6.14 PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE 13-VALENT ADSORBED VACCINE, Pre-filled syringe, 0.5 mL, Prevenar 13®, Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission sought a change to the listing for 13vPCV, on the National Immunisation Program (NIP) for use in infants and children *for the prevention of pneumococcal disease.*

1.2 The proposed amendment is a consequence of a review by the Australian Technical Advisory Group on Immunisation (ATAGI), and requests a change to the recommended vaccine schedule on the NIP, with no impact on the number of doses patient groups would receive.

2 Requested NIP listing

2.1 The submission did not propose an amended listing for 13vPCV.

2.2 The PBAC recommended the following changes to the current NIP listing for 13vPCV (Prevenar 13®) in Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of the *National Health (Immunisation Program – Designated Vaccines Determination 2014 (No.1))*:

Table 1: Current listing for Prevenar 13 on the National Immunisation Program with recommended amendments

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Vaccine Pneumococcal (conjugate, 13-valent) **Circumstances** Vaccine may be provided: (a) to a child who is: i. about 2 *months old, and* ii. *about* 4 *months old; and* ~~or~~ ~~6 months old~~ iii. *in their second year of life*; *and* (b) to a child who is about ~~12~~ *6* months of age and is a member of a medical risk group; or (c) Vaccine may be provided in the circumstances set out in subsection 7 (1)	Prevenar 13	Injection (0.5mL)	Polysaccharides of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F - 2.2 µg of each of serotype, and 4.4 µg of serotype 6B	2 or 3 doses of a primary course plus a booster dose or a single supplementary dose

The submission proposed two additional changes to the detail of the circumstances:

1) A tightening of the age for the 12-18 month dose to 12 months for Aboriginal and Torres Strait Islander children in at risk areas.

2) That the recommended catch-up schedules for 13vPCV vaccinations for children who are unvaccinated, or only partially vaccinated, be amended using the same principles as for routine vaccinations. Children who have received 3 previous doses of 13vPCV <12 months of age and present prior to 12 months of age be recommended to receive 1 further dose of 13vPCV at 12 months of age with a minimum interval of 2 months after the previous dose of 13vPCV. This will mean that a small cohort of children would receive a '3+1' schedule in the first year of the change in dosing schedule.

For more detail on the PBAC's view, see section 6 PBAC outcome.

3 Background

3.1 13vPCV is TGA registered 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 and 23F in adults and children aged more than 6 weeks of age.

3.2 13vPCV replaced 7vPCV in the childhood pneumococcal vaccination program under the National Immunisation Program (NIP) in 2011.

3.3 Given the evidence available at the time, the dosing schedule for 7vPCV was maintained for 13vPCV (see table below).

Table 2: Comparison of current and proposed 13vPCV vaccine schedules in children.

Cohort		Schedule in current recommendation	Schedule in proposed recommendation
Children without underlying medical conditions associated with increased risk of IPD	All children in ACT, NSW, TAS or VIC	'3+0' (2, 4 and 6 months)	'2+1' (2, 4 and 12 months)
	Non-Indigenous children in NT, QLD, SA or WA		
	Aboriginal and Torres Strait Islander children in NT, QLD, SA or WA	3+1 (2, 4, 6 and 12–18 months)	3+1 (2, 4, 6 and 12 months)
All children with underlying medical conditions associated with increased risk of IPD (Attachment A of ATAGI's Public Consultant Document)		3+1 (2, 4, 6 and 12 months)	3+1 (2, 4, 6 and 12 months)

Source: ATAGI's Public Consultation Document on the infant pneumococcal vaccination schedule, Table 1; Minor submission Table 1.1, p8.

3.4 The proposed changes in vaccine schedule presented in the minor submission (see table above) were the consequence of a review by ATAGI of invasive pneumococcal data since the childhood pneumococcal schedule moved from a 7vPCV to 13vPCV in 2011. This review identified a continuing increase in cases of invasive pneumococcal disease (IPD) in fully vaccinated children which was much higher than observed in countries giving a booster dose in the second year of life using a 2+1 or 3+1 dosing schedule.

3.5 In addition, ATAGI advised that the indirect impact of the childhood 13vPCV program on IPD in older age groups was considerably less with the current 3+0 schedule.

3.6 The PBAC noted that the proposed changes to the vaccine schedule for 13vPCV aligned with vaccine schedules commonly used in Europe.

For more detail on the PBAC's view, see section 6 PBAC outcome.

4 Current Situation

4.1 The minor submission proposed changes to the childhood pneumococcal vaccination schedule based on recommendations made by ATAGI, so that children currently recommended to receive three infant doses of 13vPCV (at 2, 4 and 6 months of age) would receive two infant doses (at 2 and 4 months of age) followed by a booster dose at 12 months of age ('2+1' schedule) based on a continued and increasing occurrence of breakthrough IPD in children since introduction of the 13vPCV vaccine program in 2011 that is not observed in similar countries. A tightening of the age for

the 12-18 month dose to 12 months for Aboriginal and Torres Strait Islander children in at risk areas was also proposed.

4.2 Based on the recommendations in the ATAGI review, the submission also proposed revision to the recommended catch-up schedules for 13vPCV vaccinations for children who are unvaccinated, or only partially vaccinated, using the same principles as for routine vaccinations. Relevant to this submission, children who have received 3 previous doses of 13vPCV <12 months of age and present prior to 12 months of age will be recommended to receive 1 further dose of 13vPCV at 12 months of age with a minimum interval of 2 months after the previous dose of 13vPCV. This means a small cohort of children would receive a '3+1' schedule in the first year of the change in recommendation, but the total number of 13vPCV doses provided in the year would not change. No other changes to the NIP were proposed.

4.3 ATAGI recommended the proposed changes to the childhood pneumococcal vaccination schedule based on a review of clinical evidence. ATAGI's advice is summarised below.

4.4 ATAGI considered that moving from the current 3+0 schedule to a 2+1 schedule would not change the total number of doses required in the vaccination program, therefore the proposed change would be cost neutral.

4.5 In advice provided to the Department dated 19 June 2017, ATAGI considered:

- That the evidence reviewed demonstrated an urgent need to change the current 13vPCV schedule used for children.
- Of the two alternate schedules reviewed (3+1 and 2+1), the 2+1 schedule (doses at age 2, 4 and 12 months) was considered both effective and implementable given the number of doses required for the vaccination program would remain unchanged and therefore effecting the schedule change would be cost neutral.
- That the current evidence did not indicate a sufficient incremental benefit of the 3+1 schedule to justify the additional cost of an extra 13vPCV dose for all children. However, it was considered important to maintain the current 3+1 schedule used in children with increased risk of IPD (i.e. Indigenous children living in the Northern Territory, Queensland, South Australia, Western Australia and those with specific underlying at risk conditions) to ensure optimum protection during infancy and beyond.

4.6 ATAGI noted a number of points relevant to the implementation of changes to the NIP schedule for 13vPCV in healthy children:

- The existing schedule point of 12 months should be used for the administration of the booster dose of 13vPCV in the 2+1 schedule. The dose of 13vPCV could be administered concomitantly with the other two NIP funded vaccines given at 12 months (the first dose of mumps, measles and rubella vaccine and Haemophilus influenza type b and meningococcal C combined vaccine). The PBAC recalled its

January 2018 recommendation for the NIP listing of meningococcal polysaccharide serogroups A, C, W135 and Y conjugate vaccine (MenACWY-TT) vaccine in noted that the Haemophilus influenza type b vaccine will move to be given at 18 months of age with the quadrivalent meningococcal vaccine given at 12 months of age.

- It will be important to ensure timeliness of the 13vPCV booster dose at age 12 months to avoid any potential compromise to protection by lengthening the window between the 2nd dose and the booster dose. Minor increases in cold chain capacity and storage space requirements will occur due to the addition of an alternative vaccine.
- Education and communication to providers would need to be managed carefully to ensure a smooth transition and minimise any confusion around the new schedule requirements. The change would need to be communicated to the public with the rationale clearly explained.
- Eligibility for the 2+1 schedule would be defined as all children that reach 6 months of age after the schedule change comes into effect. Accordingly a cut off birth date would be specified to identify eligible children. The Australian Immunisation Handbook (AIH) would be updated with revised recommendations for catch up doses in children who present without having completed the age appropriate course of 13vPCV.

For more detail on the PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website.

Summary of evidence

5.3 Below is a summary of the evidence underpinning ATAGI's proposed childhood 13vPCV schedule recommendation:

- Surveillance data demonstrating inferior direct protection provided by the current 3+0 schedule. The breakthrough cases were predominantly due to serotypes 19A and 3, with the majority of cases occurring in children in the second year of life.
- Unpublished data on the incidence of IPD in vaccinated children in the UK and USA for comparison with Australian data.

- Surveillance data demonstrating inferior indirect protection provided by the current 3+0 schedule compared to the UK and USA, particularly in the 2-4 years age group.
- Vaccine effectiveness estimates for 3+0, 3+1 and 2+1 schedules of 13vPCV using comparative data from the UK, USA and Germany.
- Vaccine immunogenicity and colonisation data for various PCV schedules.
- Modelled potential impact of a change in the childhood schedule to 2+1 or 3+1 schedule on the expected number of breakthrough cases.

5.4 On review of the evidence outlined above, ATAGI noted that:

- Regarding cases of breakthrough IPD in children ≥12 months of age, there was a substantial excess in Australian children (rate 3.4 per 100,000) compared to those in the UK (2+1 schedule, rate 0.4 per 100,000) and USA (3+1 schedule, rate 0.6 per 100,000).
- The proportional reductions in incidence of IPD overall in the first five years of 13vPCV use has been substantially less in Australia than those observed in the UK and the USA. Specifically, in the 2–4 years age group, the reduction in IPD due to 13v-non7v types (i.e. serotypes in the 13-valent vaccine but not the previous 7-valent vaccine) observed in Australia has been significantly less than that in the UK and the USA. ATAGI estimated that the introduction of a 2+1 schedule instead of a 3+0 schedule would have led to 269 fewer cases of 13vPCV type IPD in Australians of all ages in the 5th year post introduction, or a reduction of 268 cases with a 3+1 schedule. This was translated to be a reduction of 90 IPD cases in children aged ≥12 months over a 4 year period for a 2+1 or 3+1 schedule.
- The vaccine effectiveness estimates, immunogenicity and colonisation data across the three schedules were consistent with differences observed in changes of IPD incidence between the three schedules.

5.5 The ATAGI advice noted that the second most prevalent serotype present in breakthrough cases or vaccine failures was serotype 3 (26% of breakthrough cases). The data presented in the ATAGI advice noted that for serotype 3 only, the 3+1 schedule showed statistically significant vaccine effectiveness, suggesting that protection against this serotype could be lower with three 13vPCV doses. Serotype 19A is responsible for 58.3% of breakthroughs.

5.6 ATAGI noted that assessment of vaccine effectiveness in Australian children showed a decline in the point estimate of VE of 18% after the first 12 months of completing a 3 dose schedule with a further reduction of about 46% in the next 12 months. Waning based on a 3+1 schedule was not discussed.

5.7 The ATAGI advice included data showing rates of breakthrough cases in the <12 months infant age group compared across the UK, Australia and the USA, where the

UK had higher breakthrough rates (1.14 per 100,000 compared to 0.40 and 0.30 respectively). The UK children had had two primary doses by this age, the Australian and US children had had three primary doses. Similarly, ATAGI modelling found that the introduction of a 2+1 schedule would increase the number of breakthrough cases in children aged 6 to 12 months of age by 11 over four years. The Australian data shows that the majority of breakthrough cases (57%) occur in the second year of life.

5.8 ATAGI advised that immunogenicity data for 13vPCV showed that a 2nd or 3rd infant dose >5 months of age improved immunogenicity in the first year of life, whilst no differences in immunogenicity were observed between the different infant schedules (i.e. 2 or 3 dose) in children receiving a second year of life booster.

5.9 In summary, ATAGI considered that there was clear evidence to suggest that the current 3+0 schedule for 13vPCV in the childhood vaccination program was inferior to 2+1 and 3+1 schedule due to earlier waning of immunity and poorer protection in the toddler age group, and due to indirect impacts on older age groups. ATAGI advised that it was feasible to move to a 2+1 schedule for healthy children and that a booster dose in the 2nd year of life was critical in the 13vPCV schedule to optimise both direct and indirect benefits of the 13vPCV program for all children in Australia.

5.10 The PBAC considered ATAGI's advice and noted the data relating to the revised dosing schedule, including the estimated reduction of IPD with the proposed change to the dosing schedule. The PBAC considered that the evidence provided supported the change to the dosing schedule, given the early waning of immunity, poorer protection in the >2 year old age groups and poorer indirect impacts on older age groups for the current dosing schedule.

5.11 The PBAC advised that the current evidence did not indicate sufficient incremental benefit of the '3+1' schedule to justify the cost of an additional vaccination for all children, but that the additional dose for special groups should continue as is.

5.12 The PBAC noted ATAGI's advice that having a booster dose in the second year of life provided a higher immune response than having additional immunisations prior to the second year of life. The PBAC noted that ATAGI's preferred age for the booster dose was 12 months of age to limit the duration since the 6 month dose, however the PBAC advised that in order to ensure flexibility for NIP scheduling, for the PBAC recommendation, doses would be recommended for dosing within the second year of life, as supported by the data. The PBAC noted that this did not preclude a more specific NIP listing, such as 12 months of age.

5.13 The PBAC noted that the United Kingdom has recently moved to a 1 + 1 schedule, and that it would be useful to consider the outcomes of this schedule in the future.

5.14 The PBAC accepted ATAGI's advice that the proposed dosing schedule is superior in comparative effectiveness, as supported by the data and international experience.

5.15 The PBAC accepted ATAGI's advice that the proposed dosing schedule will be non-inferior in comparative safety.

Estimated NIP usage & financial implications

5.16 The minor submission estimated that the proposed changes to the 13vPCV schedule to be essentially cost-neutral to the NIP. The minor submission estimated a small saving because the volume of doses with the 2+1 schedule would be slightly lower than with the 3+0 schedule.

Table 3: Estimated financial implications to the NIP

		2018	2019	2020	2021	2022	2023
'2+1'schedule							
a.	Number infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b.	Number doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c.	Overall costs	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
'3+0'schedule							
c.	Number infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d.	Number doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
e.	Overall costs	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall costs							
f	Overall cost to NIP	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

(a) Table 4.1 row e. (b)Table 4.2 row f. (c) Row b. x $[redacted] (NIP price of 13vPCV). (d) Table 4.3 row e. (e)Table 4.4 row d. (f) Row e. x $[redacted] (NIP price of 13vPCV). (g) Row c. – row e.
Source: Prevenar utilisation-and-cost-model_Section 4.xlsx – Spreadsheets 3b– Impact –PUB and 4b-displaced PUB

5.17 The minor submission proposed that, in order to improve compliance and accelerate the expected improvements in protection for vaccinated children, the change in schedule should be implemented as quickly as possible. The proposed method of implementation was for vaccination for all children in the eligible cohort to be ceased at the 6 month time point and started at the 12 month time point.

5.18 In this implementation method, a small cohort of children aged between 6 and 12 months at the time of implementation would receive a booster dose of 13vPCV at 12 months of age after receiving their 3 doses of 13vPCV at 2, 4 and 6 months of age. This would only occur over the first 6 months following the change in schedule.

5.19 The total number of doses provided through the NIP would not increase as during that 6 month period, the children who would previously have received their 13vPCV dose at a 6 month vaccination time point would have it delayed by 6 months to the new 12 month vaccination time point. Therefore, the estimation of use would remain the same throughout the 5-year projections.

5.20 The PBAC noted ATAGI's advice and agreed that the change would be cost-neutral to the NIP.

For more detail on the PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended that the circumstances of listing for 13vPCV under the *National Health Act 1953* for the prevention of pneumococcal disease should change. The PBAC recommended that:

- The general dosing schedule move from a '3+0' to a '2+1' schedule with doses provided to children at around 2 and 4 months of age with a booster in the second year of life.
- For children in at risk conditions, the additional dose be provided at 6 months of age to adjust for the booster dose now to be given in the second year of life.
- For Aboriginal and Torres Strait Islander children in at risk areas, the additional dose be provided at 6 months of age to adjust for the booster dose now to be given in the second year of life.

  That the catch-up program should proceed as proposed, but aligned under the same principles as for routine vaccinations. That is, children who have received 3 previous doses of 13vPCV <12 months of age and present prior to 12 months of age are recommended to receive 1 further dose of 13vPCV in their second year of life with a minimum interval of 2 months after the previous dose of 13vPCV.

6.2 The PBAC considered that the change to the dosing schedule of the 13vPCV was cost neutral, and may present a small cost saving, to the NIP as the number of doses provided would not change.

6.3 The PBAC accepted ATAGI's advice regarding the effectiveness of the change to the dosing schedule. The PBAC noted that despite a slight increase in IPD that may occur in infants under 12 months of age with the recommended dosing schedule, that overall the proposed dosing schedule is superior in comparative effectiveness, as supported by the data and international experience, and would decrease IPD rates significantly in the 0-4 year old age group.

6.4 The PBAC accepted ATAGI's advice that the proposed dosing schedule will be non-inferior in comparative safety.

6.5 The PBAC further noted that:

- In progressing listing on the NIP, the AIH would need to be updated and education of healthcare providers provided.
- In order to progress the listing on the NIP, the Office of Health Protection within the Department of Health will need to review and update subsection 7(1) of the National Health (Immunisation Program – Designated Vaccines Determination 2014 (No.1) to facilitate the changed aged for the additional dose for Aboriginal and Torres Strait Islander children in at risk areas to be provided at about 6 months of age. Alternatively the change could be addressed directly in the

listing. The PBAC noted that this submission is not eligible for an Independent Review because it is a request for an amendment to a listing on the NIP, not the PBS.

Outcome:
Recommended

7 Context for Decision

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

8 Sponsor's Comment

Pfizer Australia welcomes the PBAC recommendation to change the listing of 13vPCV from a '3+0' to a '2+1' schedule with doses provided to infants at 2 and 4 months of age with a booster in the second year of life to prevent pneumococcal disease.