic pneumonia. Assuming a zero protective benefit with 23vPPV results in the incremental benefit with 13vPCV being maximised. The ESC noted that the ATAGI pre-PBAC submission advice stated that '...ATAGI accepts the sponsor's proposal of using zero as the base case for vaccine effectiveness of 23vPPV against CAP due to pneumococci.'

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 pneumonia								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
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 pneumonia							
Pneumococcal pneumonia								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
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
Pneumonia (all-cause)								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
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)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
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)							
Bacteraemic pneumococcal pneumonia								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
CAPiTA	34/ 42,240	66/ 42,256	-	0.51 (0.33, 0.79)	0.08	0.16	-	-0.0008 (-0.0012, -0.0003)
23vPPV RCTs pooled, 3 trials	-	1/ 1,048	8/ 1,038	0.18 (0.03, 1.03) Heterogeneity p- value=0.85	-	0.10	0.77	Not reported
Non-bacteraemic pneumococcal pneumonia (included in ATAGI Advice but not submission)								
	13vPCV	PBO ^a	23vPPV	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					13vPCV	PBO ^a	23vPPV	
CAPiTA	90/ 42,240	109/ 42,256	-	0.83 (0.62, 1.10)	0.21	0.26	-	-0.0004 (-0.0011, 0.0002)
23vPPV RCTs pooled, 3 trials	-	50/ 1,154	32/ 1,139	0.60 (0.16, 2.23) Heterogeneity p- value=0.005	-	4.33	2.81	Not reported

Harms						
	13vPCV	23vPPV	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				13vPCV	23vPPV	
Pain at injection site						
004	265/331	221/301	<i>0.92 (0.84, 1.00)</i>	80.1	73.4	0.066 (-0.00, 0.13)
3010	256/370	102/175	<i>0.84 (0.73, 0.97)</i>	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; Orqvist 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: Table B(i).6.2 of the Commentary; Table 28, p B.50 of the submission; CAPiTA CSR Table 47; *values in italics added during the evaluation*

- 6.18 Based on the qualitative indirect comparison using placebo/no vaccine as the common comparator, it was not clear whether 13vPCV was worse or better than 23vPPV in the prevention of invasive pneumococcal disease.
- 6.19 On the basis of a trial comparing 13vPCV with placebo, 1,057 adults aged ≥65 years would need to be vaccinated with 13vPCV to prevent one case of VT pneumonia. Clinical trial data assessing the effect of 23vPPV in the prevention of VT pneumonia are not available.
- 6.20 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 appeared to be comparable.
- 6.21 The ATAGI post-PBAC submission advice stated that ‘while some adverse effects are expected, no major safety concerns have been identified in immunogenicity studies where 13vPCV is given to adults pre-immunised with 23vPPV (with a minimum interval of 12 months since the last 23vPPV dose).’

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

Clinical claim

- 6.22 The submission described 13vPCV as superior to 23vPPV in terms of preventing VT pneumonia, persistence of vaccine efficacy, superior in terms of comparative safety and equivalent to 23vPPV against IPD. The claim of superiority was not adequately supported.
- The 23vPPV trials were substantially underpowered to detect a reduction in the incidence of VT pneumonia.
 - In 23vPPV naïve subjects, the incidences of local and systemic adverse events with 13vPCV and 23vPPV were similar.
- 6.23 The PSCR argued that while ‘an indirect comparison of 13vPCV and 23vPPV was not statistically appropriate’, ‘a qualitative comparison of the results...confirms that 13vPCV is superior to 23vPPV for pneumonia events’.

- 6.24 The submission's claim of superiority is well supported for VT pneumococcal pneumonia by the CAPiTA study with respect to placebo. However, the claim of superiority against VT pneumococcal pneumonia, compared to 23vPPV, was not well supported. Although 23vPPV appears to be effective against IPD, 23vPPV has no clearly demonstrated effect against VT pneumococcal pneumonia. The ESC acknowledged that it was difficult for the submission to demonstrate superior efficacy against 23vPPV for VT pneumococcal pneumonia due to the lack of evidence of the efficacy of 23vPPV.
- 6.25 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 pneumonia. The PBAC considered that the magnitude of superiority, however, was unclear.
- 6.26 The claims of superiority of persistence of vaccine efficacy and comparative safety, however, were not adequately supported.

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

Economic analysis

- 6.27 The submission presented cost-effectiveness analyses for the primary program (non-Indigenous adults aged 65 years) and catch-up program (non-Indigenous adults aged 70-84 years) with the outcome being cost per life year (LY) saved. The submission also presented a secondary economic analysis with an outcome of cost per QALY saved. The submission applied zero utility penalties to the alive state.

Summary of model structure and rationale

Component	Summary
Time horizon	Primary prevention model: 20 years vs 2-4 years in trials Catch-up model: ≤13 years vs 4 years in the trial
Outcomes	LY gained
Methods used to generate results	Cohort expected value analysis
Health states	Alive, no meningitis complications; Alive meningitis complications ^a ; Dead
Events modelled	IPD (bacteraemia; meningitis); Hospital treated pneumonia; GP treated pneumonia
Cycle length	1 year, half cycle correction applied
Transition probabilities	Transition to 'Dead': Australian population death rates if no event or GP treated pneumonia; 12.5% for IPD; 10.0% for hospitalised pneumonia Transition to 'Alive, meningitis complications': 35% of meningitis events

^a The health state 'Alive, meningitis cx' is only required for the cost/QALY sensitivity analysis; the base case model could be implemented with 2 health states, 'Alive' and 'Dead'.

Source: compiled during the evaluation

- 6.28 The key model drivers are summarised in the following table.

Key drivers of the model

Description	Method/Value	Impact
Time horizon	13-20 years; assumed from 2-4 year trial duration	High, favoured 13vPCV
13vPCV efficacy for hospitalised pneumonia	Sourced from CAPiTA trial (37.7%), a RCT in 84,496 subjects	High
23vPPV efficacy for hospitalised pneumonia	Zero protective benefit assumed based on 5 underpowered RCTs in a total of 3,246 subjects	High, favoured 13vPCV
Decline in 13vPCV efficacy over time	5% assumed, no justification provided in submission	High, favoured 13vPCV
Incidence of VT hospitalised pneumonia	<ul style="list-style-type: none"> • 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) • 35.1% due to 13vPCV serotypes (ATAGI; IPD serotype data) • No herd protection from 13vPCV infant program assumed 	<p>High, assumption of no herd protection favoured 13vPCV</p> <p>The incidence in the model was higher than in the placebo arm of CAPITA.</p>
Death rate for hospitalised pneumonia	10.0%, sourced from Australian study of 855 cases of pneumonia, estimate recommended by ATAGI	High
Discount rate	5% in base case, 0-10% in sensitivity analyses	High

Source: compiled during the evaluation

- 6.29 The model calculations provided with the submission applied the 13vPCV vaccine efficacy for pneumonia events twice. The PSCR agreed this calculation was erroneous. This error had a large impact on the results. Additionally there was also an error in the calculation of the incidence of pneumonia events with 13vPCV (although this had minimal impact on the results). The PSCR disagreed that this calculation was an error, claiming that the evaluator misunderstood the formula. The ESC disagreed with the PSCR and agreed with the evaluator that incidence of pneumonia events with 13vPCV was incorrectly calculated. The following table presents the cost per LY gained presented in the submission, evaluation and the PSCR. The ESC considered that the ICERs presented in the evaluation were the most appropriate.

ICERs (cost/LYG) in submission, evaluation and Pre-Sub-Committee Response

Source (changes vs submission)	Primary program	Catch-up program (70-84 years)
Submission: (i) 13vPCV efficacy applied for 13vPCV-non7vPCV serotypes and used 2012 serotype data; (ii) 13vPCV efficacy applied twice	██████	\$██████
Evaluation: (i) 13vPCV efficacy applied for all 13vPCV serotypes and used 2013/2014 serotype data; (ii) 13vPCV efficacy applied once	\$██████	\$██████
Pre-Sub-Committee Response: (i) 13vPCV efficacy applied for 13vPCV-non7vPCV serotypes and used 2012 serotype data; (ii) 13vPCV efficacy applied once	\$██████	\$██████

Source: Table 7, p 6.06.COM.13 of the Commentary; page 3 of the Pre-Sub-Committee Response

- 6.30 For primary prevention, the submission estimated a reduction in 16.67 hospital treated pneumonia events and 8.49 GP treated pneumonia events per 1,000 population. The corrected estimates were 4.69 and 2.26 (6.95 in total) per 1,000, respectively. The PSCR claimed that the corrected figure for the sum of GP and hospital treated pneumonia events should be 7.06. The ESC agreed with the figures used in the evaluation which were estimated from an analysis that used corrected incidence and corrected the modelling error for vaccine efficacy (see paragraph 6.28).
- 6.31 For the catch-up program, the submission estimated a reduction in 5.96 hospital treated pneumonia events and 3.86 GP treated pneumonia events per 1,000 population. The corrected estimates were 1.64 and 1.02 per 1,000, respectively. The cost/LY gained estimates calculated during the evaluation are presented in the table below.

Results of the economic evaluation (per 1,000 population; corrected during the evaluation)

Step and component	13vPCV	23vPPV	Increment
Primary prevention model			
Costs	\$ [REDACTED]	\$264,614	\$ [REDACTED]
LY gained	11,153	11,151	2.73
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra LY gained (as presented in submission)			[REDACTED]
Catch-up program			
Costs	\$ [REDACTED]	\$126,352	\$ [REDACTED]
LY gained	6,002.06	6,001.35	0.71
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra LY gained (as presented in submission)			\$ [REDACTED]

Source: Table D.5.4 and Table D.5.5 of the Commentary.

- 6.32 Based on the primary prevention model, the number needed to vaccinate with 13vPCV was 213 for hospital treated pneumonia and 442 for GP treated pneumonia. There was an additional 0.07 IPD events per 1,000 population with 13vPCV compared with 23vPPV due to the reduced serotype coverage with 13vPCV. Based on the catch-up model, the number needed to vaccinate with 13vPCV was 608 for hospital treated pneumonia, 976 for GP treated pneumonia and 8,490 for IPD.
- 6.33 In the economic evaluation, the 23vPPV vaccine efficacy for VT IPD from Menzies 2014 (61%) was lower than for 13vPCV (76% from CAPiTA). This favoured the submission.
- 6.34 The submission presented the primary economic evaluation in terms of LYs gained and a secondary economic analysis with an outcome of cost per QALY saved. This analysis applied zero utility penalties to the alive state which effectively assumed that 1 LY equals 1 QALY. The ESC considered it was inappropriate to ascribe equal values for LYs and QALYs since this does not take account of general population norms for QALY weights. The ESC noted that a QALY weight of 1 (that is QALY=LY) implies a population in full health, whereas in practice, a general population will have a distribution of health states, and an average QALY weight of less than 1.

- 6.35 The evaluation applied a utility value of 0.74 for the alive states (which was sourced from Norman R, Church J, van den Berg B and Goodall S. Australian health-related quality of life population norms derived from the SF-6D. Aust NZ J Public Health 2013; 37:17-23, as the population norm for adults aged 61-70 years) to account for population quality of life norms. This resulted in a cost/QALY gained of less than \$15,000 for the primary program and \$105,000/QALY - \$200,000/QALY for the catch-up program. The PSCR argued that there was no justification for applying a 'quality of life norm' utility of 0.74. The ESC considered that it may be reasonable to consider the ICER in terms of LY gained, but that it was not appropriate to assume that a LY equals 1 QALY in a general population.
- 6.36 In response to the corrected model and increased ICER for the five year catch-up program proposed in the submission (of 70-84 years), the PSCR proposed two alternative five year catch-up programs: 66-74 years or 70-74 years. The PSCR presented revised ICERs of \$15,000 - \$45,000 and \$45,000 - \$75,000 per LY gained for the 66-74 and 70-74 years programs, respectively. The ICER for the 66-74 years program was not able to be reproduced as the submission model did not include subjects aged 66-69 years. However, the results presented were consistent with expected results.
- 6.37 The cost-effectiveness estimates were driven by the reduction in the number of non-bacteraemic pneumonia events with 13vPCV. This was potentially overestimated because:
- VE for non-bacteraemia pneumonia was assumed to be zero for 23vPPV. The ESC noted that five of the six studies this estimate was based on excluded aged care homes. While ATAGI agreed with the assumption of zero efficacy in the base case, ATAGI also considered it reasonable to assume 46% as the upper limit of the vaccine efficacy estimate (based on a meta-analysis that included aged care homes).
 - 13vPCV vaccine efficacy was assumed to decline slowly over time. Beyond four years an annual decline in vaccine efficacy of 5% is assumed which results in 13vPCV vaccine efficacy after 5, 10 and 20 years being 95%, 74% and 44% of the initial estimates, respectively. The ESC considered that the evidence presented in the submission did not adequately support protection duration of more than 4 years. There may be a waning immunity with age as the vaccine efficacy was lower against VT pneumococci and IPD from 75-84 years compared with 65-74 years.
 - The baseline risk of pneumonia was overestimated due to no herd protection from the 13vPCV infant program being assumed for pneumonia. ATAGI considered that a reduction in non-bacteraemic pneumonia in adults due to the infant 13vPCV would be expected but data were not yet available to evaluate this empirically (ATAGI pre-PBAC submission advice). The ESC noted the economic model did include a herd immunity effect from the infant program for IPD.
- 6.38 An economic analysis was not presented for the Indigenous population. The burden of pneumococcal disease is greater in Indigenous compared with non-Indigenous adults and, on this basis, the submission claimed the health and economic benefits would be greater in Indigenous people. This claim was uncertain because there are many factors that differ for the two populations including the proportional distribution of serotypes causing IPD (ATAGI pre-PBAC submission advice).

- 6.39 The economic evaluation did not consider serotype replacement and hence the incremental benefits of 13vPCV may have been overestimated. In the 3 years post the 13vPCV infant program, an increase in IPD due to 23v-non13v serotypes in adults aged ≥ 65 years have been observed (21% in 2011/2012 to 30% in 2013/2014). ATAGI noted serotype replacement by non-13v serotypes could result in a resurgence of pneumococcal disease, especially IPD, which would attenuate the overall benefit of reducing disease caused by vaccine serotypes (ATAGI pre-PBAC submission advice).
- 6.40 Univariate sensitivity analyses were presented in the submission. The cost-effectiveness estimates were driven by the reduction in the number of hospital treated pneumonia events with 13vPCV. For the primary program:
- If ATAGI's upper estimate for 23vPPV vaccine efficacy against pneumonia (46%) was used, 13vPCV was dominated by 23vPPV, i.e. 13vPCV was more costly and less effective.
 - Assuming beyond the trial periods that vaccine efficacy declines by 10% or 25% annually increased the cost/LY gained to less than \$15,000 and \$15,000/QALY - \$45,000/QALY, respectively.
 - Reducing the baseline risk of hospital treated pneumonia to that observed in CAPiTA increased the cost/LY gained to \$15,000 - \$45,000 for the primary program.
 - Similarly, incorporating a reduction in baseline pneumonia risk due to herd immunity from the 13vPCV infant program would increase the cost/LY gained.
 - Using the 95% confidence limits for the case fatality rate for hospital treated pneumonia resulted in the cost/LY gained ranging from less than \$15,000 to \$15,000 - \$45,000.
 - The model results were also sensitive to the time horizon (\$15,000/LY - \$45,000/LY for 10 years) and discount rate (less than \$15,000 per LY for 0%; \$15,000/LY - \$45,000/LY for 10%).
- 6.41 The catch-up model was sensitive to the same parameters as the primary prevention model, and the average age at vaccination. The cost/LY gained increased in older individuals because they have fewer years to benefit from the vaccine (\$45,000 - \$75,000 for the cohort aged 70-74 years; \$105,000 - \$200,000 for 75-79 years and more than \$200,000 for 80-84 years). The model did not consider that 13vPCV may be less effective in older individuals (ATAGI Pre-Submission Advice) which would further increase the cost/LY gained in the older cohorts.

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

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

- 6.42 The 13vPCV cost per dose was \$ [REDACTED]. The 23vPPV cost per dose was \$34.13.

Estimated PBS usage & financial implications

- 6.43 This submission was not considered by the 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.

Estimated use and financial implications, primary program

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Population					
Uptake ^a	%	%	%	%	%
13vPCV doses					
Estimated net cost to NIP^b					
Cost to NIP for 13vPCV ^c	\$	\$	\$	\$	\$
Cost of substituted 23vPPV ^d	\$2,251,455	\$2,593,244	\$3,007,605	\$3,369,178	\$3,812,228
Net cost to NIP ^d	\$	\$	\$	\$	\$

a Uptake of 35% assumed for years 1 to 5 for the Indigenous population

b No additional administration cost, and hence no MBS cost, assumed for the primary program as 13vPCV is proposed to replace 23vPPV

c includes 5% wastage

d Revised during the evaluation assuming substitution of 75% of 13vPCV doses with 23vPPV

Source: Table 2, pE.6; Table 3, pE.7; Table 8, p E.9 of the submission; Table E.3.4 of the Commentary; *Values in italics revised during the evaluation*

- 6.44 The redacted table above shows that at Year 5, the estimated total doses from the primary program would be over 200,000 and the total net financial implication for the Australian Government health budget would be less than \$10 million.
- 6.45 The estimated use and financial implications of the catch-up program were based on the originally proposed cohort of 70-84 years. The PSCR proposed a reduced catch-up program for adults aged 66-74 years of 70-74 years. If one of the reduced catch-up programs was recommended for listing, the net cost to the NIP and MBS would be smaller than indicated in the following table.

Estimated use and financial implications, catch-up program

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Population					
Uptake	%	%	%	%	%
13vPCV doses					
Estimated net cost to NIP/MBS					
Cost to NIP for 13vPCV ^a	\$	\$	\$	\$	\$
Net cost to MBS ^b	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to NIP/MBS	\$	\$	\$	\$	\$

a No substitution of 23vPPV assumed for the catch-up program; includes 5% wastage

b Administration cost of \$16.95 (MBS item 3) assumed for 50% of doses; includes 5% wastage

Source: Table 9, p E.10; Table 10, pE.11; Table 15, p E.13 of the submission

- 6.46 The cost of the primary program may be higher in the initial years if the steady state uptake of █% is achieved before year five (five year cost of \$60 - \$100 million vs \$30 - \$60 million; excluding 23vPPV substitution). The extent of substitution of 23vPPV may be less if adults are vaccinated with both 13vPCV and 23vPPV. For the catch-up program the costs may not be evenly distributed over the five years of the program.
- 6.47 ATAGI noted that there were no reliable data to inform the likely uptake for the catch-up program (ATAGI pre-PBAC submission advice) and thus the estimated cost was uncertain (7% uptake [base case]: \$60 - \$100 million over five years; 6% annual uptake: \$60 - \$100 million; 12% annual uptake: more than \$100 million).

- 6.48 For the primary program at year 5, the estimated number of patients was 100,000-200,000 and the net cost to the NIP would be less than \$10 million. For the catch-up program at year 5, the estimated number of patients was 100,000 – 200,000 and the net cost to the NIP/MBS would be \$10 - \$20 million.

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

Quality Use of Medicines

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

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

Financial Management – Risk Sharing Arrangements

- 6.50 The submission stated that the sponsor was willing to undertake a risk sharing arrangement (RSA). No details were provided. The PSCR stated that the sponsor acknowledged the possibility of a RSA and was willing work with relevant stakeholders.

- 6.51 ATAGI considered ongoing monitoring of the incremental benefits of the proposed 13vPCV program and the relative benefits of programmatic use of 13vPCV over 23vPPV is critical and should form part of the RSA (ATAGI pre-PBAC submission advice).

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

7 PBAC Outcome

- 7.1 The PBAC rejected the submission to list 13vPCV for the prevention of pneumococcal disease on the NIP for the requested population on the basis of uncertain cost-effectiveness. While the PBAC considered that 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT pneumonia, the submission did not provide sufficient evidence to allow the PBAC to be confident that recommending 13vPCV at the requested price would be cost effective.
- 7.2 The PBAC noted that the requested listing for the primary program was only for a specific year of age (65 and 50 years for non-Indigenous and Indigenous adults, respectively) and may result in confusion and some adults missing the chance to receive the 13vPCV. The PBAC noted that the ATAGI 'recommended that, in the primary program, a single dose of 13vPCV is offered for non-Indigenous adults from their 65th birthday and for Indigenous adults from their 50th birthday. Rather than single year of age target cohorts (non-Indigenous adults to their 66th birthday and Indigenous adults to their 51st birthday), ATAGI recommended that persons who become age-eligible under the primary program have continued eligibility for a single 13vPCV dose until they reach their 85th birthday, which is the current upper age limit of evidence of efficacy from the CAPiTA trial. This continued eligibility for a first dose

of 23vPPV is consistent with the current NIP program eligibility.’ (ATAGI post-PBAC submission advice)

- 7.3 The PBAC noted the PSCR proposed a revised catch-up program for adults aged either 66-74 years or 70-74 years. The PBAC noted that the ATAGI ‘...recommended that those adults who had attained their 65th birthday (or 50th for Indigenous adults) prior to the commencement date of any primary 13vPCV NIP program receive a single dose of 13vPCV through the proposed 5-year catch-up program regardless of their previous 23vPPV vaccination history.’ However, the ATAGI ‘noted the [sponsor’s] revised proposal...to consider limiting the eligible age window for the 5 year catch-up program to 70–74 years and supported this proposal from the perspective of program implementation’ (ATAGI post-PBAC submission advice).
- 7.4 The PBAC considered that the comparators nominated in the submission, of 23vPPV for the primary program and no vaccine for the catch-up program, were appropriate. However, the PBAC considered that using no vaccine as the comparator was not reasonable for a sub-population of the catch-up program. Adults with risk factors for pneumococcal infections may have already received an initial dose of 23vPPV. Accordingly, the PBAC considered that the 13vPCV dose may replace the second dose of 23vPPV for this population. Indeed, the ATAGI recommended that the 13vPCV dose provided through the catch-up program for those with risk factors should replace the recommended second dose of 23vPPV in those who have already received their first dose of 23vPPV under the existing program (ATAGI post-PBAC submission advice).
- 7.5 The PBAC noted that the inclusion criteria for the CAPiTA trial were narrow in terms of excluding subjects previously vaccinated with a pneumococcal vaccine, subjects with immune deficiency or suppression and residents of aged care facilities. Accordingly, the efficacy of 13vPCV may be lower in the NIP population compared with the CAPiTA population.
- 7.6 The PBAC considered that the CAPiTA trial showed good evidence for the efficacy of 13vPCV against pneumococcal pneumonia compared with placebo. While noting the limitations in the available evidence for 23vPPV, the PBAC considered that 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT pneumonia. However, the PBAC considered that the magnitude of this superiority was unclear due to a lack of evidence of the efficacy of 23vPPV.
- 7.7 The PBAC agreed with the ESC that the methodology used to calculate the event rates in the evaluation were more appropriate than those presented in the submission or the PSCR. For primary prevention, the submission estimated a reduction of 16.67 hospital treated pneumonia events and 8.49 GP treated pneumonia events per 1,000 population. The corrected estimates were 4.69 and 2.26 (6.95 in total) per 1,000, respectively.
- 7.8 The PBAC noted that the cost-effectiveness estimates were driven by the reduction in the number of non-bacteraemia pneumonia events with 13vPCV. This has potentially been overestimated because:
- VE for non-bacteraemia pneumonia was assumed to be zero for 23vPPV. While the PBAC noted that the ATAGI agreed with the assumption of zero efficacy in the

- base case, the ATAGI also considered it reasonable to assume 46% as the upper limit of the vaccine efficacy estimate.
- The PBAC noted that the submission assumed 13vPCV vaccine efficacy declines slowly over time, with a 5% annual decline in vaccine efficacy beyond 4 years. The PBAC considered that the evidence presented in the submission did not adequately support protection duration of more than 4 years.
 - The PBAC considered that as no herd immunity was assumed from the 13vPCV infant program, the baseline risk of pneumonia was overestimated, resulting in an underestimated cost-effectiveness estimate for the primary and catch-up programs. The PBAC noted the ATAGI considered that a reduction in non-bacteraemia pneumonia in adults due to the infant 13vPCV would be expected but data are not yet available to evaluate this empirically.
- 7.9 In addition, the PBAC considered the reduced serotype coverage of low risk people getting only 13vPCV vaccination was a potential issue that was not considered in the economic evaluation. As discussed in paragraph 6.38, serotype replacement by non-13v serotypes could result in resurgence of IPD which would attenuate the overall benefit of reducing disease caused by vaccine serotypes.
- 7.10 The PBAC acknowledged that, given the lack of evidence of the efficacy of 23vPPV, it was difficult for the submission to establish the incremental cost-effectiveness of 13vPCV compared with 23vPPV at the requested price (being more than twice the price per dose of 23vPPV).
- 7.11 While noting the ATAGI's pragmatic support for the 70-74 years catch-up option (as opposed to the ATAGI's preferred catch-up program which would apply to all adults that had attained their 65th birthday prior to the commencement date of any primary 13vPCV program), the PBAC considered that the cost-effectiveness of the revised catch-up program for 70-74 years was unacceptably high at a cost per life year gained of \$45,000 - \$75,000.
- 7.12 The PBAC considered that there were no reliable data to inform the likely uptake for the catch-up program, which could be substantially different to that estimated in the submission.
- 7.13 The PBAC considered that a major resubmission would be required to demonstrate comparative efficacy to 23vPPV. The PBAC noted that, given the lack of evidence of the efficacy of 23vPPV, and that the implementation of the 23vPPV program predated the requirement for a PBAC recommendation for vaccines to be funded under the NIP, it may be appropriate for the clinical and cost effectiveness of the current listing of 23vPPV for the prevention of pneumococcal pneumonia and IPD to be reviewed.
- 7.14 A resubmission should also consider that the ATAGI recommended in its post-PBAC submission advice that the primary program through the NIP should offer a single dose of 13vPCV to non-Indigenous adults aged ≥ 65 years or Indigenous adults aged ≥ 50 years who have never previously received 13vPCV or 23vPPV, rather than the single year of age cohorts proposed in the submission.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Pfizer Australia is disappointed with the outcome. Due to the significant burden of pneumococcal pneumonia in older Australians, the Sponsor is willing to work with the PBAC to ensure timely and equitable access to Prevenar 13.