

**5.11 PNEUMOCOCCAL 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 National Immunisation Program (NIP) listing for 15-valent pneumococcal conjugate vaccine (15vPCV), for protection against pneumococcal disease in the following paediatric populations:
- Non-Indigenous infants and Aboriginal and Torres Strait Islander infants living in ACT, NSW, Vic and Tas: 3 doses at ages 2, 4 and 12 months (2+1 doses);
 - Infants with specified medical risk conditions and Aboriginal and Torres Strait Islander infants living in WA, NT, SA and Qld: 4 doses at ages 2, 4, 6 and 12 months (3+1 doses);
 - Children and adolescents between 12 months and 18 years newly diagnosed with a specified medical risk condition (1 dose);
 - Recipients of haematopoietic stem cell transplant (HSCT) aged 12 months to <18 years: 3 doses at 6, 8, and 12 months after HSCT (3 doses); these patients would also receive 2 doses of 23-valent pneumococcal polysaccharide vaccine (23vPPV) (one dose 2-12 months after third dose of 15vPCV or at 4 years of age, whichever is later; followed by a second dose at least 5 years later).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus 13-valent pneumococcal conjugate vaccine (13vPCV).
- 1.3 The Australian Technical Advisory Group on Immunisation (ATAGI) pre-submission advice to the PBAC on this product was provided on September 1, 2022.
- 1.4 Table 1 shows the key components addressed by the submission.

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Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	The submission is requesting the same listing as 13vPCV in infant, children and adolescent populations: <ul style="list-style-type: none"> • Non Indigenous infants and Indigenous infants living in ACT, NSW, Vic and Tas, three doses at ages 2, 4 and 12 months • Infants with specified medical risk conditions and Indigenous infants living in WA, NT, SA and Qld, 4 doses at ages 2, 4, 6 and 12 months, followed by two doses of 23vPPV at 4 years and then 5 years later • Children and adolescents between 12 months and 18 years newly diagnosed with a specified medical risk condition, 1 dose followed by two doses of 23vPPV, 2-12 months later or at 4 years, then 5 years later. • Recipients of HSCT recipients aged 12 months to <18 years, 3 doses of 15vPCV at 6, 8, and 12 months after HSCT and 2 doses of 23vPPV (one dose 2-12 months after 3rd dose of 15vPCV or at 4 years of age whichever is later; a second dose at least 5 years later)
Intervention	Each dose is an intramuscular dose of 15vPCV 0.5 mL. 15vPCV is a 15-valent pneumococcal conjugate vaccine which includes serotype-specific capsular polysaccharides included in 13vPCV, plus two additional serotypes, 22F and 33F, each conjugated to a non-toxic fragment of the diphtheria toxin (CRM197 protein).
Comparator	Main comparator: 13vPCV is currently on the NIP for <u>all</u> requested populations outlined in the population section. It is expected that 23vPPV administration in the Indigenous and medically at-risk populations would remain the same
Outcomes	For all requested populations, the endpoints are: <ul style="list-style-type: none"> - Immunogenicity: <ul style="list-style-type: none"> - the proportion of participants meeting serotype-specific IgG threshold value of ≥ 0.35 $\mu\text{g/mL}$ 30 days following the toddler dose for 15vPCV compared to 13vPCV - serotype-specific IgG GMCs at 30 days following the toddler dose, measured by GMC ratio of 15vPCV to 13vPCV - Safety: <ul style="list-style-type: none"> - solicited injection site reactions day 1-14 post vaccination; - solicited systemic AEs from day 1-14 post vaccination; - vaccine-related serious adverse events from day 1 to study completion.
Clinical claim	In the paediatric and adolescent populations aged <18 years currently eligible for 13vPCV vaccination on the NIP, 15vPCV is non-inferior in terms of comparative immunogenicity for 12 of the 13 shared serotypes, has an increased immune response for serotype 3, and a superior immune response for unique serotypes, 22F and 33F. 15vPCV is non-inferior to 13vPCV in terms of safety.

Source: Table 1.1.3, pp9-10 of the submission.

GMC = geometric mean concentration; HSCT = haematopoietic stem cell transplant; NIP = National Immunisation Program; 13vPCV = 13-valent pneumococcal conjugate vaccine; 15vPCV = 15-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Clinical Evaluation Report and the Delegate's Overview were available.

2.2 The TGA Delegate provided questions for the Sponsor and requested Advisory Committee on Vaccines (ACV) advice, and stated that ‘while a decision is yet to be made, at this stage I am inclined to approve the registration of Vaxneuvance. The final wording of the indication will be determined following ACV.’

2.3 The ACV advice became available from the TGA on 9 February 2023. The ACV considered this product to have an overall positive benefit-risk profile for the indication:

VAXNEUVANCE is indicated for 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, 22F, 23F and 33F) in adults and children from 6 weeks of age.

VAXNEUVANCE may not prevent disease caused by *S. pneumoniae* serotypes that are not contained in the vaccine.

The use of VAXNEUVANCE should be guided by official recommendations.

Registration is expected by 30 April 2023.

2.4 15vPCV has been approved for use in paediatric populations in the USA and also by the European Medicines Agency (EMA).

Previous PBAC consideration

2.5 At its November 2021 meeting, the PBAC recommended that 15vPCV 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, Aboriginal and Torres Strait Islander adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥18 years.

3 Requested listing

3.1 The proposed listing on the NIP is shown below. The submission stated it is based on the proposed listing for 13vPCV from the PBAC Public Summary Document (PSD) March 2018. Suggested deletions proposed by the Secretariat are in strikethrough.

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Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Pneumococcal (conjugate, 15-valent)	Vaxneuvance	Injection (0.5mL)	Polysaccharides of the capsular antigens of <i>S. pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM197.	2 or 3 doses of a primary course plus a booster dose or a single supplementary dose
<p>Circumstances Vaccine may be provided:</p> <p>(a) to a child who is:</p> <p>(i) about 2 months old, and</p> <p>(ii) about 4 months old;</p> <p>(iii) in their second year of life; and</p> <p>(b) a dose of the vaccine may be provided to a child:</p> <p>(i) who is about 6 months of age and is a member of a medical risk group; or</p> <p>(c) the vaccine may be provided in the circumstances set out in subsection 7 (1)</p>				

3.2 The clinical management algorithms were based on the current National Immunisation Schedule and were accepted by ATAGI.

3.3 The submission requested that '(b) a dose of the vaccine may be provided to a child: (i) who is about 6 months of age and is a member of a medical risk group'. The Secretariat noted that circumstance (b) is not included in the circumstances for Prevenar 13, as that population is already covered in circumstance (c) i.e. subsection 7 (1). As such, the Secretariat proposed to remove circumstance (b) from the requested listing. The ESC considered this to be appropriate.

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

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 (community managed or hospitalised community acquired pneumonia). IPD 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 risen in Australia between 2015-2019.

4.2 The ATAGI pre-submission advice for this vaccine and population (September 1, 2022) states that in 2019 there were 460 cases of IPD in children and adolescents aged 19 or less in Australia, of which 63 were in Aboriginal or Torres Strait Islander children and adolescents. Many cases are caused by serotypes not present in 15vPCV: of the total of 460 cases, 204 (44.3%) were caused by non-15vPCV strains, and only 27 (5.9%) by strains present in 15vPCV but not 13vPCV. Non-PCV strains are predominant or a large

minority in all age groups: non-15vPCV serotypes caused 65% of IPD in children under 2 years, 40% in children aged 2-4 years, and 61% in children aged 5-19 years. Strains unique to 15vPCV are unusual causes of IPD in all age groups: 8.7% of cases in children under 2 years, 3.8% of cases in children aged 2-4 years, and 4.9% in children aged 5-19 years. Of the 63 cases of IPD in Indigenous children, 42 (66.7%) were caused by serotypes not present in 15vPCV, and 5 (7.9%) by serotypes present in 15vPCV but not 13vPCV.

- 4.3 The data from the National Notifiable Diseases Surveillance System (NNDSS) uses age groups 5-9, 10-14 and 15-19 years¹. The ATAGI review states that this results in the submission's 'data including children to 19 years rather than 17 years' – the usual cut-off for 'paediatric'. In 2019 there were 30 cases of IPD at ages 15-19, of which one was caused by a strain unique to 15vPCV (33F) and three by serotype 3. Fourteen of the 30 patients were Aboriginal and Torres Strait Islander people. If cases in persons aged 15 and over are excluded, total cases of IPD for 2019 would be 430, of which 26 were caused by strains unique to 15vPCV (6.0%), and the cases in Aboriginal and Torres Strait Islander children would be 49, of which 5 (10.2%) were caused by strains unique to 15vPCV. Overall, including data for ages 15-19, or 17-19, probably has no important effect on the estimate of disease.
- 4.4 The key statement in the ATAGI advice, which is quoted in the submission as the rationale for listing 15vPCV, is that 'There continues to be an appreciable incidence of pneumococcal disease driven in part by serotypes not included in 13vPCV and in part by serotype 3 (ST3) disease (which is a 13vPCV serotype), indicating a need for further pneumococcal vaccines in Australia'. Pneumococcal vaccine coverage in Australia in Aboriginal and Torres Strait Islander children is incomplete² so the problem of persistent pneumococcal disease due to serotype 3 is not inevitably attributable to too few vaccines, rather than, for example, to incomplete vaccine coverage. The Pre-Sub-Committee Response (PSCR) maintained that the persistence of serotype 3 disease is due to limited efficacy of 13vPCV against this serotype, rather than poor vaccination coverage.

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

5 Comparator

- 5.1 The submission nominated 13vPCV as the comparator, as it is currently funded on the NIP for the requested population. This was considered appropriate by ATAGI. There

¹ <https://www.health.gov.au/resources/publications/nndss-public-dataset-pneumococcal-disease-invasive>; accessed 15 November 2022.

² Kabir A, Newall AT, Randall D, et al. Estimating pneumococcal vaccine coverage among Australian Indigenous children and children with medically at-risk conditions using record linkage. *Vaccine* 2021; 39:1727-1735. doi: 10.1016/j.vaccine.2021.02.015. Epub 2021 Feb 20.

would be no change in the second and third doses of 23vPPV in the Indigenous and medically high-risk populations. The ESC considered the nominated comparator to be appropriate.

- 5.2 The submission noted that according to the ATAGI Pre-submission Advice to PBAC, 20vPCV is not a relevant comparator at this time as there is no serotype-specific numerical phase III data publicly available for immunogenicity or safety comparisons from the pivotal trials. Furthermore, 20vPCV has not been recommended by the PBAC for paediatric population/s.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an organisation via the Consumer Comments facility on the PBS website. The comments from the Lung Foundation Australia described a range of benefits that the listing of 15vPCV on the NIP for paediatric populations will have on the Australian population. The organisation considered it would provide an alternative line of supply and ensure continued access to required vaccines, reduce costs to health systems and services by reducing cases of invasive pneumococcal disease, reduce the risk of disease, disability and death associated with pneumococcal disease, and reduce the economic and social burden experienced by parents required to care for ill children.

Clinical trials

- 6.3 The submission was based on eight phase III trials comparing 15vPCV to 13vPCV:
- Two phase III trials (P025, P026) in healthy babies, using the 2+1 regimen, which is relevant for non-Indigenous infants and Aboriginal and Torres Strait Islander infants in NSW, Vic, ACT and Tas.
 - Two phase III trials (P029, P031) in healthy babies and a pooled analysis of preterm infants and a pooled safety analysis of healthy infants, using the 3+1 regimen to support use in infants with a specified medical risk factor and Aboriginal and Torres Strait Islander infants in Qld, NT, SA and WA.
 - Two phase III trials in children with Sickle Cell Disease, and with HIV (P023, P030) to support use in children with specified medical risk conditions.
 - Two phase III trials to support use as catch up vaccination (P024) and use of 13vPCV for some doses of the schedule and 15vPCV for others (P027).

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- 6.4 Details of the trials presented in the submission are provided in Table 2. Overall, the literature searches were satisfactory. An independent search located no other relevant trials.
- 6.5 The ATAGI advice noted an additional Phase 3 trial in Japanese infants that was found on clinicaltrials.gov (NCT04384107, P033). However, the study completion date was 1 December 2021 and it was presumed that analysis had not been conducted at the time of the submission of the Request to ATAGI. The submission stated that the trial P033 used the subcutaneous method of administration, and was done solely for the purposes of registration in Japan. As the mode of administration is not relevant in Australia, it was excluded from consideration. The submission also excluded 5 other Phase I and II trials.
- 6.6 A claim of non-inferiority of 15vPCV to 13vPCV was made for 12 of the 13 shared serotypes, an increased immune response to serotype 3 and a superior immune response to 13vPCV for the unique serotypes 22F and 33F in the requested paediatric populations.
- 6.7 The approach to establishing comparative effectiveness was based on immunobridging.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
P025	A Phase 3, Multicenter, Randomized, Double-blind, Active-comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Infants (PNEU-PED-EU-1)	Clinical Study Report P025V114 8 Nov 2021
P026	A Phase 3, Multicenter, Randomized, Double-blind, Active-comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 3-dose Regimen of V114 in Healthy Infants (PNEU-PED-EU-2)	Clinical Study Report P026V114 8 Mar 2022
P029 NCT03893448	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)	Clinical Study Report P029V114 1 Sep 2021
P031 NCT03692871	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Tolerability of V114 in Healthy Infants (PNEU-LINK)	Clinical Study Report P031V114 6 Aug 2021
P023	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU-SICKLE)	Clinical Study Report P023V114 1 April 2021
P030 NCT03921424	A Phase 3, Multicenter, 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 Children Infected With Human Immunodeficiency Virus (HIV) (PNEU-WAY PED)	Clinical Study Report P030V114 20 Aug 2021
P024 NCT03885934	Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of V114 in Healthy Infants, Children, and Adolescents (PNEU-PLAN) Bannietis et al, 2021 Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of V114 in Healthy Infants, Children, and Adolescents (PNEU-PLAN)	Clinical Study Report P024V114 27 May 2021 Open Forum Infectious Diseases, 2021. 8: SUPP 1, S678. https://doi.org/10.1093/ofid/ofab466.1367
P027 NCT0360162	A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ With Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION) Bili et al, 2021, A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13™ with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION)	Clinical Study Report P027V114 25 May 2021 Open Forum Infectious Diseases, 2021. 8:SUPPL 1, S684. 10.1093/ofid/ofab466.1376

Source: Table 2.2.2, p 46 of the submission and CSRs for dates.

6.8 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Pivotal trials					
P025	1184	15vPCV vs 13vPCV, doses at 2, 4, 11-15 mo (preterm infants 2, 3, 4, 11-15 mo), R, DB,	Low	Healthy infants; no previous pneumococcal vaccine; preterm allowed	Serotype specific IgG 30 days after 3rd/4dose; % with IgG ≥ 0.35µg/ml 30 days post dose 3 by serotype (dose 4 for preterm infants)

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
P026	1191	15vPCV vs 13vPCV, doses at 3, 5, 12 mo R, DB	Low	Healthy infants, no previous pneumococcal vaccine, <37 wk gestation excluded	Serotype specific IgG 30 days after 3 rd dose; % with IgG \geq 0.35 μ g/ml 30 days post dose 3 by serotype
P029	1720	15vPCV vs 13vPCV, doses 2, 4, 6, 12-15 mo, R, DB	Low	Healthy infants; no previous pneumococcal vaccine; preterm allowed	Serotype specific IgG 30 days after 4 th dose; % with IgG \geq 0.35 μ g/ml 30 days post dose 3 by serotype
P031	2409	15vPCV vs 13vPCV, doses 2, 4, 6, 12-15 mo, R, DB	Low	Healthy infants; no previous pneumococcal vaccine; preterm allowed	Adverse events
Trials in children with risk conditions					
P023	104	15vPCV vs 13vPCV, single dose, R, DB	Low	Sickle Cell Disease, age 5-17 years; no PCV or PnP vaccine within 3 years	Serotype specific IgG 30 days after dose
P030	407	15vPCV vs 13vPCV, single dose then 23vPPV at 8 wk, R, DB	Low	HIV aged 6-17 years; CD4 count \geq 200/ μ L, plasma HIV < 50,000 copies/mL; No previous PCV or previous PCV < 13-valent or partially vaccinated with 13vPCV or PCV vaccination \geq 3 years; No previous pneumococcal vaccine or one pneumococcal vaccination \geq 5 years	Serotype specific IgG 30 days after dose
Catch-up regimen					
P024	606	15vPCV vs 13vPCV, R, DB; 7-11 mo and no previous PCV, 3 doses; 12-23 mo and no previous PCV, 2 doses; 2-17 years and no previous PCV, one dose; 2-17 years and previous PCV one dose > 8 wk after last PCV	Low	Healthy	Serotype specific IgG 30 days after final dose
Interchangeability of 15vPCV and 13vPCV					
P027	900	15vPCV v. 13vPCV, R, DB, 4 doses total as: - All 13vPCV doses - 1 15vPCV + 3 13vPCV doses - 2 15vPCV + 2 13vPCV doses - 3 15vPCV + 1 13vPCV doses - All 15vPCV doses	Low	Healthy infants; no previous PCV if < 2 years; if \geq 2 years no previous PCV or last PCV > 8 wk before study entry	Serotype specific IgG 30 days after 4 th dose

Source: Table 2.3-1, pp49-51 of the submission.

CD4 = cluster of differentiation 4; DB = double blind; HIV = human immunodeficiency virus; IgG = immunoglobulin G; mo = months; PCV = pneumococcal conjugate vaccine; R = randomised; wk = weeks.

- 6.9 Key efficacy outcomes in the trials were immunological responses and included immunoglobulin G (IgG; measured in geometric mean concentration; GMC) at Day 30 post-vaccination as the primary outcome (with the exception of study P031, which had adverse events as the primary outcome) and the level of opsonophagocytic activity (OPA; measured in geometric mean titre, GMT). The comparative efficacy was expressed as the proportion of children with an IgG antibody titre of 0.35 µg/mL or greater, and the ratio between 15vPCV and 13vPCV for OPA GMT and IgG GMC.
- 6.10 OPA GMTs were conducted on a sample of patients only; ATAGI noted that 'Additional data to support a claim of non-inferior OPA would be desirable'.
- 6.11 The specified non-inferiority criteria for the primary outcomes of the trials were that the lower bound of the 2-sided 95% CI of the IgG GMC ratio [15vPCV/13vPCV] be greater than 0.5, and the lower bound of the 95% CI of the proportion of children with IgG \geq 0.35 µg/mL be greater than -10%. The ATAGI advice noted that some authorities recommend a lower bound of the confidence interval for the ratio of 0.67, because of the concern that accepting a lower bound of the 95% CI of 0.5 may allow downward drift of efficacy: 'by approving vaccines based on noninferiority to a prior vaccine, which itself was justified based on non-inferiority, it is possible that subsequent vaccines could be accepted despite having inferior immunogenicity to an originally licensed vaccine.'
- 6.12 The PSCR stated that a bridge-to-bridge approach and non-inferiority margin of 0.5 has been accepted by key regulatory bodies in USA, EU, UK, Canada for 15vPCV in the paediatric population. The PSCR further stated that the PBAC have previously acknowledged that a more stringent non-inferiority threshold creates practical challenges for the conduct of clinical trials and is not suited for multiple antigen vaccines such as PCV15 (referring to paragraph 7.6, 15vPCV PSD, November 2021).
- 6.13 In the trials P025, 026 and 029, there were 4/13, 5/13 and 4/13 serotypes, respectively, for which the lower bound of the 95% CI for the IgG GMC ratio was below 0.67. In 2/4, 3/5 and 3/4 cases, respectively, however, the point estimate of the ratio was itself below 0.67.

Comparative effectiveness

- 6.14 The assessment of comparative effectiveness was based on bridging immunogenicity data, such that immunogenicity for 15vPCV was compared to that of 13vPCV, while 13vPCV immunogenicity was in turn previously compared to that of PCV7, for which there is clinical evidence. A similar approach was previously accepted by the PBAC for the assessment of 15vPCV in adults, although in that case (a) the PBAC based its decision mainly on the equivalence of OPA, not IgG levels; (b) downward drift was a lesser concern because the bridge was only 15vPCV to 13vPCV, and (c) 15vPCV has

been shown to reduce pneumonia in a placebo-controlled randomised trial in older adults.³

- 6.15 The opsonophagocytic activity results for selected serotypes are shown in Table 4. The serotypes selected were those for which the IgG GMC ratios were low, and those specified by the submission as of importance. OPA was very high for both vaccines for all other serotypes. Data for all serotypes are presented in Tables 2.5-7 and 2.5-8, pp109-112 of the submission.

Table 4: Opsonophagocytic activity results for selected serotypes at serotype specific threshold titres

			1 ≥ 1:9	3 ≥ 1:19	5 ≥ 1:27	6A ≥ 1:232	22F ≥ 1:15	33F ≥ 1:20
P025	15vPCV N = 116	Pos./test.	96/101	98/98	102/102	97/98	97/98	96/96
		% (95% CI)	95% (88.8, 98.4)	100% (96.3, 100)	100% (96.4, 100)	99% (94.4, 100)	99% (94.4, 100)	100% (96.2, 100)
	13vPCV N = 122	Pos./test.	106/108	101/103	102/102	99/99	27/96	99/101
		% (95% CI)	98.1% (93.2, 99.8)	98.1% (93.2, 99.8)	100% (96.4, 100)	100% (96.3, 100)	28.1% (19.4, 38.2)	98% (93.0, 99.8)
P026	15vPCV N = 123	Pos./test.	106/108	101/102	108/108	100/100	104/104	105/105
		% (95% CI)	98.1% (93.5, 99.8)	99.0% (94.7, 100)	100% (96.6, 100)	100% (96.4, 100)	100% (96.5, 100)	100% (96.5, 100)
	13vPCV N = 113	Pos./test.	92/94	90/92	95/95	93/93	24/91	94/95
		% (95% CI)	97.9% (92.5, 99.7)	97.8% (92.4, 99.7)	100% (96.2, 100)	100% (96.1, 100)	26.4% (17.7, 36.7)	98.9% (94.3, 100)
P029	15vPCV N = 176	Pos./test.	147/170	169/169	165/171	166/171	169/170	168/170
		% (95% CI)	86.5% (80.4, 91.2)	100% (97.8, 100)	96.5% (92.5, 98.7)	97.1% (93.5, 99.0)	99.4% (96.8, 100)	98.8% (96.5, 99.9)
	13vPCV N = 168	Pos./test.	142/162	158/158	159/162	156/159	9/155	88/155
		% (95% CI)	87.7% (81.6, 92.3)	100% (97.7, 100)	98.1% (94.7, 99.6)	98.1% (94.6, 99.6)	5.8% (2.7, 10.7)	56.8% (48.6, 64.7)

Source: Table 2.5-7, pp109-110 of the submission

N = number of participants randomised; CI = confidence interval; PCV = pneumococcal conjugate vaccine; Pos./test. = positives/tested.

- 6.16 The ratios of OPA GMT were, except for serotype 22F, close to unity. The submission and the trial CSRs do not provide 95% CI for the ratios, but the ATAGI Advice contains a table similar to Table 5 from the PBAC's consideration of 15vPCV for adults (paragraph 6.17, 15vPCV PSD, November 2021) constructed by the review group. This table is reproduced in Table 5 below.

³ Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New Engl J Med* 2015; 372:114-1125.

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Table 5: OPA GMT ratios (15vPCV/13vPCV) at day 30 post final dose (and post dose 3 P029) for shared serotypes

Serotype	P025 2+1, Primary Healthy infants	P026 2+1, Primary Healthy infants	P025 2+1, Toddler Healthy infants	P026 2+1, Toddler Healthy infants	P029 3+1, Primary Healthy infants	P029 3+1, Toddler Healthy infants	Pooled 3+1 Primary Preterm	Pooled 3+1 Toddler Preterm	P023 Sickle cell disease	P030 HIV
1	0.83	1.41	0.83	0.83	0.73	0.61	0.62	0.65	0.96	0.89
3	1.35	1.56	1.06	1.08	1.35	0.85	1.25	0.87	1.13	1.09
4	1.06	1.19	0.70	0.81	0.83	0.73	0.82	0.68	0.67	0.66
5	0.78	1	0.84	0.84	0.76	0.69	0.92	0.78	1.15	1.32
6A	0.74	0.67	0.61	0.71	0.76	0.71	0.64	0.45	1.35	1.20
6B	1.2	1.15	0.77	1.01	0.98	0.79	0.60	0.64	1.70	1.17
7F	0.75	0.88	0.63	0.74	0.68	0.82	0.66	0.56	1.15	0.95
9V	0.86	1.16	0.73	0.80	0.79	0.64	0.83	0.51	1.16	0.82
14	0.74	1.21	1.02	1.46	1.30	1.51	0.87	1.02	0.81	1.03
18C	0.86	0.87	0.94	1.10	0.88	0.74	0.89	0.80	1.70	1.29
19A	0.74	0.72	0.70	0.74	0.60	0.60	0.46	0.40	1.52	0.94
19F	0.92	0.88	0.89	0.85	0.83	0.87	0.69	0.74	1.49	1.13
23F	0.88	0.87	0.57	0.54	0.57	0.45	0.44	0.20	0.90	0.98
Number per serotype	222-226	130-132	196-210	193-202	325-333	161-169	112-117	84-89	~50 15vPCV/ ~20 13vPCV	321-324

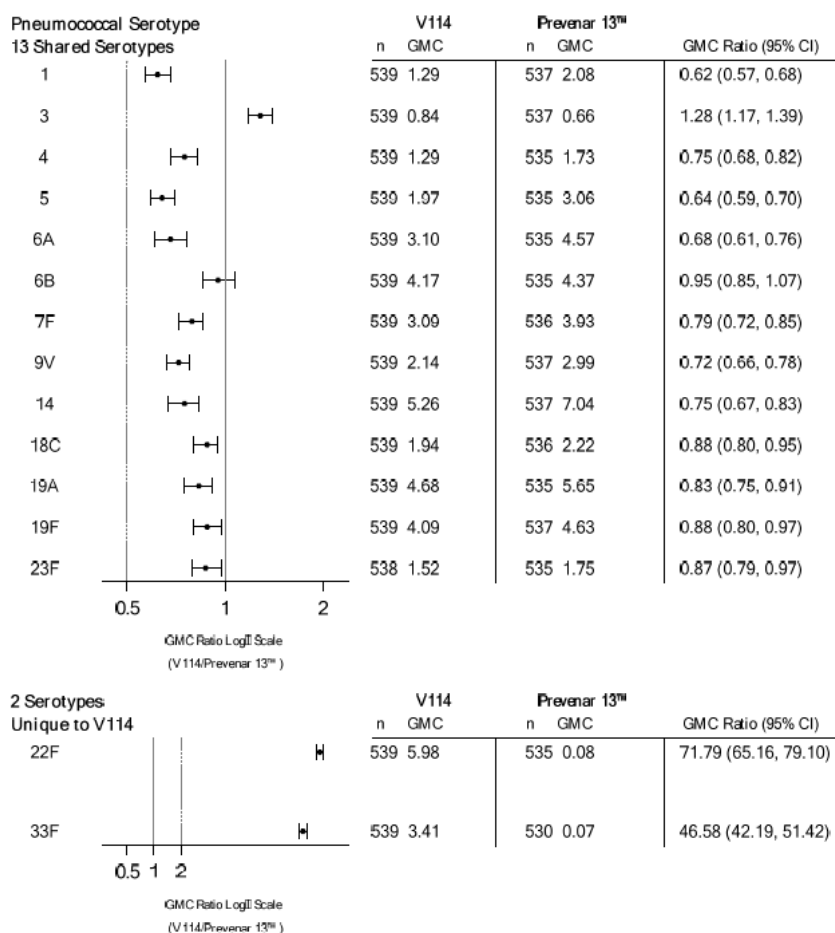
Source: Table 2.4-4, p28, ATAGI Advice.

Ratios of point estimates (15vPCV/13vPCV) were calculated by ATAGI evaluators, as a proxy indication of relative immunogenicity.

Ratio: Orange indicates ratio is >0.5 to ≤ 0.67 , red ≤ 0.5 , favouring 13vPCV. Blue indicates ratio >1.5 , favouring 15vPCV. These levels are used only to indicate ratios that are moderately lower or higher than 1.

- 6.17 The Forest plots for the results for the proportion of participants with IgG ≥ 0.35 $\mu\text{g}/\text{mL}$ at 30 days post toddler dose are shown in Figure 1 (Study P025), Figure 2 (Study P026) and Figure 3 (Study P029).
- 6.18 The ATAGI advice noted that the immune response to concomitant vaccines were not altered with 15vPCV compared to 13vPCV.

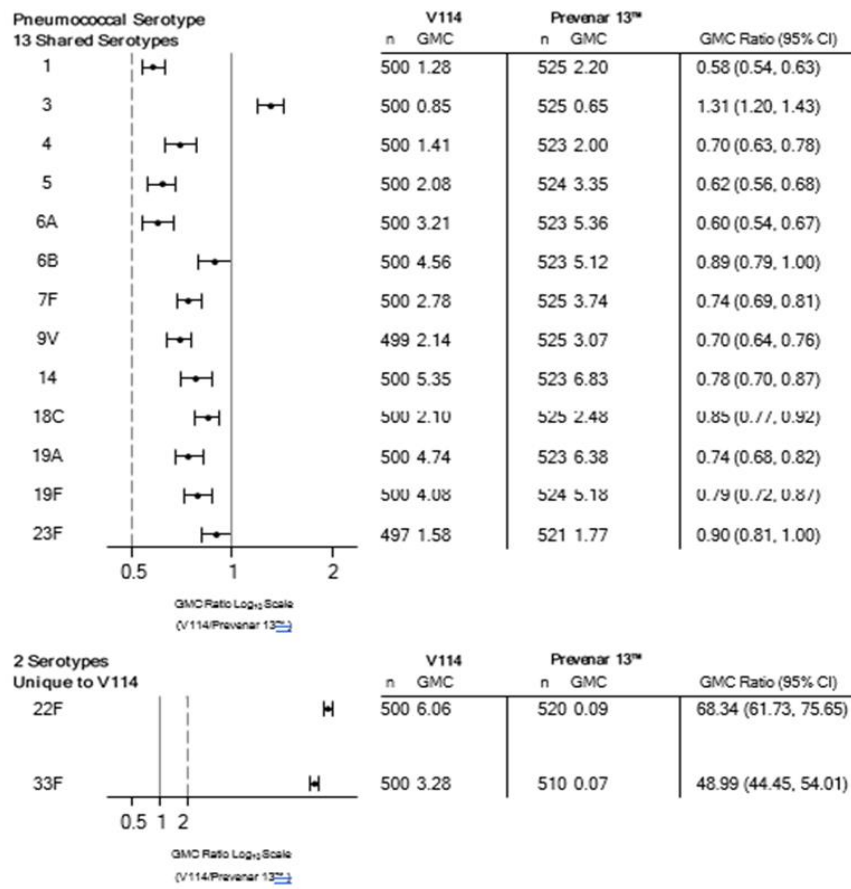
Figure 1: Forest Plot of IgG GMC Ratios at 30 days post dose 3 (per protocol population): Study P025



Source: Figure 14.2-2 P025, CSR

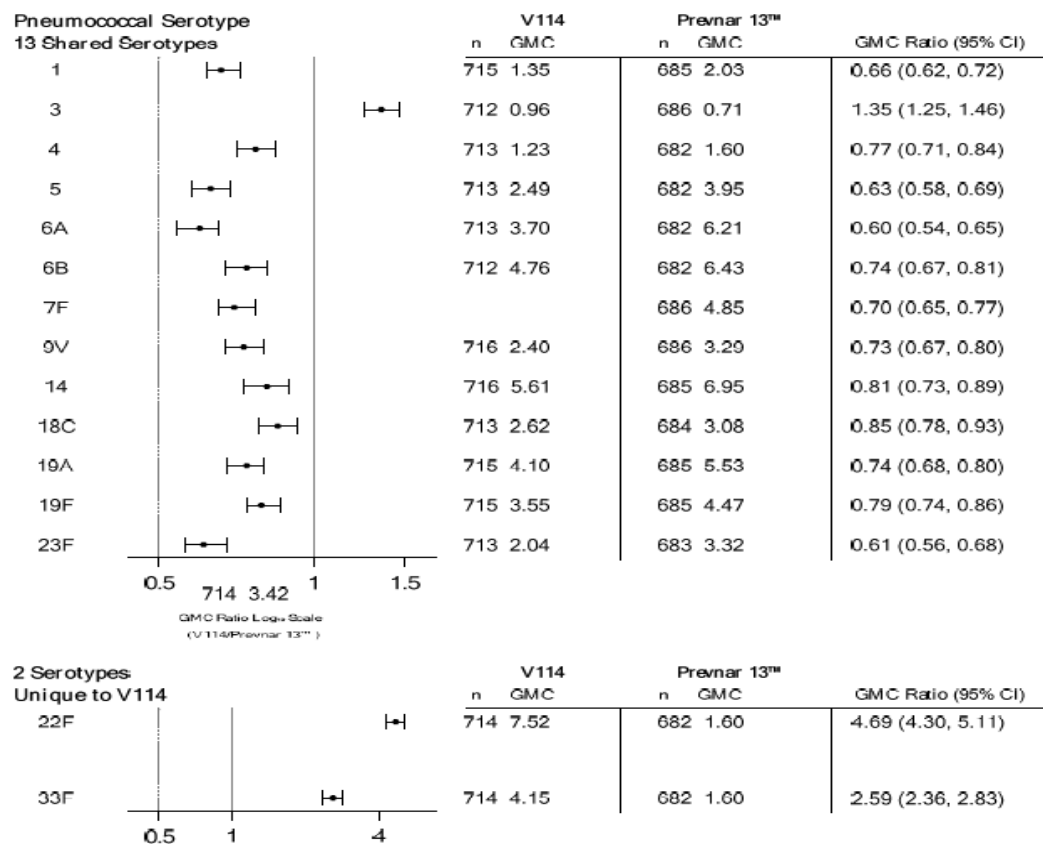
GMC = geometric mean concentration; V114 = 15vPCV; Prevenar = 13vPCV

Figure 2: Forest Plot of IgG GMC Ratios at 30 days post dose 3 (per protocol population) (P026)



Source: Figure 14.2-2 P026, CSR
 GMC = geometric mean concentration; V114 = 15vPCV; Prevenar = 13vPCV

Figure 3: Forest plot of IgG GMCs Ratios at 30 Days post dose 3 and post dose 4 (per protocol population) P029 Post dose 4



Source: Figure 14.2-2, 14.2-7 P029 CSR.

Note: 22F and 33F are compared on the basis of non-inferiority to 13vPCV serotype 4 post dose 3, the lowest responding 13vPCV serotype excluding serotype 3.

GMC = geometric mean concentration; V114 = 15vPCV; Prevnar = 13vPCV.

6.19 The ATAGI advice also noted that there were no key differences between the Australian setting and the trial setting that would influence the immunogenicity results.

Comparative harms

6.20 The adverse event as reported in the trials are summarised in Table 6.

Table 6: Summary of key adverse events in the trials

		Any AE, n (%)	Any injection- site reaction n (%)	Injection site pain n (%)	Moderate or severe injection site pain n (%)	Systemic reactions n (%)	Any SAE n (%)
P025	15vPCV, N = 587	555 (94.5)	427 (72.7)	238 (40.5)	138 (28.5)	536 (91.3)	57 (9.7)
	13vPCV, N = 591	550 (93.1)	398 (67.3)	173 (29.3)	81 (13.8)	526 (89.0)	70 (11.8)
	Difference (%), 15v-13v, (95% CI)	1.5 (-1.3, 4.3)	5.4 (NR)	11.2 (NR)	14.7 (NR)	2.3 (NR)	-2.1 (-5.7, 1.4)
P026	15vPCV, N = 595	591 (99.3)	525 (88.2)	375 (63.0)	236 (39.7)	588 (98.8)	30 (5.0)
	13vPCV, N = 594	592 (99.7)	531 (89.4)	354 (59.6)	187 (31.5)	587 (98.8)	28 (4.7)
	Difference (%), 15v-13v, (95% CI)	-0.3 (-1.4, 0.6)	-1.2 (NR)	3.4 (NR)	8.2 (NR)	0	0.3 (-2.2, 2.8)
P029	15vPCV, N = 858	805 (93.8)	598 (69.7)	427 (49.8)	234 (27.3)	785 (91.5)	88 (10.3)
	13vPCV, N = 855	790 (92.4)	595 (69.6)	401 (46.9)	214 (25.0)	766 (89.6)	81 (9.5)
	Difference (%), 15v-13v, (95% CI)	1.4 (-1.0, 3.9)	0.1 (NR)	2.9 (NR)	2.3 (NR)	1.9 (NR)	0.8 (NR)
P031	15vPCV, N = 1965	1840 (93.6)	1349 (68.7)	843 (42.9)	460 (23.4)	1789 (91.0)	192 (9.8)
	13vPCV, N = 433	404 (93.3)	266 (61.4)	158 (36.5)	72 (16.6)	393 (90.8)	45 (10.4)
	Difference (%), 15v-13v, (95% CI)	0.3 (-2.0, 3.3)	7.3 (NR)	6.4 (NR)	6.8 (NR)	0.2 (NR)	-0.6 (-4.1, 2.3)
P023	15vPCV, N = 69	56 (81.2)	48 (69.6)	42 (60.9)	12 (17.4)	42 (60.9)	13 (18.8)
	13vPCV, N = 34	27 (79.4)	26 (76.5)	23 (67.6)	4 (11.8)	19 (55.9)	8 (23.5)
	Difference (%), 15v-13v, (95% CI)	-1.8 (NR)	-6.9 (NR)	-6.7 (NR)	5.6 (NR)	5.0 (NR)	-4.7 (NR)
P030	15vPCV, N = 203	160 (78.8)	145 (71.4)	112 (55.2)	28 (13.8)	107 (52.7)	1 (0.5)
	13vPCV, N = 204	142 (69.6)	122 (59.8)	110 (53.9)	33 (16.2)	90 (44.1)	1 (0.5)
	Difference (%), 15v-13v, (95% CI)	9.2 (NR)	11.6 (NR)	1.3 (NR)	-2.4 (NR)	8.6 (NR)	0

Source: Table 2.5-33, p156; Table 2.5-34, p157; Table 2.5-37, p160; Table 2.5-38, p161; Table 2.5-39, p164; Table 2.5-41, pp165-6 of the submission.

NR = not reported; PCV = pneumococcal conjugate vaccine; SAE = serious adverse event.

6.21 As noted by ATAGI, there appeared to be differences in the number of reports of moderate to severe injection site pain, which were more frequent with 15vPCV than with the comparator. Statistical comparisons were not reported for this outcome. ATAGI noted that the frequency of moderate to severe injection site pain was already rather high with 13vPCV (mean rate in the six trials = 19.2%), so that it is unclear whether an increase of the order of one third with 15vPCV (mean difference in the six trials = 5.9%) would have important effects on outcomes such as acceptance of later doses.

Benefits/harms

6.22 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.23 The submission claimed non-inferiority of 15vPCV to 13vPCV in 12 of the 13 shared serotypes, an increased immune response to serotype 3, and a superior immune

response to 13vPCV for the unique serotypes 22F and 33F in the requested paediatric populations. The ESC considered that the claim for an increased immune response for specific serotypes is difficult to assess, as it is uncertain whether this would translate to meaningfully improved clinical protection. The ESC and the PBAC agreed with the evaluation that 15vPCV is non-inferior in terms of effectiveness compared to 13vPCV.

- 6.24 The submission described 15vPCV as non-inferior in terms of safety compared to 13vPCV. The evaluation noted that moderate and severe pain at the injection site was more frequent with 15vPCV. While the ESC agreed with the evaluation that the claim of non-inferior safety was not adequately supported, it considered it is uncertain whether this would impact on tolerability/acceptability of the vaccine. In its consideration of the November 2021 submission for adult populations, the ESC considered that the safety of 15vPCV was comparable to that of 13vPCV (paragraph 6.28, 15vPCV PSD, November 2021). The PSCR referred to the ATAGI comment that 'The Sponsor's claim of non-inferiority with respect to safety is likely reasonable'. While the PBAC noted the concerns regarding tolerability, it considered that the claim of noninferior comparative safety was reasonable.

Economic analysis

- 6.25 The submission presented a CMA using 13vPCV as the comparator. The key components and assumption used are shown in Table 7.
- 6.26 The equi-effective doses were estimated as 15vPCV 0.5 mL injection and 13vPCV 0.5 mL injection.

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

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior.
Evidence base	Direct comparison to 13vPCV based on eight phase III comparative trials and two pooled analyses in those aged <18 years of age.
Equi-effective doses	<p><u>Non-Indigenous Infants and Aboriginal and Torres Strait Islander Infants living in ACT, NSW, Vic and Tas (2+1 doses)</u> 1 dose (0.5 mL) 15vPCV at 2, 4, 12 months = 1 dose (0.5 mL) 13vPCV at 2, 4, 12 months.</p> <p><u>Infants with Specified Medical Risk Conditions and Aboriginal and Torres Strait Islander infants living in WA, NT, SA and Qld (3+1 doses)</u> 1 dose (0.5 ml) 15vPCV at 2, 4, 6, 12 months = 1 dose (0.5 mL) 13vPCV at 2, 4, 6, 12 months.</p> <p><u>Children and adolescents between 12 months and 18 years diagnosed with a specified medical risk condition (1 dose)</u> 1 dose (0.5 mL) 15vPCV = 1 dose (0.5 mL) 13vPCV</p> <p><u>Haematopoietic stem cell transplant (HSCT) recipients aged 12 months to <18 years (3 doses)</u> After HSCT, 1 dose (0.5 mL) 15vPCV at 6, 8, 12 months = 1 dose (0.5 mL) 13vPCV at 6, 8, 12 months.</p>
Direct medicine costs	The submission stated that the sponsor would match the nationally negotiated price of 13vPCV in children and infants, once recommended for listing.
Other costs or cost offsets	None

Source: Table 3.1.1, p203 of the submission.

HSCT = haematopoietic stem cell transplant; PCV = pneumococcal conjugate vaccine.

- 6.27 As the nationally negotiated price for 13vPCV is not available, the submission used the publicly available market price for the analysis, \$114.99 per dose. The submission stated that the sponsor would accept the nationally negotiated price of 13vPCV for children and infants. The results of this analysis are shown in Table 8.

Table 8: Results of cost minimisation in the paediatric population

Population	Vaccine	Cost per dose	Total Cost Per Regimen
Non-Indigenous Infants and Aboriginal and Torres Strait Islander Infants living in ACT, NSW, Vic and Tas (2+1 doses)	15vPCV	All doses \$114.99	\$114.99 x 3 = \$344.97
	13vPCV	All doses \$114.99	\$114.99 x 3 = \$344.97
	Cost Difference		\$0.00
Infants with Specified Medical Risk Conditions and Aboriginal and Torres Strait Islander Infants living in WA, NT, SA and Qld (3+1 doses)	15vPCV	All doses \$114.99	\$114.99 x 4 = \$459.96
	13vPCV	All doses \$114.99	\$114.99 x 4 = \$459.96
	Cost Difference		\$0.00
Children and adolescents between 12 months and 18 years newly diagnosed with a specified medical risk condition (1 dose)	15vPCV	\$114.99	\$114.99
	13vPCV	\$114.99	\$114.99
	Cost Difference		\$0.00
Haematopoietic stem cell transplant (HSCT) recipients aged 12 months to <18 years (3 doses)	15vPCV	All doses \$114.99	\$114.99 x 3 = \$344.97
	13vPCV	All doses \$114.99	\$114.99 x 3 = \$344.97
	Cost Difference		\$0.00
Administration costs (MBS item 3)	15vPCV	\$18.20	
	13vPCV	\$18.20	
	Cost difference	\$0.00	

Source: Table 3.4.1, pp204-5 of the submission.

HSCT = haematopoietic stem cell transplant; PCV = pneumococcal conjugate vaccine.

Vaccine cost/patient/course

6.28 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

6.29 This submission was not considered by DUSC.

6.30 The submission used an epidemiological approach to estimate the number of doses required for each population: (1) Non-Indigenous infants and Aboriginal and Torres Strait Islander infants living in ACT, NSW, Vic and Tas; (2) Aboriginal and Torres Strait Islander infants living in NT, Qld, SA and WA and medically at risk infants ≤12 months; (3) medically at-risk 12 months to 18 years; haematopoietic stem cell transplant patients up to 18 years.

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6.31 The submission assumed that as only one PCV has been on the NIP, all 13vPCV doses will be replaced by 15vPCV following a nationally negotiated tender process.

6.32 Data sources are listed in Table 9.

Table 9: Data sources for financial estimates

population	Data source	Vaccine coverage rate	Number of doses	Comment
Non-Indigenous infants and Aboriginal and Torres Strait Islander infants living in ACT, NSW, Vic and Tas	ABS data, forecast 2021-2029	June 2022 immunisation rate for 1 year olds, 94.18%	2+1 per person	Reasonable
Aboriginal and Torres Strait Islander infants living in NT, Qld, SA and WA and medically at risk infants ≤12 months	ABS data, extracted 2013-2020 Incidence rate per 100,000 from various sources	94.18%	3+1 per person	Coverage rate not consistent with Kabir et al, 2021: may be an overestimate. See Para 4.4.
Medically at-risk 12 months to 18 years	Incidence rate per 100,000 from various sources	94.18%	Single dose	May be reasonable
Haematopoietic stem cell transplant patients up to 18 years	Calculated from proportion of population <18 years applied to number of stem cell transplants per year in Australia (n=2,000)	100%	3 doses	Probably reasonable

Source: text pp 207-8 of the submission.

ABS = Australian Bureau of Statistics.

6.33 The estimated total number of doses for the period 2024-2029 is shown in Table 10. The estimated extent of use and financial implications are shown in Table 11.

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Table 10: Estimated number of doses for 15vPCV

	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)
Non-Indigenous babies and Aboriginal and Torres Strait Islander infants born in ACT, NSW, Vic and Tas	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
% uptake 15vPCV - 94.18% June 2022	94.18%	94.18%	94.18%	94.18%	94.18%	94.18%
Population vaccinated with 15vPCV	█ ²	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. of doses of 15vPCV - 3 doses	█ ³	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Aboriginal and Torres Strait Islander infants in SA, WA, Qld and NT and infants with specified medical risk factors	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
% uptake 15vPCV - 94.18% June 2022	94.18%	94.18%	94.18%	94.18%	94.18%	94.18%
Population vaccinated with 15vPCV	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
No. of doses of 15vPCV - 4 doses	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁸	█ ⁸
Children >12 months and adolescents with specified medical risk factors	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
% uptake 15vPCV - 94.18% June 2022	94.18%	94.18%	94.18%	94.18%	94.18%	94.18%
Population vaccinated with 15vPCV	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
No. of doses of 15vPCV - 1 dose	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Haematopoietic stem cell transplant patients	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
% uptake	100%	100%	100%	100%	100%	100%
Population vaccinated with 15vPCV	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
No. of doses of 15vPCV - 3 doses	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Total 15vPCV doses	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁹	█ ⁹

Source: Table 4.2.1, p208-9 of the submission.

15vPCV = 15-valent pneumococcal conjugate vaccine.

The redacted values correspond to the following ranges:

¹ 300,000 to < 400,000

² 200,000 to < 300,000

³ 800,000 to < 900,000

⁴ 10,000 to < 20,000

⁵ 60,000 to < 70,000

⁶ 500 to < 5,000

⁷ 900,000 to < 1,000,000

⁸ 70,000 to < 80,000

⁹ 1,000,000 to < 2,000,000

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of 15vPCV doses						
Non-Indigenous babies and Aboriginal and Torres Strait Islander infants born in ACT, NSW, Vic and Tas	1	4	4	4	4	4
Aboriginal and Torres Strait Islander infants in SA, WA, Qld and NT and infants with specified medical risk factors 4 doses per child)	2	2	2	2	3	3
Children >12 months and adolescents with specified medical risk factors	3	3	3	3	3	3
Haematopoietic stem cell transplant patients	3	3	3	3	3	3
Total	4	4	4	4	9	9
Estimated financial implications of 15vPCV						
Cost to NIP (\$)	5	5	5	5	5	5
Estimated financial implications for other medicines (13vPCV)						
Cost to NIP (\$)	6	6	6	6	6	6
Net financial implications						
Net cost to NIP (\$)	7	7	7	7	7	7

Source: Tables 4.2.1, 4.2.2, 4.3.1, 4.4.1, p208-212 of the submission

NIP = National Immunisation Program; PCV = pneumococcal conjugate vaccine; yrs = years.

The redacted values correspond to the following ranges:

¹ 800,000 to < 900,000

² 60,000 to < 70,000

³ 500 to < 5,000

⁴ 900,000 to < 1,000,000

⁵ \$100 million to < \$200 million

⁶ net cost saving

⁷ \$0 to < \$10 million

⁸ 70,000 to < 80,000

⁹ 1,000,000 to < 2,000,000

6.34 The submission presented a sensitivity analysis reducing the vaccine coverage rate in the medically at risk cohort from 94.18% to 53%, as stated in ATAGI Advice relating to paragraph 6.36, 13vPCV PSD, November 2018. The submission stated that as this assumption affects the 13vPCV and 15vPCV costs equally, there would be no difference in the net cost to government.

Quality Use of Medicines

6.35 The submission stated that the sponsor will provide educational materials, including face to face sessions, to health professionals about 15vPCV with input from peak bodies such as the Royal Australian College of General Practitioners (RACGP), the Australian College of Nursing (AuCN), the Royal Australasian College of Physicians (RACP) and vaccine safety surveillance bodies, for example AusVaxSafety. The submission also stated that the existing 1800 medical information service will be able to provide information about the vaccine.

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 (15vPCV, Vaxneuvance®) be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in the following paediatric populations:

- Non-indigenous infants and Aboriginal and Torres Strait Islander infants living in ACT, NSW, Vic and Tas: 3 doses at ages 2, 4 and 12 months (2+1 doses);
- Infants with specified medical risk conditions and Aboriginal and Torres Strait Islander infants living in WA, NT, SA and Qld: 4 doses at ages 2, 4, 6 and 12 months (3+1 doses);
- Children and adolescents between 12 months and 18 years newly diagnosed with a specified medical risk condition (1 dose);
- Haematopoietic stem cell transplant recipients aged 12 months to <18 years: 3 doses at 6, 8, and 12 months after HSCT (3 doses).

The PBAC's recommendation for listing for the existing NIP paediatric populations was based on, among other matters, its assessment that the cost-effectiveness of 15vPCV would be acceptable if it were cost-minimised against the nominated comparator, 13-valent pneumococcal conjugate vaccine (13vPCV).

7.2 The PBAC considered that nomination of 13vPCV as the main comparator was appropriate.

7.3 The PBAC advised that the equi-effective doses were 1 x 0.5 mL 15vPCV and 1 x 0.5 mL 13vPCV.

7.4 The submission was based on eight phase III trials comparing 15vPCV to 13vPCV. The PBAC noted that the assessment of comparative effectiveness was based on bridging immunogenicity data, such that immunogenicity for 15vPCV was compared to that of 13vPCV, while 13vPCV immunogenicity was in turn previously compared to that of 7vPCV, for which there was clinical evidence. The PBAC considered this appropriate for paediatric populations, noting other advisory bodies such as ATAGI and the TGA had previously accepted this approach.

7.5 The PBAC noted the submission claimed non-inferiority of 15vPCV to 13vPCV in 12 of the 13 shared serotypes, an increased immune response to serotype 3, and a superior immune response to 13vPCV for the unique serotypes 22F and 33F. The PBAC agreed with the ESC that the claim for an increased immune response for specific serotypes is difficult to assess, as it is uncertain whether this would translate to meaningfully improved clinical protection. The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

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- 7.6 While the PBAC noted that moderate and severe pain at the injection site was more frequent with 15vPCV than 13vPCV, it was uncertain whether this would impact on tolerability/acceptability of the vaccine and considered overall that the claim of noninferior comparative safety was reasonable.
- 7.7 The PBAC welcomed input from the Lung Foundation Australia that described a range of benefits that the listing of 15vPCV for paediatric populations on the NIP will have on the Australian population.
- 7.8 The PBAC noted that 15vPCV doses will replace 13vPCV doses and, as the submission stated it would accept a cost-minimisation to the nationally negotiated price of 13vPCV for children and infants, there would be no net cost to government.
- 7.9 The PBAC noted that the submission requested that '(b) a dose of the vaccine may be provided to a child: (i) who is about 6 months of age and is a member of a medical risk group'. The PBAC agreed with the Secretariat's proposal to remove circumstance (b) from the requested listing to be consistent with the 13vPCV listing.
- 7.10 The 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:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Pneumococcal (conjugate, 15-valent)	Vaxneuvance	Injection (0.5mL)	Polysaccharides of the capsular antigens of <i>S. pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM197.	2 or 3 doses of a primary course plus a booster dose or a single supplementary dose
Circumstances Vaccine may be provided: (a) to a child who is: (iv) about 2 months old, and (v) about 4 months old; (vi) in their second year of life; and (c) the vaccine may be provided in the circumstances set out in subsection 7 (1)				

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

MSD is pleased that Vaxneuvance now has PBAC recommendations in paediatrics and adults and will therefore be eligible to enter into the National Immunisation Program. As ATAGI have already noted, there is a clinical need for a new pneumococcal vaccine in Australia. This is especially pertinent given the high burden of Serotype 3 disease in children and adults. It is important therefore that there is opportunity for Vaxneuvance to address this need through the national tendering process.