

**5.10 PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE
VACCINE, 15 VALENT ADSORBED,
0.5 mL pre-filled syringe,
Vaxneuvance®
Merck Sharp & Dohme (Australia) Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested listing on the National Immunisation Program (NIP) for a 15-valent pneumococcal conjugate vaccine (PCV15) for prevention of pneumococcal disease in non-Indigenous adults aged ≥70 years, Indigenous adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥18 years.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus the NIP-funded 13-valent pneumococcal conjugate vaccine (PCV13), Prevenar 13®. The key components of the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	<ul style="list-style-type: none"> All non-Indigenous adults ≥ 70 years – 1 dose PCV15 only. All Indigenous adults ≥ 50 years – 1 dose PCV15 followed by 2 doses of PPV23, the 1st 2-12 months later, then the 2nd dose at least five years later. In all persons ≥ 18 years newly diagnosed with a condition putting them at-risk of pneumococcal infection – 1 dose PCV15 followed by 2 doses of PPV23, the 1st 2-12 months later, then the 2nd at least five years later. Haematopoietic stem cell transplant (HSCT) recipients should receive 3 doses of PCV15 at 6, 8, and 12 months after HSCT and PPV23 at 24 months. As noted by ATAGI, HSCT patients should receive either PCV13 or PCV15, but not a mixed schedule, unless the course cannot be completed with the same vaccine (p7, ATAGI advice).
Intervention	One intramuscular dose of PCV15 0.5 mL. PCV15 includes serotype-specific capsular polysaccharides included in PCV13, plus two additional serotypes; 22F and 33F, each conjugated to a non-toxic fragment of the diphtheria toxin (CRM197 protein).
Comparator	<p>Main comparator: One dose of PCV13 currently on the NIP (as of 1 July 2020) for all the populations outlined in the population section. It is expected that PPV23 administration in the Indigenous and medically at-risk populations will remain the same.</p> <p>Near term comparator: Clinical trial results in adults have been reported for PCV20, however TGA evaluation of PCV20 had not commenced at the time of PBAC consideration.</p>
Outcomes	<p>Immunogenicity:</p> <ul style="list-style-type: none"> Serotype-specific opsonophagocytic (OPA) geometric mean titre (vaccine strain type) for the 15 serotypes in PCV15 at day 30. Serotype-specific immunoglobulin G (IgG) geometric mean concentration (vaccine strain type) for the 15 serotypes in PCV15 at day 30. <p>Safety:</p> <ul style="list-style-type: none"> Injection site reactions day 1-5 post-vaccination. Systemic AEs from day 1 through to day 14 post-vaccination. Vaccine-related serious adverse events from day 1 to month 6 post-vaccination. Grade 3 or higher adverse events.
Clinical claim	In the adult populations aged 18+ currently eligible for PCV13 vaccination on the NIP, PCV15 is noninferior in terms of comparative immunogenicity for 12 of the 13 shared serotypes and superior to PCV13 for serotype 3. PCV15 is superior to PCV13 in terms of immunogenicity for 22F and 33F. PCV15 is noninferior to PCV13 in terms of safety.

Source: Table 1.1-3, p10 of the submission

AEs = adverse events; ATAGI = Australian Technical Advisory Group on Immunisation; HSCT = Haematopoietic stem cell transplant; IgG = immunoglobulin G; mL = millilitre; NIP = National Immunisation Program; OPA = opsonophagocytic activity; PBAC = Pharmaceutical Benefits Advisory Committee; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPV23 = 23-valent pneumococcal polysaccharide vaccine; TGA = Therapeutic Goods Administration

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the clinical evaluation report and Delegate's Overview were available. The requested indication was for use in adults aged ≥ 18 years. The United States Food and Drug Administration (FDA)

approved PCV15 for use in adults aged ≥ 18 years on 16 July 2021. The European Medicine Agency recommended marketing authorisation on 14 October 2021.

- 2.2 The TGA Delegate proposed to approve the registration of PCV15, and noted the following: “There is no immunological threshold level of antibody concentration that correlates with protection against pneumococcal disease in adults. Vaccination of adults with Prevnar elicited serotype-specific OPA titers that were found to be concordant to those in children, the population in which efficacy against IPD had been demonstrated. Licensure of Prevnar 13 in adults was based on demonstration of noninferiority of OPA responses to those elicited by PPV23. The CAPiTA study subsequently confirmed protective efficacy of Prevnar 13 for the prevention of IPD and pneumococcal pneumonia, validating the results of immunobridging. Based on this precedent and the lack of feasibility of conducting efficacy studies for new pneumococcal vaccines in settings where uptake of currently approved vaccines is high, immunobridging to Prevnar 13 for shared serotypes and demonstration of superior OPA responses to serotypes 22F and 33F has been proposed to regulatory agencies (US FDA) and accepted as basis for V114 [PCV15] licensure.”

- 2.3 The pre-PBAC Response advised that the sponsor [REDACTED].

3 Requested listing

- 3.1 The submission sought the following listing, which is presented in a format adapted from the ATAGI advice.

Table 2: Essential elements of the requested listing

Population requested	Number of doses, timing (primary series)	Booster frequency	Program setting (all that apply)	Implications for other NIP vaccines	Price per Dose
All non-Indigenous adults ≥70 years	1 dose PCV15 only	Not requested	GPs OR treating specialist OR rural/community health clinic	Unchanged (alternative brand only)	To be advised based on Nationally Negotiated Price for the PCV13 comparator
All Indigenous adults ≥50 years	1 dose PCV15 followed by 2 doses of PPV23, the first 2-12 months later, then the second dose at least five years later	Not requested	GPs OR treating specialist OR rural/community health clinic	Unchanged (alternative brand only)	To be advised based on Nationally Negotiated Price for the PCV13 comparator
All persons ≥18 years newly diagnosed with a condition putting them at-risk of pneumococcal infection (see also HSCT recipients)	1 dose PCV15 followed by 2 doses of PPV23, the first 2-12 months later, then the second dose at least five years later	Not requested	Primarily treating specialists otherwise settings as above	Unchanged (alternative brand only)	To be advised based on Nationally Negotiated Price for the PCV13 comparator
HSCT recipients	3 doses of PCV15 at 6, 8, and 12 months after HSCT and PPV23 at 24 months ^a	Not requested			

Source: p7, ATAGI advice

^a There is no evidence to support a mixed schedule. The 3-dose series should be given using either PCV13 or PCV15. It is recommended that interchangeability may only be allowed if the course cannot be completed with the same vaccine.

HSCT = Haematopoietic stem cell transplant; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PPV23 = 23-valent pneumococcal polysaccharide vaccine.

- 3.2 The submission did not propose a price for PCV15, however it stated the sponsor would accept the Nationally Negotiated Price for PCV13 for adults for PCV15. In the cost-minimisation approach and financial estimates, the price was assumed to be \$114.99 which was based on a published private market price (Chemist Warehouse). The actual price paid for PCV15 would depend on the outcome of a competitive tender process.
- 3.3 The clinical evidence presented in the submission was less applicable to Indigenous adults aged ≥50 years and adults at increased risk of pneumococcal disease aged ≥18 years. As a proxy for the Indigenous population in Australia, the submission presented a subgroup analysis on North American Indians. In addition, the evidence did not represent the majority of risk conditions currently subsidised for pneumococcal vaccines under the NIP. Of the conditions currently subsidised for pneumococcal vaccines under the NIP, the evidence only included patients with human immunodeficiency virus (HIV).

4 Population and disease

- 4.1 Pneumococcal disease, caused by the pathogen *Streptococcus pneumoniae*, can be broadly divided into IPD (invasive pneumococcal disease; meningitis, bacteraemia and pneumonia associated with bacteraemia) and non-invasive pneumococcal disease (GP-treated community acquired pneumonia (CAP) and hospitalised CAP). It can be fatal and was associated with 2,434 hospital admissions in 2016 and 622 deaths between 1997 and 2016 (AIHW 2018). Despite a longstanding pneumococcal disease vaccination program in both children and adults, cases of IPD have been rising in Australia between 2015-2019.
- 4.2 Prior to NIP funding of PCV13 on 1 July 2020 for children and the same populations as those requested by the submission for PCV15, data from 2015 to 2019 showed that serotype 3-related IPD was steadily increasing, and in 2019, it accounted for 18.5% of IPD cases (based on data from non-Indigenous adults ≥ 70 years; National Notifiable Disease Surveillance System; NNDSS data), making it the leading contributor to IPD in Australia. These data also showed that IPD caused by serotypes 19F and 19A accounted for 7.1% and 5.0% of all serotypes respectively (based on ≥ 70 years non-Indigenous adults; NNDSS data). The current incidence of pneumococcal disease of PCV13-covered serotypes, including these three serotypes, is unknown given that PCV13 is relatively new to Australia in the proposed adult populations. The ESC noted that these incidence rates did not account for the effect of PCV13 on the epidemiology of the disease as it was only included on the NIP for adults in July 2020.
- 4.3 Protection against serotypes 22F and 33F is unique to PCV15. Of these, 22F was the second most prevalent serotype causing 8.4% of all IPD in 2019, whilst serotype 33F contributed to 3.9% of cases in Australia (based on non-Indigenous adults ≥ 70 years; NNDSS data). The ESC noted that based on NNDSS data from 2019, more than 50% of all IPD cases were due to serotypes not included in either PCV13 or PCV15.
- 4.4 The ESC noted that in the financial estimates, the sponsor assumed that PCV15 would be listed in 2023 and that it would fully replace PCV13 in the proposed (i.e. adult) populations. ATAGI had noted that the market share of pneumococcal vaccines supplied on the NIP would depend on the outcome of a competitive tender process (p8 of the ATAGI advice). The ESC considered that the sponsor's assumption of replacement was unjustified, and noted there may be programmatic concerns around supply issues with one supplier. At the same time, however, the ESC advised that there was potential for prescriber confusion if PCV15 was included on the NIP for adults but not those aged under 18 years, as this would mean that different pneumococcal vaccines would need to be administered depending on age. The ESC noted that the sponsor intended to seek regulatory approval and reimbursement for use of PCV15 in those aged under 18 years. If this potentially staged approach (i.e. extending PCV15 first to adults and then potentially to children) was considered appropriate, then well-developed communication activities around the appropriate administration and timing of different vaccines would be critical to the effective implementation of any

listing on the NIP. The pre-PBAC Response indicated that the sponsor was open to further discussions regarding broadening the NIP supplier base for pneumococcal vaccines, to support any programmatic concerns.

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

5 Comparator

- 5.1 The submission nominated the NIP-funded PCV13 as the main comparator, which was appropriate.
- 5.2 The submission also nominated PCV20 as a potential near market comparator. PCV20 covers an additional 7 and 5 serotypes compared to PCV13 and PCV15, respectively. PCV20 was approved by the FDA in June 2021. Clinical evidence for PCV20 in the submission was limited, and no economic evaluation was included. The comparison was not relevant for PBAC consideration at the present time given the PBAC had not received a submission to list PCV20 on the NIP.

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 the following evidence:
 - One head-to-head, randomised, noninferiority trial (P019) comparing PCV15 to PCV13 (N=1,202).
 - Supplementary trials that included 6 head-to-head randomised trials comparing PCV15 to PCV13: P020 (N=2,221), P016 (N=600), P017 (N=1,500), P018 (N=300), P006 (690) and P007 (N=253).
 - Subgroup analysis of participants aged ≥ 70 pooled from P019, P020 and P016.
 - Subgroup analysis of the North American Indian population from P017.
 - An indirect treatment comparison (ITC) comparing PCV15 with PCV20 using PCV13 as the common comparator.
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
P019	Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-AGE)	<i>Clinical Study Report P019V114</i>
P020	Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-TRUE)	<i>Clinical Study Report P020V114</i>
P016	A Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 One Year Later in Healthy Adults 50 Years of Age or Older (PNEU-PATH)	<i>Clinical Study Report P016V114</i>
P017	A Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 Six Months Later in Immunocompetent Adults Between 18 and 49 Years of Age at Increased Risk for Pneumococcal Disease (PNEU-DAY).	<i>Clinical Study Report P017V114</i>
P018	A Phase 3, Multicentre, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 Eight Weeks Later in Adults Infected with HIV (PNEU-WAY)	Mohapi et al, 2020 Safety and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine (PCV), in Adults Infected With Human Immunodeficiency Virus (HIV): A Phase 3 Trial, Poster at ISPPD, June 2020
P006	Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults	Stacey et al, 2019 <i>Human Vaccines and Immunotherapeutics</i> , VOL. 15, NO. 3, 530–539 https://doi.org/10.1080/21645515.2018.1532249
P007	Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine compared to 13-valent pneumococcal conjugate vaccine in adults ≥65 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	Peterson et al, 2019 <i>Human Vaccines and Immunotherapeutics</i> , VOL. 15, NO. 3, 540–548 https://doi.org/10.1080/21645515.2018.1532250

Source: Table 2.2-1, p33 of the submission.

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N ^a	Design/duration ^b	Risk of bias	Patient population	Outcomes
PCV15 vs PCV13					
P019	1,205	Phase III, R, DB, MC 6 mths	Low	Adults aged ≥50 yrs	OPA, IgG, Safety
P020	2,340 ^c	Phase III, R, DB, MC 6 mths	Low	Adults aged ≥50 yrs	OPA, IgG, Safety
P016	652	Phase III, R, DB, MC 13 mths	Low	Adults aged ≥50 yrs	OPA, IgG, Safety
P017	1,515 ^d	Phase III, R, DB, MC 6 mths	Low	Adults aged 18-49 yrs at increased risk of pneumococcal disease	OPA, IgG, Safety
P018	302	Phase III, R, DB, MC 8 weeks	Low	Adults aged ≥18 yrs with HIV	OPA, IgG, Safety
P006	690	Phase II, R, DB, MC 30 days	Low	Adults aged ≥50 yrs	OPA, IgG, Safety
P007	253	Phase II, R, DB, MC 30 days	Low	Adults aged ≥65 yrs vaccinated with PPV23 >1 yr	OPA, IgG, Safety

Source: Compiled during the evaluation

DB = double blind; IgG = immunoglobulin G; HIV = human immunodeficiency virus; MC = multi-centre; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PPV23 = 23-valent pneumococcal polysaccharide vaccine; R = randomised.

^a at randomisation

^b based on an outcome with longest duration

^c unequal randomisation with a 3:3:3:1 ratio to receive PCV15 in three arms at different doses and PCV13 in one arm

^d unequal randomisation with a 3:1 ratio to receive PCV15 and PCV13 respectively

6.6 Key efficacy outcomes in the trials were based on immunological response and included the level of opsonophagocytic activity (OPA; measured in geometric mean titre; GMT) and immunoglobulin G (IgG; measured in geometric mean concentration; GMC) at Day 30 post-vaccination. The comparative efficacy was expressed as the ratio between PCV15 and PCV13 for OPA GMT and IgG GMC.

6.7 In terms of efficacy measure, the primary objective of these trials were:

- P019: to compare serotype-specific OPA GMTs 30 days post-vaccination (Day 30) of PCV15 and PCV13 and to compare serotype-specific proportions of participants with a ≥4-fold rise from pre-vaccination (Day 1) to 30 days post-vaccination (Day 30) for OPA responses for the 2 unique serotypes in PCV15 of PCV15 and PCV13.
- P020: to describe the immunogenicity of 3 lots of PCV15.
- P016: to compare the OPA GMT ratio at Day 30 post-vaccination with PPV23 (at Month 13) for PCV15 and PCV13 recipients.
- P017: to evaluate OPA GMT ratio at Day 30 post-vaccination with PCV15 and PCV13 within each vaccination group separately.
- P018: to evaluate OPA GMT ratio and IgG at Day 30 post-vaccination with PCV15 and PCV13 within each vaccination group separately.
- P006: to compare two different formulations of PCV15 to PCV13.
- P007: to summarise IgG responses measured at Day 1 and Day 30 post-vaccination in PCV15 recipients and PCV13 recipients.

6.8 The ESC noted that only P019 was primarily designed and powered to compare the efficacy of PCV15 and PCV13. P020, P016, P017, and P018 were not primarily designed

to evaluate these efficacy outcomes (OPA GMT and IgG GMC ratios at Day 30). The Phase II P006 trial used a less stringent statistical approach compared to P019 to assess noninferiority (i.e. P006 defined a noninferiority threshold for OPA GMT ratio of 0.33 while in P019, the threshold was 0.50). P007 was a descriptive study, and therefore no hypotheses were generated. Interpretation of results from these supplementary trials and related analyses should be made with caution.

- 6.9 The pivotal trial, P019, enrolled participants that differed from the proposed listing populations (P019 included non-Indigenous adults younger than 70 years, the trial was not restricted to Indigenous adults aged ≥ 50 years, and patients were in good health according to investigator's opinion (i.e. not at increased risk of pneumococcal disease)). The ESC noted that 69.1% of participants in P019 were aged over 65 years, and considered that the population in P019 would be similar overall to the proposed population of non-Indigenous adults aged ≥ 70 years.
- 6.10 The key outcomes presented in the submission to compare the efficacy of PCV15 and PCV13 included the OPA GMT and IgG GMC ratios, which are surrogates for pneumococcal disease prevention. The use of immunogenic response as a surrogate for disease prevention had previously been accepted by the PBAC for other vaccines that also assessed a condition with a low incidence like meningococcal disease (MenACWY-TT, Public Summary Document (PSD), November 2020 PBAC meeting). ATAGI considered that using such immunogenicity outcomes was reasonable given the low incidence of pneumococcal disease, noting that it has previously accepted this approach for pneumococcal vaccines (p6 of the ATAGI advice). The PBAC previously recommended listing PCV13 for infants on the basis of noninferiority with PCV7, based on immunogenicity outcomes (with some concerns around immune persistence). At that time, the PBAC did not accept a claim of superiority for PCV13 due to uncertainty about whether the immunogenicity results from the trials would translate into clinically important benefits (PCV13, PSD, July 2010 PBAC meeting).
- 6.11 ATAGI had noted that threshold values for OPA and IgG that correlate with clinical protection have not yet been documented in adults. As such, the magnitude and precision of any resultant clinical benefit based on these outcomes remained unknown. The outcome that was used as the basis of the clinical claim was the OPA GMT ratio (PCV15/PCV13) at Day 30. In P019, the noninferiority criterion was a lower bound of the 95% confidence interval (CI) of the GMT ratio >0.50 . ATAGI had been concerned that the noninferiority threshold of 0.50 was lower than that suggested by the World Health Organization (WHO) of 0.67 as using such low threshold may potentially result in accepting a vaccine that has lower efficacy than the original vaccines (e.g. 7-valent pneumococcal conjugate vaccine; PCV7) i.e. 'downward drift' (p18 of the ATAGI advice). The Pre-Sub-Committee Response (PSCR) reiterated that 'downward drift' is less applicable to adult pneumococcal vaccines as PCV13 was the first pneumococcal conjugate vaccine licensed in adults. The PSCR noted that the use of a 1.5-fold noninferiority margin in P019 would have increased the required sample size by more than 5-6-fold, creating significant feasibility challenges. The ESC

acknowledged that it may be difficult to achieve the large sample sizes required to assess noninferiority of vaccines with multiple antigens such as PCV15.

- 6.12 Superiority was claimed if the lower 95% CI bound of the 95% CI of the GMT ratios was >2 for serotype 22F and 33F and >1.2 for serotype 3. The superiority criterion used for serotype 3 of 1.2 was not pre-specified in the original study protocol and ATAGI considered that such a criterion (1.2) was ‘poorly justified’ (p20 of the ATAGI advice). Also, this differed from the superiority criterion of 2.0 used in the same trial for serotypes 22F and 33F. The PSCR reiterated that a margin of 1.0 was typically used in superiority testing for shared serotypes and as such, the margin for serotype 3 was conservative. The PSCR contended that it would be inappropriate to apply a similar superiority margin for serotypes 22F and 33F, which are unique to PCV15. The ESC noted that the superiority criterion was added as part of an amendment in February 2020 to the original protocol dated 9 January 2019. The ESC noted that given the lack of a demonstrated OPA threshold that correlates with clinical protection against pneumococcal disease, a superiority threshold which correlates with additional clinical protection was also uncertain. Further, the ESC noted that the approach of selectively considering results for superiority without apparent adjustment for multiple testing in P019 is associated with an increased chance of Type I error (in this case, the risk of claiming effect when there is none). The pre-PBAC Response contended that the risk of Type I error in P019 was minimal as this was accounted for in the P019 protocol. The pre-PBAC Response noted that while not stated explicitly in the protocol, a sequential testing approach was used to control for Type I error where the testing of the secondary hypotheses for assessing serotype 3 superiority was gated by the success of primary hypotheses (i.e. noninferiority for the 13 shared serotypes and superiority of serotypes 22F and 33F).
- 6.13 In its consideration of PCV13 for older people (Indigenous and non-Indigenous), the PBAC’s cost-minimisation and subsequent cost-effectiveness recommendation compared with PPV23 was based on a large trial that reported clinical outcomes with a long follow-up period – CAPITA. The trial enrolled 84,496 participants (Table 2, PCV13, PSD, July 2016 PBAC meeting). The key clinical outcomes in CAPITA were incidence of IPD and CAP and the follow-up period was up to 4 years. Compared to CAPITA, P019 enrolled fewer participants, used immunological surrogate outcomes to account for efficacy and the follow-up period was limited to 30 days post-vaccination.

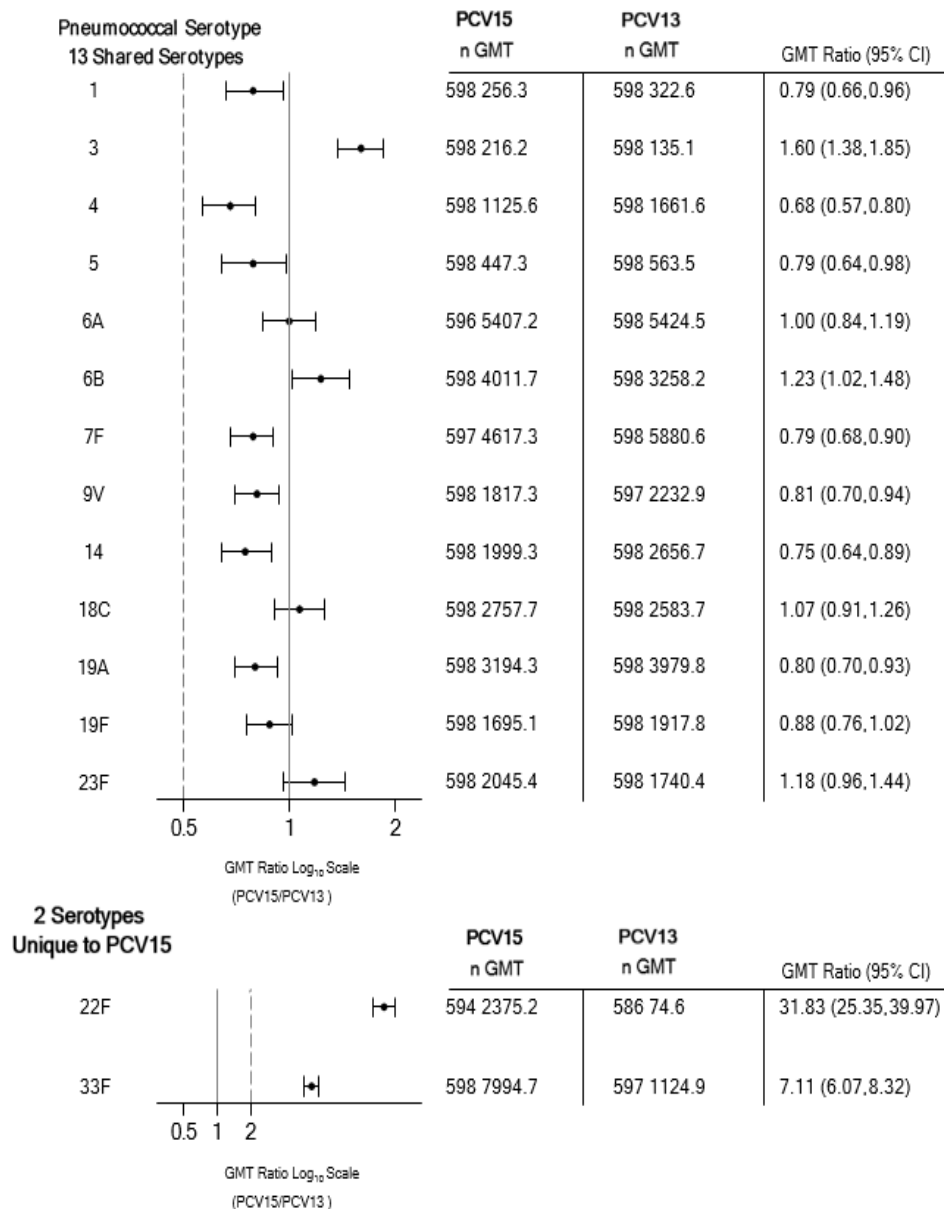
Comparative effectiveness

Results from P019

- 6.14 A summary of OPA GMT ratios at Day 30 in P019 is presented in Figure 1. All 13 shared serotypes met the noninferiority criterion of 0.5 with their lower bound of 95% CI for OPA GMT ratio ranging from 0.57 (serotype 4) to 1.38 (serotype 3). Serotypes 22F and 33F met the superiority criterion with the lower bound of the 95% CI for OPA GMT ratio being 26.35 and 6.07 for 22F and 33F, respectively. Serotype 3 also met the superiority criterion with the lower bound of the 95% CI for OPA GMT ratio being 1.38.

As shown in the figure below, the ESC noted that serotype 3 had a relatively low OPA response at baseline, which makes the ratio for serotype 3 more sensitive to any increases in absolute OPA response for PCV15. As such, the ESC considered that the result for serotype 3 was potentially an outlier. Taken together with the issues around a superiority threshold for OPA response outlined in paragraph 6.12, the ESC considered that use of PCV15 may not translate into more disease prevention for serotype 3 compared to PCV13.

Figure 1: Forest plot of OPA GMT ratios at Day 30 (per-protocol population) - P019



Source: Figure 2.5-2, p82 of the submission

CI = confidence interval; GMT = geometric mean titre; n = number of sample size; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine

- 6.15 Four of the serotypes (1, 4, 5, and 14) had a lower bound 95% CI <0.67 (WHO suggested threshold). Seven serotypes (1, 4, 5, 7, 9V, 14, and 19A) had an upper bound 95% CI below 1.00, favouring PCV13.
- 6.16 The results for the IgG GMC ratio at Day 30 were consistent with the OPA GMT ratio, where PCV15 showed noninferiority in all 13 shared serotypes and superiority for serotypes 3, 22F and 33F.
- 6.17 The ESC considered that the table below showing the 95% CIs for OPA GMT ratios for shared serotypes across the trials was a useful summary, noting that not all studies were powered for this comparison.

Table 5: 95% CI for OPA GMT ratios for shared serotypes at day 30 from the supplementary trials compared with P019

Serotype	P019 (N PCV15 = 602, N PCV13 = 600)	P020 (N PCV15 = 2,102, N PCV13 = 231)	P016 (N PCV15 = 326, N PCV13 = 325)	P017 ^a (N PCV15 = 1,133, N PCV13 = 379)	P018 (N PCV15 = 152, N PCV13 = 150)	First Nations Only in P017 (N PCV15 =445, N PCV13 =146)	Pooling of participants ≥70 years from P019, P020, P016 (N PCV15 =752, N PCV13 = 305)
1	0.66, 0.96	0.81, 1.28	0.94, 1.58	0.85, 1.25	0.72, 1.71	██████████ ¹	0.77, 1.24
3	1.38, 1.85	1.43, 2.01	1.56, 2.30	1.11, 1.47	1.17, 2.01	██████████ ¹	1.53, 2.16
4	0.57, 0.80	0.57, 0.87	0.60, 0.97	0.47, 0.64	0.38, 0.79	██████████ ¹	0.60, 0.93
5	0.64, 0.98	0.69, 1.14	0.81, 1.40	0.79, 0.95	0.69, 1.63	██████████ ¹	0.53, 0.86
6A	0.84, 1.19	0.94, 1.41	0.92, 1.53	0.96, 1.31	0.77, 1.60	██████████ ¹	0.76, 1.16
6B	1.02, 1.48	1.16, 1.74	1.31, 2.06	1.25, 1.66	0.90, 1.77	██████████ ¹	1.03, 1.59
7F	0.68, 0.90	0.74, 1.04	0.80, 1.14	0.66, 0.84	0.73, 1.29	██████████ ¹	0.66, 0.92
9V	0.70, 0.94	0.77, 1.09	0.83, 1.24	0.73, 0.93	0.93, 1.57	██████████ ¹	0.70, 1.00
14	0.64, 0.89	0.79, 1.25	0.87, 1.37	0.77, 1.03	0.83, 1.59	██████████ ¹	0.80, 1.19
18C	0.91, 1.26	1.16, 1.68	1.20, 1.84	1.62, 2.12	1.33, 2.47	██████████ ¹	0.87, 1.27
19A	0.70, 0.93	0.87, 1.20	1.06, 1.55	0.79, 1.03	0.87, 1.52	██████████ ¹	0.63, 0.89
19F	0.76, 1.02	0.85, 1.19	0.92, 1.32	0.88, 1.12	0.90, 1.57	██████████ ¹	0.79, 1.11
23F	0.96, 1.44	1.13, 1.77	1.18, 2.00	1.06, 1.47	0.66, 1.54	██████████ ¹	0.94, 1.52

Source: Table 2.5-1, p79; Figure 2.5-4, p94; Table 2.5-11, pp99-100; Figure 2.5-12, p110; Figure 2.6-1, p151; and Figure 2.6-3, p154 of the submission.

CI = confidence interval; GMT = geometric mean titre; N = number of population size; OPA = opsonophagocytic activity titre; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine

Grey highlighting indicates those with lower bounds below 0.67, blue below 0.50, yellow highlight indicates the upper 95% below 1.0 (and not already highlighted blue or grey). Light orange indicates intervals above 1.0 (favouring PCV15).

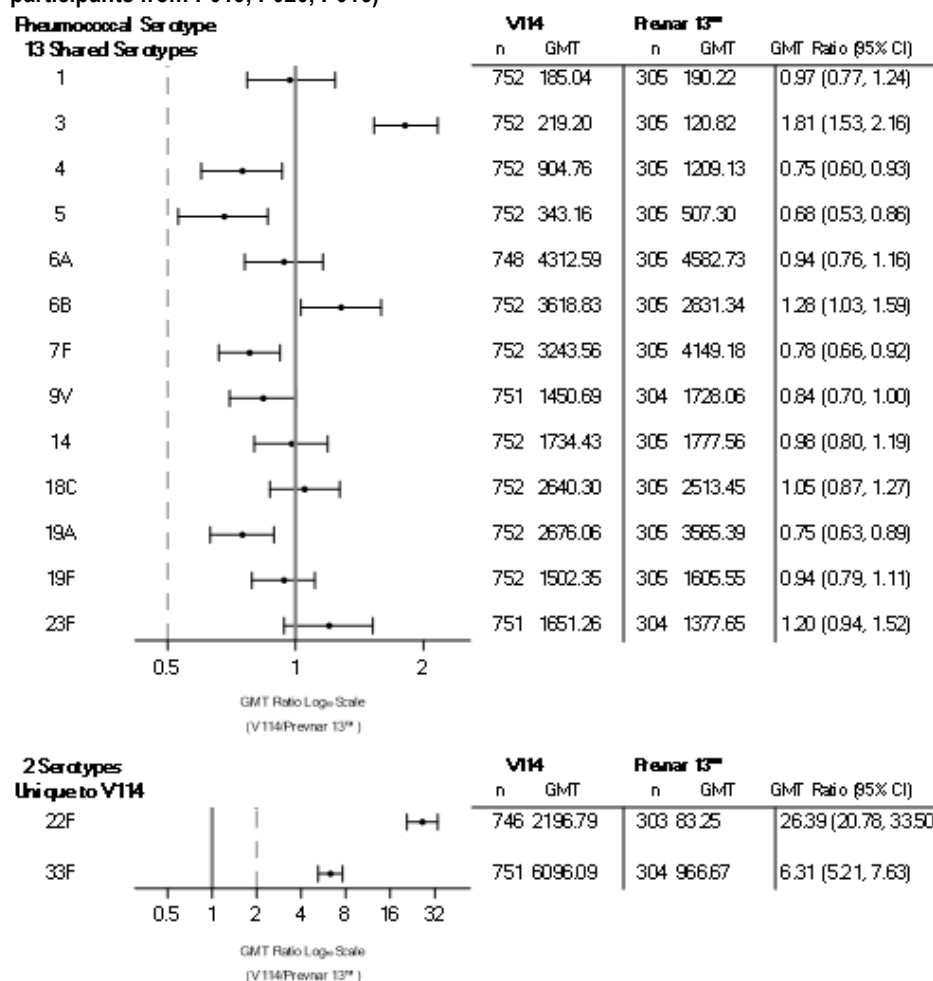
^a The submission presented incorrect results for P017 (originally referring to the results from P016) for all 13 shared serotypes (these were corrected in the evaluation).

¹ The redacted information above contains unpublished data pertaining to the North American Indian First Nations subpopulation within trial P017 (referred to as the P017 subgroup). In accordance with established procedures, publication of these data require approval from the Independent Tribal Review Board (ITRB). As this process was ongoing at the time of finalising the PSD, these data are redacted in order to respect cultural sensitivities and adhere to the established protocols. It is currently estimated to be available in the later part of 2022.

Subgroups analyses conducted for non-Indigenous aged ≥70 years

6.18 A subgroup analysis of pooled participants aged ≥70 years from P019, P020 and P016 was presented in the submission to support the listing for non-Indigenous adults aged ≥70 years. A summary of the OPA GMT ratios results in this subgroup analysis is presented in Figure 2. The results suggest that the noninferiority criterion was met for the 13-shared serotypes and that the superiority criterion was met for serotype 3, 22F and 33F. However, these results were also subject to the concerns raised for the primary analysis regarding the noninferiority and superiority margins.

Figure 2: Forest plot of OPA GMT ratios at Day 30 of age group ≥70 years old (exploratory subgroup analysis of participants from P019, P020, P016)



Source: Figure 2.6.1, p151 of the submission

CI = confidence interval; GMT = geometric mean titre; n = number of sample size; OPA = opsonophagocytic activity; V114 = 15-valent pneumococcal conjugate vaccine

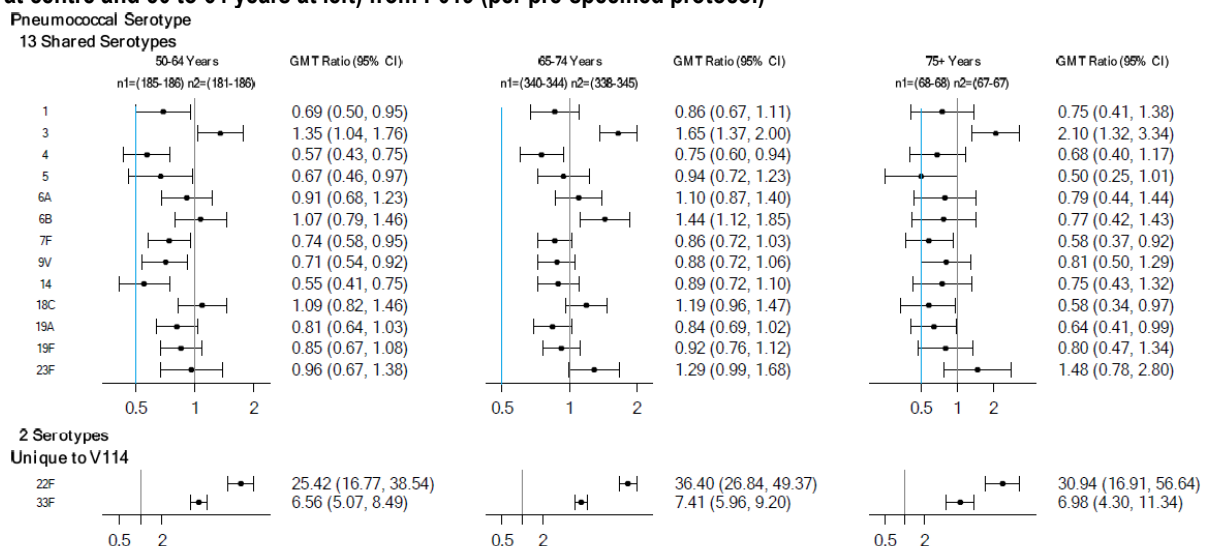
6.19 The subgroup analysis of pooled participants aged ≥70 years from P019, P020 and P016 was an exploratory analysis. Such age group stratification was not pre-specified in these trials. Moreover, P020 and P016 were not designed to assess comparative efficacy of OPA GMT at Day 30. The numbers of participants in each arm was unbalanced with higher number of participants receiving PCV15 compared to PCV13,

752 versus 305, respectively. This was due to the inclusion of participants from P020, a study designed to assess safety and tolerability across three different lots of PCV15 compared to PCV13 and with a randomisation ratio of 3:3:3:1.

6.20 Two relevant subgroup analyses were identified during the evaluation; a subgroup analysis of participants aged ≥ 70 and of participants aged ≥ 75 in P019.

- The subgroup analysis of participants aged ≥ 70 was an exploratory analysis and had consistent results with the exploratory subgroup analysis of pooled participants from P019, P020 and P016.
- The subgroup analysis of participants aged ≥ 75 was a pre-specified analysis. A summary of the OPA GMT ratios results in this subgroup analysis is presented in Figure 3. P019 was not powered to determine noninferiority of the outcomes in this subgroup and that the sample size was small with 68 and 67 participants receiving PCV15 and PCV13, respectively.

Figure 3: Subgroup analysis of participants aged ≥ 75 years (right) and its complement age groups (65 to 74 years at centre and 50 to 64 years at left) from P019 (per pre-specified protocol)



Source Figure 14.2-13, p268 of P019 CSR

CI = confidence interval; GMT = geometric mean titre; n = number of sample size; OPA = opsonophagocytic activity; V114 = 15-valent pneumococcal conjugate vaccine

6.21 The results from Figure 3 suggest that the OPA response in the subgroup aged ≥ 75 years was less consistent to the whole population compared to its complement age groups. The results show that the OPA GMT ratios for the subgroup aged ≥ 75 years were generally numerically lower than its complement age groups and the whole population. The ESC noted that only 3 of the 13 shared serotypes met the 0.5 noninferiority criterion (and only 2 met the 0.67 noninferiority criterion), while serotype 3, 22F and 33F met the superiority criteria.

6.22 The subgroup analysis for participants aged 65-74 years showed that the noninferiority criterion was met for the 13 shared serotypes and that the superiority criterion was met for serotypes 3, 22F and 33F.

Subgroup analysis conducted to support efficacy in Indigenous adults aged ≥50 years

6.23 A subgroup analysis of North American Indian participants from P017 was presented in the submission to support the listing for Indigenous adults aged ≥50 years. [REDACTED]

[REDACTED]

¹

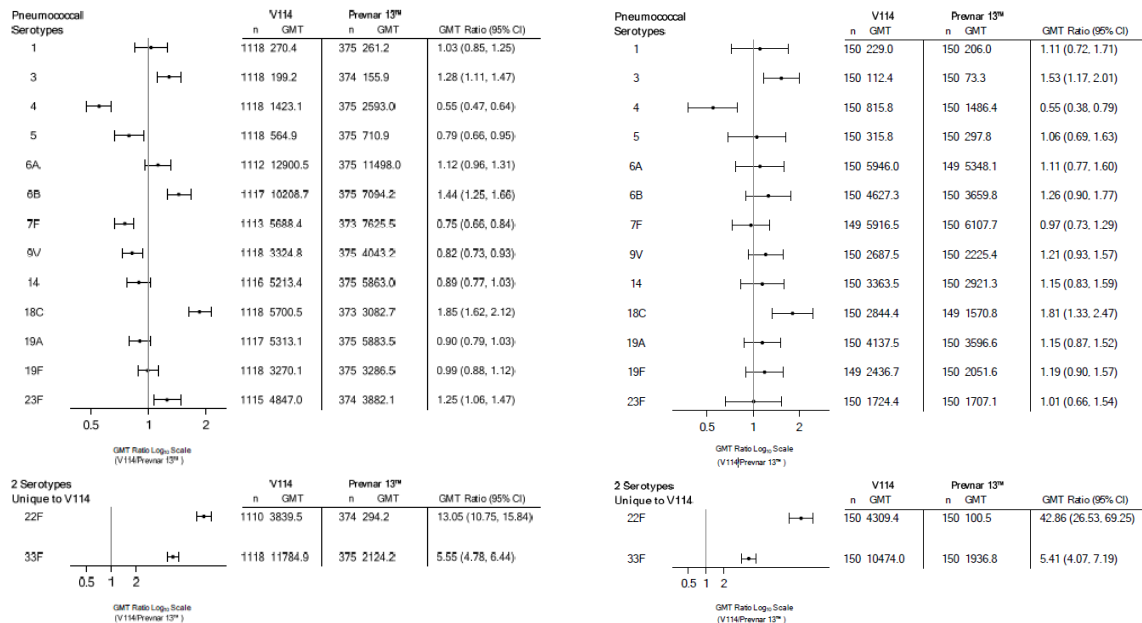
6.24 The subgroup analysis of North American Indian participants from P017 was an exploratory analysis as P017 was not designed to evaluate comparative efficacy. P017 had an unequal randomisation by design (3:1) and had higher numbers of participants receiving PCV15 (n=445) compared to PCV13 (n=146). Further, the trial included participants aged 18 to 49 years at increased risk of pneumococcal disease, which may not represent the proposed listing for Indigenous adults aged ≥50 years. ATAGI advised that it was unclear whether First Nations people in North America could be a proxy for other Indigenous populations (although they might share some similarities in historical, social and health background). The PSCR noted that PCV13 is subsidised under the NIP for Indigenous populations despite there being no direct evidence for PCV13 in these populations. The ESC was uncertain whether the P017 subgroup comparison was more informative than the primary comparison in P019, as it was unclear whether the subgroup from P017 would be more representative of Australian Indigenous populations than the participants in P019.

Results from P017 and P018 for individuals at increased risk of pneumococcal disease aged ≥18 years

6.25 The submission presented results from P017 and P018 to support the listing of individuals at increased risk of pneumococcal disease aged ≥18 years. A summary of the OPA GMT ratios results from P017 and P018 is presented in Figure 4. These results suggest that the noninferiority criterion was met for 12 of the 13-shared serotypes (it was not met in serotype 4) and the superiority criteria were met for serotypes 3, 22F and 33F.

¹ The redacted information above contains unpublished data pertaining to the North American Indian First Nations subpopulation within trial P017 (referred to as the P017 subgroup). In accordance with established procedures, publication of these data require approval from the Independent Tribal Review Board (ITRB). As this process was ongoing at the time of finalising the PSD, these data are redacted in order to respect cultural sensitivities and adhere to the established protocols. It is currently estimated to be available in the later part of 2022.

Figure 4: Forest plot of OPA GMT ratios at Day 30 (pre protocol population) in P017 (left) and P018 (right)



Source: Figure 2.5-12, p110; Figure 2.5-13, p123 of the submission

CI = confidence interval; GMT = geometric mean titre; n = number of sample size; OPA = opsonophagocytic activity titre; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine

6.26 P017 and P018 were not designed to evaluate comparative efficacy between PCV15 and PCV13 (and as noted above, P017 had an unequal randomisation by design and had higher numbers of participants receiving PCV15 compared to PCV13). None of the risk factors in P017 (diabetes mellitus, chronic liver disease, chronic lung disease including asthma, chronic heart disease, current smoker, increased alcohol use) are subsidised for pneumococcal vaccines under the NIP. P018 was a trial consisting of participants with HIV, which is one of the risk conditions subsidised for pneumococcal vaccines under the NIP. The ESC noted that the PBAC previously recommended inclusion of pneumococcal vaccines on the NIP for patients with certain risk conditions in the absence of direct evidence of pneumococcal vaccines specifically in these at-risk populations.

Comparative harms

6.27 A summary of the adverse events (AEs) for PCV15 versus PCV13 in P019 is presented in Table 6.

Table 6: Analysis of adverse event summary (all participants as treated population) (following PCV)

	PCV15	PCV13	Difference in % vs PCV13 Estimate (95% CI)
	n (%)	n (%)	
Subjects in population	602	600	
with one or more adverse events	409 (67.9)	349 (58.2)	9.8 (4.3, 15.2)
injection-site	362 (60.1)	293 (48.8)	
systemic	231 (38.4)	208 (34.7)	
with no adverse event	193 (32.1)	251 (41.8)	
with vaccine-related adverse events	385 (64.0)	329 (54.8)	9.1 (3.6, 14.6)
injection-site	362 (60.1)	293 (48.8)	
systemic	169 (28.1)	156 (26.0)	
with serious adverse events	9 (1.5)	13 (2.2)	-0.7 (-2.3, 0.9)
with serious vaccine-related adverse events	0 (0.0)	0 (0.0)	0.0 (-0.6, 0.6)
who died	1 (0.2)	1 (0.2)	-0.0 (-0.8, 0.8)
Solicited injection site adverse events	355 (59.0)	284 (47.3)	
Injection site erythema	54 (9.0)	68 (11.3)	-2.4 (-5.8, 1.1)
Injection site pain	325 (54.0)	254 (42.3)	11.7 (6.0, 17.2)
Grade 3	1 (0.2)	2 (0.3)	0.00 (-0.01, 0.00)
Injection site swelling	75 (12.5)	67 (11.2)	1.3 (-2.4, 5.0)
Solicited systemic adverse events	200 (33.2)	182 (30.3)	
Arthralgia	32 (5.3)	33 (5.5)	-0.2 (-2.8, 2.4)
Grade 3	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Fatigue	105 (17.4)	104 (17.3)	0.1 (-4.2, 4.4)
Grade 3	1 (0.2)	1 (0.2)	0.00 (0.0, 0.0)
Headache	70 (11.6)	78 (13.0)	-1.4 (-5.1, 2.4)
Grade 3	1 (0.2)	2 (0.3)	0.0 (0.0, 0.0)
Myalgia	93 (15.4)	72 (12.0)	3.4 (-0.4, 7.4)
Grade 3	0 (0.0)	0 (0.0)	0.00 (0.0, 0.0)

Source: Table 2.5-30, p134; Table 2.5-31, p135 of the submission; Table 2.5-32, p135-136 of the submission

CI = confidence interval; n = number of sample size; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine

Bold text indicates statistically significant differences.

6.28 No statistical difference in serious AEs between the two vaccines was observed, and the incidence of Grade 3 AEs was low and similar in both arms. However, injection site pain was statistically higher in PCV15 compared to PCV13 (11.7%; 95%CI: 6.0, 17.2). The supplementary trials reported similar results for AEs to P019. ATAGI considered that while an overall claim of noninferiority with respect to safety is reasonable, tolerability of PCV15 should be considered inferior to PCV13. However, ATAGI considered that from a programmatic perspective, this was unlikely to be an issue for use in adults, though may impact future use in children, for whom PCV13 injection site pain is already considered problematic (p5 of the ATAGI advice). The ESC considered that the safety of PCV15 was comparable to that of PCV13.

Benefits/harms

6.29 A benefits/harms statement has not been presented as the overarching clinical claim was one of noninferiority.

Clinical claim

- 6.30 The submission claimed that PCV15 was noninferior in terms of efficacy compared with PCV13 for 12 of the 13 shared serotypes and superior for serotype 3 and for the unique additional serotypes 22F and 33F. Noninferiority was demonstrated in terms of OPA GMT for all shared serotypes however, the evaluation raised concerns it may not have been demonstrated for all the requested populations. A subgroup analysis of pooled participants aged ≥ 70 years in P019, P020 and P016 supported the noninferiority claim in terms of immunogenicity outcomes for this population, however this analysis was exploratory. Older participants in P019 (≥ 75 years) showed less consistent immunogenicity outcomes compared to the whole trial or its complement groups, though these subgroups were not powered to detect a treatment difference.
- 6.31 While superiority was demonstrated in terms of OPA and IgG for serotypes 3, 22F and 33F, the magnitude and clinical benefit of this remains uncertain. There is insufficient evidence regarding the minimum OPA/IgG threshold required in the requested populations that would ensure these immunological endpoints are also clinically meaningful. The superiority criterion for serotype 3 of 1.2 used in P019 was not pre-specified in the original study protocol and was poorly justified. The ESC considered that while it was reasonable to conclude that PCV15 will provide expanded coverage to serotypes 22F and 33F, the claim of superiority for serotype 3 was not adequately supported.
- 6.32 The submission stated that PCV15 was noninferior in terms of safety compared to PCV13. The ESC considered this claim was appropriate (although also noted ATAGI's concerns regarding tolerability).
- 6.33 The PBAC considered that a claim of noninferior comparative effectiveness (based on immunogenicity data) for the 13 shared serotypes would be reasonable, noting that the subgroup analyses presented to support listing in specific populations on the NIP were largely consistent overall with the evidence shown in the key comparative trial P019. The PBAC considered that the available evidence did not adequately support superior comparative effectiveness of serotype 3 in PCV15 compared to PCV13.
- 6.34 The PBAC agreed with the ESC that it was reasonable to conclude that PCV15 will provide expanded coverage to serotypes 22F and 33F.
- 6.35 The PBAC considered that the claim of noninferior comparative safety was reasonable.

Economic analysis

- 6.36 The submission presented a cost-minimisation approach between PCV15 and PCV13. A summary of this approach is presented in Table 7. The submission claimed that PCV15 was noninferior in terms of efficacy and safety compared to PCV13. The submission's superiority claim for serotypes 3, 22F and 33F was not considered in the economic analysis.

Table 7: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on clinical evidence presented in the submission, effectiveness is assumed to be noninferior
Therapeutic claim: safety	Based on clinical evidence presented in the submission, safety is assumed to be noninferior
Evidence base	Direct comparison to PCV13 based on five phase III and two phase II comparative trials and subgroup analysis in those age 70+ and an Indigenous population
Equi-effective doses	<p><u>Non-Indigenous adults aged ≥70</u> 1 dose (0.5 mL) PCV15 = 1 dose (0.5 mL) PCV13</p> <p><u>Indigenous adults aged ≥50</u> 1 dose (0.5 mL) PCV15 followed by 1 dose PPV23 (2-12 months later), followed by 1 dose PPV23 (5 years later) = 1 dose (0.5 mL) PCV15 followed by 1 dose PPV23 (2-12 months later), followed by 1 dose PPV23 (5 years later)</p> <p><u>Medically at-risk individuals aged ≥18</u> 1 dose (0.5 mL) PCV15 followed by 1 dose PPV23 (2-12 months later), followed by 1 dose PPV23 (5 years later) = 1 dose (0.5 mL) PCV15 followed by 1 dose PPV23 (2-12 months later), followed by 1 dose PPV23 (5 years later)</p>
Direct medicine costs	In the absence of public information about the NNP, the sponsor assumed that 1 dose of PCV13 costs \$114.99, based on the publicly available private market price on the Chemist Warehouse website. The sponsor indicated it would match the NNP of PV13 in adults, once recommended for listing. The actual price paid for PCV15 would depend on the outcome of a competitive tender process.
Other costs or cost offsets	None

Source: Table 3.1-1, p177 of the submission.

AEMP = approved ex-manufacturer price; mL = millilitre; NIP = National Immunisation Program; NNP = Nationally Negotiated Price; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PPV23 = 23-valent pneumococcal polysaccharide vaccine

- 6.37 The estimation of equi-effective doses was based on the direct randomised comparison of PCV15 to PCV13 in P019, where noninferiority in terms of immunogenicity was demonstrated for all serotypes of PCV13. Thus, the submission estimated that 1 dose (0.5 mL) PCV15 is equivalent to 1 dose (0.5 mL) PCV13. This was applied to all of the proposed listings. This was appropriate.
- 6.38 The submission used a proxy price of \$114.99 in the cost-minimisation approach, which was the cost of PCV13 based on the publicly available private market price on the Chemist Warehouse website, as the Nationally Negotiated Price is not publicly available. The results of the cost-minimisation approach are presented in Table 8. The ESC noted that although the cost-minimisation approach only used a proxy price, it provided a framework to estimate the cost of PCV15 that is no more than PCV13.
- 6.39 As the submission claimed no difference in safety, it did not include any additional costs for treating adverse events associated with the administration of PCV15.
- 6.40 The submission claimed that while the economic evaluation was a cost-minimisation, it was highly likely that PCV15 would be cost saving compared PCV13 due to the increased coverage and superior immune response against serotype 3. This claim was inappropriate as the superiority claim for serotype 3 was not justified. The ESC considered the claimed cost saving was unlikely to be realised in practice given there

was insufficient evidence that the superiority threshold applied for serotype 3 would correlate to additional clinical protection.

Table 8: Results of the cost-minimisation analysis

	PCV15 cost per dose	PCV13 cost per dose	Incremental cost
Vaccine cost	\$114.99	\$114.99	\$0.00
Administration costs (MBS item 3)	\$17.90	\$17.90	\$0.00
Total Cost per dose	\$132.89	\$132.89	\$0.00

Source: Table 3.4-1, p178 of the submission.

MBS = Medicare Benefits Schedule; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine

Vaccine cost/patient/course

6.41 Vaccine cost per patient per course was estimated at \$114.99 based on the publicly available private market price (based on 1 dose, the same cost/patient/course was applied in the financial estimates).

Estimated PBS usage & financial implications

6.42 This submission was not considered by DUSC.

6.43 The submission used an epidemiological approach to estimate the extent of use and financial impact of reimbursing PCV15 for the proposed populations. The submission assumed that PCV15 would be listed in 2023 and that it would fully replace PCV13 in the proposed populations. ATAGI noted that the market share of pneumococcal vaccines supplied on the NIP would depend on the outcome of a competitive tender process (p8 of the ATAGI advice). Noting this ATAGI advice, and in the context of a cost-minimisation approach, the listing would be expected to be cost-neutral to the NIP. A summary of key inputs used in the estimation is presented in the table below.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Non-Indigenous adults aged ≥70 years		
Vaccine naïve (70-year-old)	█ ¹ in Yr 1 to █ ¹ in Yr 6. Annual projected 70-year-old population from ABS.	Appropriate.
Uptake rate: vaccine naïve	55% based on ATAGI's advice for PCV13 in older adults (para 6.28, PCV13, PSD, July 2015 PBAC meeting).	Appropriate.
Available population for catch up (71 to 84 years)	█ ² in Yr 1 to █ ³ in Yr 6. ABS and estimated. This number corresponds to those who did not receive PCV13 in the previous three years (since 1 July 2020).	Uncertain.
Uptake rate: catch up (71 to 84 years)	35% based on ATAGI's advice for PCV13 in adults (para 6.29, PCV13, PSD, July 2015 PBAC meeting).	Uncertain. The PBAC had previously considered that there were no reliable data to inform the likely uptake for the catch-up program (para 6.29, PCV13, PSD, July 2015 PBAC meeting). This rate was applied each year which resulted in most of the catch up population being vaccinated by Yr 6.
Indigenous adults aged ≥50 years		
Vaccine naïve (50-year-old)	█ ⁴ in Yr 1 to █ ⁴ in Yr 6. Estimate based on annual projected 70-year-old population from ABS	Appropriate.
Uptake rate: vaccine naïve	35%, the uptake rate used in PCV13 in adults submission (for catch-up population, para 6.29, PCV13; PSD, July 2015 PBAC meeting)	Uncertain. The PBAC had previously considered that there were no reliable data to inform the likely uptake for the catch-up program (para 6.29, PCV13, PSD, July 2015 PBAC meeting).
Available population for catch up (≥51 years)	█ ⁵ in Yr 1 to █ ⁶ in Yr 6. ABS and estimate. This number corresponds to those who did not receive PCV13 in the previous three years (since 1 July 2020).	Uncertain.
Uptake rate: catch up (≥51 years)	20%. Assumption.	In line with evidence suggesting lower coverage of pneumococcal vaccines in Australia in Indigenous adults aged 50 – 64 years. ^a
Individuals at increased risk of pneumococcal disease aged ≥18 years		
Newly diagnosed aged ≥18	█ ⁷ in Yr 1 to █ ⁷ in Yr 6. Estimate based on ATAGI advice for Yr 1 and assumed 1.7% annual growth (ABS) for the later years.	Likely overestimated. The data provided by ATAGI included people aged 5-years old and above. It was also noted that prevalence, not incidence, was available for patients with asplenia.
Uptake rate	53%. Uptake rate used in PCV13 in increased risk individuals submission (para 6.36, PCV13, PSD, November 2018 PBAC meeting)	The PBAC had previously considered such a rate used in PCV13 in increased risk individuals was uncertain (para 6.37, PCV13, PSD, November 2018 PBAC meeting).

Source: sheet Dose estimation, Budget Impact Model Excel.

ABS = Australia Bureau of Statistics; ATAGI = Australian Technical Advisory Group on Immunisation; PBAC = Pharmaceutical Benefits Advisory Committee; PCV13 = 13-valent pneumococcal conjugate vaccine; PSD = Public Summary Document; PCV15 = 15-valent pneumococcal conjugate vaccine; Yr = year

^a Webster et al., 2019 (<https://onlinelibrary.wiley.com/doi/full/10.1111/1753-6405.12944>)

The redacted values correspond to the following ranges:

¹ 200,000 to < 300,000

² 500,000 to < 600,000

³ < 500

⁴ 5,000 to < 10,000

⁵ 70,000 to < 80,000

⁶ 30,000 to < 40,000

⁷ 20,000 to < 30,000

- 6.44 The submission used an uptake rate per year of 55% for vaccine-naïve non-Indigenous adults aged ≥ 70 years. This rate was based on ATAGI's advice for the PCV13 submission in adults (para 6.28, PCV13; PSD, July 2015 PBAC meeting). The submission applied a catch-up rate per year of 35% (those aged 71-84 years who were not vaccinated at 70 years old). This was also based the ATAGI's advice for the PCV13 submission in adults (para 6.29, PCV13, PSD, July 2015 PBAC meeting). The use of these rates applied annually in the submission resulted in a high proportion of the whole eligible catch-up population being vaccinated within year 6 of the estimates (e.g. those who miss the vaccine in the early years of the estimate, will still have a constant rate of 35% per year for catch up at the later years). This might not have been reasonable.
- 6.45 The submission used an uptake rate per year of 35% for vaccine-naïve Indigenous adults aged ≥ 50 years. This rate was based on ATAGI's advice for the PCV13 submission in adults (para 6.29, PCV13, PSD, July 2015 PBAC meeting). The submission assumed a catch-up rate per year of 20% (those aged 51 years who are not vaccinated at 50 year). The use of these low rates appears to be in line with evidence showing low coverage of pneumococcal vaccines in Australia for Indigenous populations aged 50 to 64 years (Webster et al., 2019).
- 6.46 For the catch-up population uptake, the PBAC previously considered that there were no reliable data to inform the likely uptake for the catch-up program (para 6.29, PCV13, PSD, July 2015 PBAC meeting). Thus, assuming a constant rate of 35% per year was uncertain.
- 6.47 The submission used data from 2020 provided by ATAGI (Table A2, p58 of the ATAGI advice) to estimate the number of individuals at increased risk of pneumococcal disease aged ≥ 18 years who are eligible for PCV15. These data showed that 24,304 individuals of all age groups were at high-risk for pneumococcal disease in Australia. The submission used linear extrapolation to estimate a population growth rate of 1.7% and applied this for each year. Based on such data, the submission estimated that in 2023, there will be 20,000 to < 30,000 newly diagnosed individuals with increased risk of pneumococcal disease who will be eligible for PCV15. It was noted that the incidence data used in the submission included individuals <18, for which PCV15 listing is not being sought. Therefore, the submission may have overestimated the eligible population. The PSCR acknowledged that the population of individuals with increased risk of pneumococcal disease may be overestimated however, the PSCR noted that this population was a small subset of the overall population and therefore any adjustments would have minimal impact on the financial estimates.

6.48 A summary of the estimated use and financial implications of PCV15 is presented in the table below. This is based on the assumed (private market) price in the submission.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of PCV15 recipients						
Non-Indigenous adults ≥70 yrs	█ ¹	█ ²	█ ²	█ ³	█ ³	█ ³
Indigenous adults ≥50 yrs	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁵
Individuals at increased risk of pneumococcal disease ≥18 yrs	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Total	█ ¹	█ ²	█ ²	█ ²	█ ³	█ ³
Number of scripts dispensed	█ ¹	█ ²	█ ²	█ ²	█ ³	█ ³
Estimated financial implications of PCV15						
Cost to NIP	█ ⁶	█ ⁷	█ ⁸	█ ⁸	█ ⁸	█ ⁹
Estimated financial implications for other medicines (PCV13)						
Cost to NIP	-█ ⁶	-█ ⁷	-█ ⁸	-█ ⁸	-█ ⁸	-█ ⁹
Net financial implications						
Net cost to NIP	█ ¹⁰	█ ¹⁰	█ ¹⁰	█ ¹⁰	█ ¹⁰	█ ¹⁰

Source: Table 4.2-1, p181; Table 4.4.1, p183 of the submission

NIP = National Immunisation Program; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; yrs = years

The redacted values correspond to the following ranges:

¹ 300,000 to < 400,000

² 200,000 to < 300,000

³ 100,000 to < 200,000

⁴ 10,000 to < 20,000

⁵ 5,000 to < 10,000

⁶ \$40 million to < \$50 million

⁷ \$30 million to < \$40 million

⁸ \$20 million to < \$30 million

⁹ \$10 million to < \$20 million

¹⁰ \$0 to < \$10 million

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

7 PBAC Outcome

- 7.1 The PBAC recommended that 15-valent pneumococcal conjugate vaccine (PCV15, Vaxneuvance) be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in non-Indigenous adults aged ≥70 years, Indigenous adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥18 years. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Vaxneuvance would be acceptable if it were cost-minimised against the nominated comparator, 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar 13).
- 7.2 The PBAC considered that nomination of Prevenar 13 as the main comparator was appropriate, noting that Prevenar 13 was TGA-approved and NIP-funded for certain

paediatric populations, whereas Vaxneuvance had only sought TGA-approval and NIP-funding for certain populations aged ≥ 18 years and older (outlined in the previous paragraph). The PBAC advised that the NIP listing for Vaxneuvance should be consistent with the Prevenar 13 NIP-funded circumstances for the relevant adult populations above.

- 7.3 The PBAC advised that the equi-effective doses were 1 x 0.5 mL Vaxneuvance and 1 x 0.5 mL Prevenar 13.
- 7.4 The PBAC considered that having an additional pneumococcal vaccine on the NIP would help to manage programmatic risks associated with a sole supplier of PCV13 on the NIP. The PBAC considered that there would need to be effective communication with health professionals regarding the appropriate timing and administration of Vaxneuvance and Prevenar 13. If PCV15 were implemented on the NIP for adults prior to receiving a potential regulatory approval and NIP-listing for the paediatric population, the populations for each vaccine would need to be clearly communicated with health professionals.
- 7.5 The PBAC noted that the submission was based on one randomised, noninferiority trial (P019) comparing PCV15 to PCV13 and six supplementary randomised trials comparing PCV15 to PCV13. The PBAC noted that only P019 was powered to compare the efficacy of PCV15 and PCV13 and that outcomes of the trials were based on immunogenicity data rather than avoided cases of IPD. The PBAC recalled that it previously recommended PCV10 and PCV13 for infants and children based on immunogenicity data, but that its consideration of PCV13 for adults (Indigenous and non-Indigenous) compared with PPV23 was based on a large trial that reported clinical outcomes with a long follow-up period. Noting the ATAGI's advice that the use of immunogenicity outcomes as a surrogate for disease prevention was reasonable for a low-incidence disease, as well as the TGA Delegate's comment around the lack of feasibility of conducting efficacy studies for new pneumococcal vaccines in settings where uptake of currently approved vaccines is high, the PBAC considered that the evidence base presented was appropriate to support the current submission's noninferiority claims.
- 7.6 The PBAC considered it would be reasonable to conclude that Vaxneuvance was noninferior compared to Prevenar 13 in terms of effectiveness, based on the clinical data presented. The PBAC noted that the noninferiority criterion specified in P019 of 0.50 for the lower bound of the 95% confidence interval of the OPA GMT ratio, was lower than the threshold of 0.67 recommended in the WHO guidelines on clinical evaluation of vaccines. However, the PBAC noted that the WHO guidelines were established at a time when multiple antigen vaccines were less common and acknowledged there may be practical issues with achieving the large sample sizes required to assess noninferiority of these vaccines at the WHO margin within a trial.
- 7.7 The PBAC did not accept the claim of superior effectiveness for serotype 3 in Vaxneuvance compared to Prevenar 13, noting that a superiority threshold which

correlates with additional clinical protection was uncertain. However, the PBAC agreed with the ESC that it was reasonable to conclude that PCV15 will provide expanded coverage to serotypes 22F and 33F.

- 7.8 The PBAC considered that the clinical data provided supported the claim of noninferior safety of Vaxneuvance compared to Prevenar 13 (although PBAC also noted ATAGI’s concerns regarding tolerability).
- 7.9 The PBAC noted the various analyses presented to support listing in the particular subgroups requested for listing. The PBAC noted there was no specific trial data available for Indigenous adults aged ≥50 years and specific trial data was only available for one of the risk conditions currently funded by the NIP for pneumococcal vaccines (HIV). The PBAC considered that the immunogenicity results for P017 and P018, which included adults at risk of pneumococcal disease and adults with HIV respectively, were largely comparable between PCV15 and PCV13. The PBAC recalled it had previously recommended Prevenar 13 for Indigenous adults ≥50 years and for those with certain risk conditions in the absence of direct evidence specifically in these populations. Overall, the PBAC considered it would be reasonable to conclude that Vaxneuvance would be similarly immunogenic to Prevenar 13 in all requested populations.
- 7.10 The PBAC noted the uncertainties in the financial estimates with respect to the assumed uptake rate in the catch-up population and the estimated number of individuals at risk at increased risk of pneumococcal disease aged ≥18 years who would be eligible for Vaxneuvance. However, the PBAC considered that including Vaxneuvance on the NIP would not result in an incremental cost to the program, in the context of a cost-minimisation to Prevenar 13.
- 7.11 PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item to the Determination:

Essential elements of the requested listing

Name, restriction, manner of administration, form	Nationally Negotiated Price	Proprietary name and manufacturer
Pneumococcal polysaccharide conjugate vaccine, 15 valent adsorbed, 0.5 mL pre-filled syringe	\$■	Vaxneuvance®, Merck Sharp & Dohme (Australia) Pty Ltd
(a) a dose of the vaccine may be provided to a person: <ul style="list-style-type: none"> (i) who is at least 18 years of age and has one or more of the following medical risk conditions: <ul style="list-style-type: none"> (A) functional or anatomical asplenia including sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia (e.g. splenectomy) or hyposplenia; or 		

- (B) immunocompromising conditions including congenital or acquired immune deficiency including symptomatic IgG subclass or isolated IgA deficiency, haematological malignancies, solid organ transplant haematopoietic stem cell transplant (HSCT) or HIV infection; or
 - (C) chronic respiratory disease including suppurative lung disease, bronchiectasis and cystic fibrosis or chronic lung disease of prematurity; or
 - (D) chronic renal disease including: end stage renal disease – eGFR <15mL/min or relapsing or persistent nephrotic syndrome; or
 - (E) proven or presumptive cerebrospinal fluid (CSF) leak; or
 - (F) cochlear implants; or
 - (G) intracranial shunts; or
 - (H) previous episode of invasive pneumococcal disease (IPD); or
 - (I) born less than 28 weeks gestation; or
 - (J) trisomy 21; or
 - (K) chronic heart disease including cyanotic heart disease and heart failure;
 - (ii) who is at least 18 years of age and has been newly diagnosed with one or more of the medical risk conditions contained in subparagraph (a)(i);
- (c) a dose of the vaccine may be provided to a person:
- (i) who is an Aboriginal and/or Torres Strait Islander; and
 - (ii) who is at least 50 years.
- (d) a dose of the vaccine may be provided to a person:
- (i) who is not an Aboriginal and/or Torres Strait Islander; and
 - (ii) who is at least 70 years.
-

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor welcomes PBAC approval of this vaccine with expanded coverage for pneumococcal disease and looks forward to working with the Department of Health for V114 to be listed on the NIP.