

7.08 PNEUMOCOCCAL CONJUGATE VACCINE (13-VALENT), 0.5 mL injection, Prevenar 13[®], Pfizer Australia Pty Ltd

1 Purpose of Application

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

2 Requested listing

- 2.1 The re-submission requested the following new listing:

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

NIP population:

- 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 March 2015 PBAC PSD recommended that a re-submission should consider the ATAGI 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 and Indigenous adults aged ≥50 years who have never previously received 13vPCV or 23-valent capsular polysaccharide vaccine (23vPPV) (paragraph 7.14 of the March 2015 Public Summary Document (PSD)).
- 2.3 The re-submission affirmed that the Sponsor accepted the primary vaccination schedule approach recommended by ATAGI and ESC.
- 2.4 ATAGI recommended continued eligibility for a single dose of 13vPCV through the primary program up to age 85 years, which is the current upper age limit of evidence of efficacy from the CAPiTA trial (ATAGI post-PBAC submission advice).
- 2.5 The re-submission did not discuss how the pneumococcal vaccination status of adults would be determined (i.e. whether naïve or not). While currently there is no vaccination register for adults, ATAGI considered the establishment of such a register would be essential (ATAGI post-PBAC submission advice). The pre-PBAC response argued that the majority of eligible patients would be able to access their previous medical records at their current GP. Further, the pre-PBAC response noted the 2015-16 Budget included the establishment of an adult vaccination register to record all adult vaccines received under the NIP from 1 September 2016.

- 2.6 ATAGI recommended that individuals in specified risk groups should receive a single booster dose of 23vPPV five years after the primary 13vPCV dose (ATAGI post-PBAC submission advice). ATAGI considered this would simplify the existing recommendations for differential dosing (i.e. three doses for Indigenous adults with at-risk conditions and two doses for Indigenous adults without at-risk conditions and non-Indigenous adults with at-risk conditions; ATAGI post-PBAC submission advice p4).
- 2.7 ATAGI also recommended a catch-up program, coinciding with commencement of the primary 13vPCV program, in which age-eligible individuals would be offered a single dose of 13vPCV, regardless of previous receipt of a dose of 23vPPV (ATAGI post-PBAC submission advice). This program was not requested in the minor re-submission.

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

3 Background

- 3.1 13vPCV was TGA registered on 28 October 2011 for adults aged 50 years and older. The current registered indication is “active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age. The use of Prevenar 13 should be guided by official recommendations.”
- 3.2 A major submission for 13vPCV for adults was rejected at the March 2015 PBAC meeting 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) pneumonia, but 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 (paragraph 7.1 of the March 2015 PSD). The PBAC considered that a major re-submission would be required to demonstrate comparative efficacy to 23vPPV (paragraph 7.13 of the March 2015 PSD).
- 3.3 The following table provides a summary of the key differences between the March 2015 submission and this current minor re-submission, including PBAC comments on the March 2015 submission.

Table 1: Key differences between the March 2015 submission and the July 2015 re-submission

	March 2015 submission	July 2015 re-submission
Requested PBS listing	<p><u>Primary program</u>: A single dose for non-Indigenous adults at age 65 years and Indigenous adults at age 50 years.</p> <p><u>Catch-up program</u>: 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 (revised in PSCR to a single dose for non-Indigenous adults aged either 66-74 years or 70-74 years and Indigenous people aged 55 years and older).</p> <p>PBAC comment (PSD paragraph 7.2, 7.14, 7.3):</p>	<p><u>Primary program</u>: A single dose for pneumococcal vaccine naive non-Indigenous adults at age 65 years and over, and pneumococcal vaccine naive Indigenous people at age 50 years and over or those with at-risk condition(s) identified at a younger age.</p> <p><u>Catch-up program</u>: Not requested.</p>

Public Summary Document – July 2015 PBAC Meeting

	March 2015 submission	July 2015 re-submission
	<ul style="list-style-type: none"> 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. A re-submission should consider that the ATAGI recommended the primary program 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. The PBAC noted that the ATAGI supported the PSCR proposed revised catch-up program for individuals aged 70-74 years from the perspective of program implementation. 	
Requested price	\$ [REDACTED]	\$ [REDACTED]
Main comparator	<p>Primary program: 23vPPV Catch-up program: no vaccine</p> <p>PBAC comment (PSD paragraph 7.4): Comparators 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.</p>	Primary program: 23vPPV
Clinical evidence	<ul style="list-style-type: none"> CAPiTA, a randomised double-blind trial of 13vPCV vs placebo in 84,496 subjects 6 randomised efficacy trials of 23vPPV vs placebo/no vaccine in 191 to 1,006 subjects 17 non-randomised studies of 23vPPV 14 immunogenicity studies of 13vPCV <p>PBAC comment (PSD paragraph 7.5): 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.</p>	No new data presented.
Clinical claim	<p>13vPCV is superior in terms of comparative effectiveness and comparative safety compared to 23vPPV.</p> <p>PBAC comment (PSD paragraph 7.6): 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 due to a lack of evidence of the efficacy of 23vPPV.</p>	Clinical claim not stated. Economic model is based on superior efficacy.

Public Summary Document – July 2015 PBAC Meeting

	March 2015 submission	July 2015 re-submission
Economic evaluation	<p><u>Primary program</u>: single cohort vaccinated at age 65 years</p> <p><u>Catch-up program</u>: three cohorts vaccinated at age 72 (44.3% of cohort), 77 (32.0%) or 82 (23.6%) years</p> <p><u>Time horizon</u>: 20 years</p> <p><u>Vaccine efficacy (VE) for VT hospitalised pneumonia</u> 13vPCV: 37.7% for first 4 years; 5% annual decline after 4 years 23vPPV: 0% for model duration</p> <p><u>Incidence of hospitalised pneumonia</u>: 1,364/100,000 person years of which 7.2% are due to 13vPCV serotypes</p> <p><u>Deaths from hospitalised pneumonia</u>: 10%</p> <p><u>Utility value for alive health states</u>: 1</p> <p><u>Base case</u>: less than \$15,000/LY for primary program; \$105,000/LY - \$200,000/LY for catch-up program Revised catch-up program as per PSCR: \$15,000/LY - \$45,000/LY and \$45,000/LY - \$75,000 for vaccination at ages 66-74 years and 70-74 years, respectively</p> <p>PBAC comment (PSD paragraph 7.8, 7.10, 7.11):</p> <ul style="list-style-type: none"> • The ICERs were driven by the reduction in the number of non-bacteraemia pneumonia events with 13vPCV and this was potentially overestimated. • 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). • The cost-effectiveness of the revised catch-up program for 70-74 years was unacceptably high at a cost per life year gained of \$60,754. 	<p><u>Primary program</u>: four cohorts vaccinated at age 67 (35.4% of cohort), 72 (27.2%), 77 (20.8%) or 82 (16.6%) years</p> <p>No change to time horizon, 13vPCV efficacy, 23vPPV efficacy, incidence of hospitalised pneumonia or percent of pneumonia hospitalisation resulting in death.</p> <p>Utility value for alive health states: 0.74 based on Australian population norm for individuals aged 61-70 years.</p> <p><u>Base case</u>: less than \$15,000/LY and \$15,000/QALY - \$45,000/QALY</p>
Number of 13vPCV doses	<p>Primary program: 100,000 – 200,000 in year 5 (over 200,000 over 5 years)</p> <p>Catch-up program: 100,000 – 200,000 in year 5 (over 200,000 over 5 years)</p>	<p>Primary program: over 200,000 in year 5 (over 200,000 over 5 years)</p>
Est. net cost to Govt	<p>Primary program: less than \$10m in year 5 (\$30m - \$60m over 5 years)</p> <p>Catch-up program: \$10m - \$20m in year 5 (\$60m - \$100m over 5 years)</p> <p>PBAC comment (PSD paragraph 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.</p>	<p>Primary program: \$10m – \$20m in year 5 (\$60m - \$100m over 5 years)</p>
PBAC decision	Reject	

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life year; VE = vaccine efficacy; VT = vaccine type.

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 IPDs such as meningitis, septicaemia and bacteraemic pneumonia, and other forms of disease such as non-bacteraemic pneumonia. The pneumococcal vaccine currently listed on the NIP for adults is a 23vPPV. The requested 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 pneumonia. In this regard, the pre-PBAC response emphasised the greater burden of disease from CAP not associated with IPD, compared with IPD.
- 4.2 The minor re-submission proposed that for non-Indigenous adults without at-risk conditions, a single dose of 13vPCV would replace the single dose of 23vPPV. For non-Indigenous adults with at-risk condition(s) and Indigenous adults, a single dose of 13vPCV would replace the initial dose of 23vPPV.

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

5 Comparator

- 5.1 The March 2015 major submission nominated 23vPPV as the comparator for the primary program and no vaccine for the catch-up program. The PBAC considered the nominated comparators appropriate, although noted 23vPPV may be the appropriate comparator for adults with risk factors treated in the catch-up program (paragraph 7.4 of the March 2015 PSD). The re-submission nominated 23vPPV as the comparator for the revised primary program.

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 No new clinical data were presented in the re-submission.

- 6.4 The PBAC noted that the inclusion criteria for the CAPiTA trial were narrow: subjects were excluded if they had previously been vaccinated with a pneumococcal vaccine, possessed immune deficiency or suppression, or were residents of aged care facilities. Accordingly, it was considered the efficacy of 13vPCV may be lower in the NIP population compared with the CAPiTA population (paragraph 7.5 of the March 2015 PSD).
- 6.5 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 the 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT pneumonia, however the magnitude of this superiority was unclear (paragraph 7.6 of the March 2015 PSD).
- 6.6 The ATAGI advised in its post-PBAC submission advice for the March 2015 major submission that there was high-level evidence for vaccine efficacy of 13vPCV against community-acquired pneumonia (CAP) due to 13vPCV serotypes, with duration of protection of at least 4 years. In contrast, there was low level and variable evidence of efficacy/effectiveness of 23vPPV against CAP in older adults derived primarily from observational studies.

Economic analysis

- 6.7 In the March 2015 submission, a cost-effectiveness analysis was presented against 23vPPV for the primary program. The PBAC acknowledged (paragraph 7.10 of the March 2015 PSD) 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 (more than twice the price per dose of 23vPPV).
- 6.8 In the March 2015 submission, a cost-effectiveness analysis was also presented against no vaccine for the catch-up 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 (LY) gained of \$45,000 - \$75,000 (paragraph 7.11 of the March 2015 PSD).
- 6.9 The minor re-submission presented a cost-effectiveness analysis against 23vPPV.
- 6.10 The major submission's economic model for the primary program modelled a single cohort of 1,000 subjects vaccinated at age 65 years; whereas the catch-up program model included three cohorts vaccinated at age 72 years (443 subjects), 77 years (320 subjects) or 82 years (236 subjects).
- 6.11 The economic model presented in the minor re-submission modelled four cohorts vaccinated at age 67 (354 subjects), 72 years (272 subjects), 77 years (208 subjects) or 82 years (166 subjects). The distribution across the cohorts was based on the age distribution of the Australian population in 2011. With the exception of the number of cohorts modelled, the re-submission's model was structurally unchanged from that of the major submission.

- 6.12 The event rates in the re-submission were calculated using the methodology in the evaluation for the March 2015 submission which was considered appropriate by the ESC and PBAC (paragraph 7.7 of the March 2015 PSD).
- 6.13 In the re-submission, the following model inputs were changed:
- The cost of a dose of 13vPCV was reduced from \$ [redacted] to \$ [redacted].
 - The cost per quality adjusted life year (QALY) gained was estimated by applying a utility value of 0.74 for the alive states rather than a utility value of 1. For the major submission, the ESC considered it inappropriate to assume a LY equals 1 QALY in a general population (paragraph 6.34 of the March 2015 PSD). The 0.74 value was based on a population quality of life norm for Australians aged 61-70 years.
 - The costs for treating pneumococcal events were revised based on comments included in the evaluation for the major submission (cost of treating bacteraemia reduced from \$11,043 to \$10,515; meningitis without complications reduced from \$7,756 to \$7,010; meningitis with complications increased from \$20,306 to \$20,475; hospitalised pneumonia reduced from \$6,698 to \$6,363; GP-treated pneumonia reduced from \$134 to \$114).
- 6.14 The re-submission used the same cost per dose for 23vPPV (\$34.13) as the March 2015 submission. As of 1 April 2015, the cost per dose for 23vPPV increased to \$35.12.

The new base case ICERs presented in the re-submission were less than \$15,000/LY gained and \$15,000/QALY - \$45,000/QALY gained. Incorporating the price increase for 23vPPV reduced the ICERs to less than \$15,000/LY gained and \$15,000/QALY - \$45,000/QALY gained (see Table 2).

Table 2: Results of the economic evaluation (per 1,000 population)

Component	13vPCV	23vPPV	Increment
Costs	\$ [redacted]	\$ [redacted] ^a	\$ [redacted] ^a
LY	7,462.959	7,461.768	1.191
Incremental cost/extra LY gained			\$ [redacted]^a
QALY	5,500.201	5,499.323	0.88
Incremental cost/extra QALY gained			\$ [redacted]^a

^a Cost per dose for 23vPPV increased from \$34.13 to \$35.12.

Source: Table 5 of the re-submission, p8.

Abbreviations: LY = life year; QALY = quality adjusted life year.

- 6.15 The re-submission model estimated a reduction of 2.46 hospital-treated pneumonia events and 1.36 GP-treated pneumonia events per 1,000 population.
- 6.16 The cost-effectiveness estimates were driven by the reduction in the number of hospital-treated pneumonia events with 13vPCV. Sensitivity analyses for parameters affecting this outcome are summarised in the table below. The ICERs are also sensitive to the discount rate and time horizon.

Table 3: One way sensitivity analysis results

Variable changed	Cost/LYG ^a	Cost/QALY ^a
Base case (as presented in minor submission)	\$ [REDACTED]	\$ [REDACTED]
Baseline risk (rate per 100,000 population) of pneumonia hospitalisation		
Lower limit: 281→188 (i.e. % of hospitalisations due to pneumococci reduced from 20.6% to 13.8%; % due to 13vPCV serotypes not adjusted)	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 281→372 (20.6%→27.3%)	\$ [REDACTED]	\$ [REDACTED]
13vPCV efficacy for pneumonia hospitalisations		
Lower limit: 37.7%→14.3%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 37.7%→55.1%	\$ [REDACTED]	\$ [REDACTED]
23vPPV efficacy for pneumonia hospitalisations		
Upper limit: 0%→46.0%	Dominated	Dominated
Waning (annual percent reduction in efficacy)		
5%→10%	\$ [REDACTED]	\$ [REDACTED]
5%→25%	\$ [REDACTED]	\$ [REDACTED]
5%→50%	\$ [REDACTED]	\$ [REDACTED]
Case fatality for pneumonia hospitalisation		
Lower limit: 10.0%→3.8%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 10.0%→20.5%	\$ [REDACTED]	\$ [REDACTED]
Cost of treating pneumonia hospitalisations		
Lower limit: \$6,363→\$3,000	\$ [REDACTED]	\$ [REDACTED]
Upper limit: \$6,363→\$10,000	\$ [REDACTED]	\$ [REDACTED]
Annual discount rate		
Lower limit: 5%→0%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 5%→10%	\$ [REDACTED]	\$ [REDACTED]
Time horizon		
20 years→4 years	\$ [REDACTED]	\$ [REDACTED]
20 years→10 years	\$ [REDACTED]	\$ [REDACTED]
20 years→15 years	\$ [REDACTED]	\$ [REDACTED]

^a Calculation errors not corrected. Price increase for 23vPPV not included.

Source: Table 6 of the re-submission, p8.

Abbreviations: LY = life year; QALY = quality adjusted life year.

- 6.17 The PBAC noted that two errors were identified in the re-submission's model calculations, and that the most current cost of 23vPPV had not been used. The pre-PBAC response provided the following updated results of the economic evaluation and sensitivity analyses:

Table 4: Updated results of the economic evaluation (per 1,000 population)

Component	13vPCV	23vPPV	ICER
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	7,462.959	7,461.768	1.191
Incremental cost per extra LY gained			\$ [REDACTED]
QALY	5,500.201	5,499.323	0.878
Incremental cost per extra QALY gained			\$ [REDACTED]

Source: Pre-PBAC response for 13vPCV minor submission July 2015

Table 5: Updated results of the univariate sensitivity analyses

Univariate analyses	\$/LYG	\$/QALY
Base case	\$ [REDACTED]	\$ [REDACTED]
Pneumococcal disease rates per 100,000 population		
PNE hospitalisations		
Lower limit: 281→188 (20.6%→13.8%)	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 281→372 (20.6%→27.3%)	\$ [REDACTED]	\$ [REDACTED]
PNE GP visits		
Lower limit: 287→192 (65-74yr) and 516→345 (75-84yr) (20.6%→13.8%)	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 287→380 (65-74yr) and 516→683 (75-84yr) (20.6%→27.3%)	\$ [REDACTED]	\$ [REDACTED]
13vPCV efficacy		
PNE hospitalisations		
Lower limit: 37.7%→14.3%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 37.7%→55.1%	\$ [REDACTED]	\$ [REDACTED]
PNE GP visits		
Upper limit: 14.3%→37.7%	\$ [REDACTED]	\$ [REDACTED]
IPD		
Lower limit: 75.8%→46.5%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 75.8%→90.3%	\$ [REDACTED]	\$ [REDACTED]
Same efficacy as 23vPPV: 75.8%→61.1%	\$ [REDACTED]	\$ [REDACTED]
23vPPV effectiveness		
VT-IPD		
Lower limit: 61.1%→55.1%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 61.1%→82.0%	\$ [REDACTED]	\$ [REDACTED]
PNE (all-cause)		
Upper limit: 0%→46.0%*	Dominated	Dominated
Probability of long-term complications following meningitis		
Lower limit: 35%→27%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 35%→72%	\$ [REDACTED]	\$ [REDACTED]
Waning efficacy		
5%→10%	\$ [REDACTED]	\$ [REDACTED]
5%→25%	\$ [REDACTED]	\$ [REDACTED]
5%→50%	\$ [REDACTED]	\$ [REDACTED]
Annual discount rate		
Lower limit: 5%→0%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 5%→10%	\$ [REDACTED]	\$ [REDACTED]
Case-fatality rates		
IPD, upper limit: 12.5%→20.9%	\$ [REDACTED]	\$ [REDACTED]
PNE hospitalisations		
Lower limit: 10.0%→3.8%	\$ [REDACTED]	\$ [REDACTED]
Upper limit: 10.0%→20.5%	\$ [REDACTED]	\$ [REDACTED]
Cost of treating PNE hospitalisation		
Lower limit: \$6,363→\$3,000	\$ [REDACTED]	\$ [REDACTED]
Upper limit: \$6,363→\$10,000	\$ [REDACTED]	\$ [REDACTED]
Time horizon		
20 years→4 years	\$ [REDACTED]	\$ [REDACTED]

Univariate analyses	\$/LYG	\$/QALY
20 years→10 years	\$ [REDACTED]	\$ [REDACTED]
20 years→15 years	\$ [REDACTED]	\$ [REDACTED]

*Assumes 23vPPV effective against an additional 30% of serotypes (i.e. 23vPPV-non-13vPCV serotypes) and not effective against serotype 6A (1.0% of serotypes), assumes 23vPPV efficacy against GP treated pneumonia is VE against hospital treated pneumonia x 14.3/37.7 (i.e. the efficacy is reduced by the same ratio as for 13vPCV) (refer 6.06.COM.64).

Source: Pre-PBAC response for 13vPCV minor submission July 2015

6.18 In March 2015, the PBAC noted that the reduction in the number of non-bacteraemic events was potentially over estimated. The ICERs were underestimated due to the following issues:

- VE for non-bacteraemia pneumonia was assumed to be zero for 23vPPV. The PBAC noted that the ATAGI agreed with the assumption of zero efficacy in the base case, and that the ATAGI accepted 46% as the upper limit of the vaccine efficacy estimate, but noted there was low level and variable evidence of efficacy/effectiveness of 23vPPV against CAP in older adults derived primarily from observational studies. The base case for the re-submission assumed zero efficacy for 23vPPV for non-bacteraemia pneumonia. If ATAGI's upper estimate for 23vPPV vaccine efficacy against pneumonia (46%) is used, 13vPCV is dominated by 23vPPV, i.e. 13vPCV is more costly and less effective.
- 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 re-submission assumed the same decline in 13vPCV vaccine efficacy beyond 4 years (5% annually). This favoured the cost-effectiveness of 13vPCV.
- No herd immunity was assumed from the 13vPCV infant program. The PBAC noted the ATAGI considered that a reduction in non-bacteraemia pneumonia in adults due to the infant 13vPCV program would be expected but data are not yet available to evaluate this empirically.

(Paragraph 7.8 of the March 2015 PSD)

6.19 The minor re-submission also assumed no additional herd immunity from the 13vPCV infant program, beyond that observed for IPD in the most recently available IPD data for the 65+ years population 3 years after introduction of the infant 13vPCV program in Australia. The PBAC recalled the ATAGI pre-PBAC advice for the major submission which noted a marked reduction in the prevalence of the 7-valent serotypes among IPD cases in the greater than 65 year old population due to presumed strong herd protective effects from the infant 7vPCV immunisation program. The PBAC noted that unlike for IPD, the impact of infant pneumococcal vaccination on serotype distribution among Australian pneumococcal CAP cases 65+ years is not known directly. However, the PBAC noted that the CAPiTA study was conducted in the context of an infant 7vPCV program rather than an infant 13vPCV program, and further noted the supplementary appendix to the CAPiTA study (Bonten et al, 2015, Table S10), which showed that approximately 80% of VT-CAP in adults aged 65 years or older in the placebo group (i.e. did not receive 13vPCV) was caused by the 6 additional serotypes present in 13vPCV but not 7vPCV. The PBAC recalled that the 13vPCV infant program was introduced in Australia in 2011, replacing the 7vPCV for infants aged 2, 4 and 6 months. The PBAC considered that when extrapolating the CAPiTA trial data to the Australian context, a markedly lower prevalence of the 6 additional (non 7vPCV) serotypes among pneumococcal CAP in

age groups other than those vaccinated (including the ≥ 65 year old population) should be assumed because of herd effects from Australia's infant 13vPCV program, and therefore the future preventable burden of pneumococcal CAP could be much less than assumed in the submission.

- 6.20 In March 2015, the PBAC considered the reduced serotype coverage with 13vPCV compared with 23vPPV was a potential issue that was not considered in the economic evaluation. Serotype replacement by non-13v serotypes could result in resurgence of IPD, especially for people without at risk conditions receiving only 13vPCV, which would attenuate the overall benefit of reducing disease caused by vaccine serotypes (paragraph 7.9 of the March 2015 PSD). Serotype replacement was not considered in the re-submission.
- 6.21 The proportion of people in each of the age cohorts was not tested in the re-submission's sensitivity analyses. Based on the catch-up model in the March 2015 submission, the ICERs increase in older individuals because they have fewer years to benefit from the vaccine.

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

- 6.22 The 13vPCV cost per dose in the re-submission was \$ [REDACTED]. The 23vPPV cost per dose in the re-submission was \$34.13. As of 1 April 2015 the 23vPPV cost per dose was \$35.12.

Estimated PBS usage & financial implications

- 6.23 The re-submission provided updated estimates of the financial implications to account for the revised listing and the proposed lower price for 13vPCV.
- 6.24 In the March 2015 submission, the number of 13vPCV doses for the primary program was calculated by multiplying the assumed uptake rate by the estimated Australian population aged 65 years (50 years for Indigenous adults). In the March 2015 submission, the number of 13vPCV doses for the catch-up program was calculated in a similar fashion, multiplying the assumed uptake rate by the estimated Australian population aged 70-84 years (≥ 55 years for Indigenous adults).
- 6.25 In the re-submission, the number of 13vPCV doses was calculated by multiplying the assumed uptake rate by the population aged 65 years (50 years for Indigenous adults) plus the pneumococcal vaccine naïve population aged 66-84 years (≥ 51 years for Indigenous adults).
- 6.26 The naïve population was estimated in year 1 by assuming that 55.4% of adults aged 66-84 years have been previously vaccinated with 23vPPV. The pool of ineligible adults diminished in subsequent years as individuals that attained their 85th birthday were no longer eligible for 13vPCV. From year 2 onwards, individuals previously vaccinated with 13vPCV through the proposed program were ineligible. The pool of ineligible adults increased over time as more individuals were vaccinated with 13vPCV. The estimated financial implications over the first five years of listing as presented in the re-submission are summarised below.

Table 6: 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					
Estimated net cost to NIP					
Total 13vPCV cost, including 5% wastage	\$	\$	\$	\$	\$
Cost of substituted 23vPPV ^b	\$	\$	\$	\$	\$
Net cost to NIP	\$	\$	\$	\$	\$

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

^b assumes 65.5% of 13vPCV doses replace 23vPPV doses

Source: Tables 7, 8 and 9 of the re-submission, p10-11.

- 6.27 The redacted table above shows that at year 5, the estimated number of doses of 13vPCV was over 200,000 and the net cost to the NIP would be \$10 - \$20 million.
- 6.28 For the primary program, the March 2015 submission assumed 35% uptake in year 1, increasing to 55% by year 5. The ATAGI post-PBAC submission advice recommended 55% uptake from year 1. In the re-submission an uptake of 55% was assumed from year 1 for non-Indigenous adults aged 65 years.
- 6.29 For the catch-up program, the March 2015 submission assumed 7% uptake. The ATAGI post-PBAC submission advice recommended an uptake of 35%. 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 (paragraph 7.12 of March 2015 PSD). In the re-submission an uptake of 35% was assumed for pneumococcal vaccine naïve non-Indigenous adults aged 66-84 years, and for pneumococcal vaccine naïve Indigenous adults aged 50 years and above.
- 6.30 The higher uptake rates assumed in the re-submission compared with the March 2015 submission resulted in a large increase in the estimated number of 13vPCV doses over the first five years of listing (March 2015 submission [PBAC PSD paragraph 6.42 and 6.43]: 587,312 for the primary program, 759,187 for the catch-up program; Re-submission: 2,103,955). Similarly, the number of 23vPPV doses substituted with 13vPCV is higher in the re-submission (March 2015 submission [Commentary, p 6.06.COM.71: 440,483 for the primary program, 0 for the catch-up program; Re-submission: 1,378,090).
- 6.31 The net cost to the NIP was calculated assuming 65.5% of 13vPCV doses replace a 23vPPV dose. Page 6.06.70 of the Commentary for the March 2015 submission was provided as a reference for this estimate. The Commentary assumed for the primary program that 75% of 13vPCV doses would replace a 23vPPV dose. The re-submission did not explain how the 65.5% was calculated for the revised primary program included in the re-submission.

- 6.32 The re-submission assumed no administration cost for 13vPCV as 13vPCV is proposed to replace 23vPPV. The financial estimates in the re-submission assume 65.5% of 13vPCV doses will replace 23vPPV doses and hence for 34.5% of 13vPCV doses there may be an additional administration cost.
- 6.33 The financial estimates in the re-submission also assumed only vaccine naïve individuals will be vaccinated with 13vPCV and the re-submission did not discuss the likelihood of previously vaccinated individuals receiving 13vPCV through the primary program.

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

7 PBAC Outcome

- 7.1 The PBAC recommended including the 13vPCV on the NIP for the prevention of pneumococcal pneumonia and IPD in adults on the basis of cost-minimisation to the 23vPPV vaccine. 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. 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.
- 7.2 The PBAC noted that if 13vPCV were included on the NIP for adults, then individuals in specified at-risk groups would continue to receive a booster dose of 23vPPV five years following the primary dose of 13vPCV.
- 7.3 The PBAC considered the equivalent doses to be 13vPCV 0.5 mL injection and 23vPPV 0.5 mL injection.
- 7.4 The PBAC accepted the simplifications to the requested immunisation programme, compared with that requested in the major submission in March 2015. The PBAC noted that the catch-up programme proposed in the major submission (which the PBAC considered to have an unacceptably high cost per life year gained in March 2015) had been removed.
- 7.5 The PBAC considered that the 23vPPV was the appropriate comparator for the revised immunisation program.
- 7.6 The PBAC noted that the evidence for 13vPCV over no vaccination was of higher quality than that for 23vPPV over no vaccination. In the absence of directly 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.
- 7.7 The PBAC recalled that it had rejected the major submission for 13vPCV in March 2015 on the basis of uncertain cost-effectiveness. Although the PBAC considered

that 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT pneumonia, 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. In this regard, 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 pneumonia.

- 7.8 In addition, the PBAC rejected the re-submission’s assumptions that there would be no additional herd immunity effect from the 13vPCV infant programme for IPD or pneumococcal CAP, and that the incidence of the 13vPCV strain pneumonia and IPD would not continue to fall (see paragraph 6.19). 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.
- 7.9 The PBAC noted advice from ATAGI that the establishment of a register recording the pneumococcal vaccination status of adults remained essential. In this regard, the PBAC noted that the 2015-16 Commonwealth Budget included the establishment of an adult vaccination register to record all adult vaccines received under the NIP from 1 September 2016.
- 7.10 The PBAC noted the financial estimates presented in the re-submission were overestimated if the listing of 13vPCV on the NIP were to be implemented on its recommended basis of cost-minimisation to 23vPPV.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listing on the NIP as follows:

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

NIP population:

- 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

While Pfizer acknowledges the positive recommendation for Prevenar 13 (13vPCV) to be listed on the National Immunisation Program (NIP) for older Australians, it is disappointed that this recommendation is on the basis of cost-minimisation to the 23-valent pneumococcal polysaccharide vaccine (23vPPV) despite a cost effectiveness submission.

Pfizer believes the data presented in its submission demonstrates significant clinical benefit of 13vPCV compared to 23vPPV. CAPiTA was a very large randomised, double-blind, placebo controlled trial that showed significant vaccine efficacy against vaccine type strains of community acquired pneumonia, non-bacteraemic and non-invasive community acquired pneumonia and invasive pneumococcal disease. Pfizer believes that cost-effectiveness has been adequately demonstrated and that cost-minimisation is not a reasonable outcome.

In Australia, the greatest burden of pneumococcal disease in adults is from community acquired pneumonia. Pfizer notes the advice from the Australian Technical Advisory Group on Immunisation (ATAGI) that the incremental benefit of 13vPCV in older adults, over and above any benefit from 23vPPV use, is in the reduction of community acquired pneumonia not associated with invasive pneumococcal disease.

Pfizer understands that there is a significant unmet need for an effective vaccine against pneumococcal community acquired pneumonia, so will continue to work with ATAGI and PBAC through further submissions to seek to ensure that this immunisation option is available for Australian adults on the NIP.