

7.06 MULTI-COMPONENT MENINGOCOCCAL GROUP B VACCINE Injection, 0.5mL, Bexsero[®], Novartis Vaccines Diagnostics Pty Ltd

1 Purpose of Application

- 1.1 The minor re-submission sought listing on the National Immunisation Program (NIP) for a four component meningococcal group B (recombinant, adsorbed) vaccine (4CMenB) for the prevention of meningococcal B disease in infants and adolescents.

2 Requested listing

- 2.1 The minor re-submission sought the following new listing on the NIP:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
MENINGOCOCCAL GROUP B (NEISSERIA 1 MENINGITIDIS) VACCINE 1 x 0.5 mL syringe	1	0	\$ [REDACTED]	Bexsero	Novartis Vaccines & Diagnostics
MENINGOCOCCAL GROUP B (NEISSERIA 1 MENINGITIDIS) VACCINE 10 x 0.5 mL syringes	1	0	\$ [REDACTED]	Bexsero	Novartis Vaccines & Diagnostics

- 2.2 The requested price was lower than the previous submission (\$ [REDACTED] per dose).
- 2.3 The minor re-submission also offered [REDACTED] cohort should a vaccination program that includes both infant (with catch-up to 24 months of age) and adolescent (with catch-up to those aged 16 to 19 years) be included on the NIP. This was unchanged from that proposed in the Pre-PBAC response in July 2014.
- 2.4 The minor re-submission stated the following is the preferred vaccination schedule. This was unchanged from the previous submission.

Table 1: Proposed Australian NIP dosage schedule by age for 4CMenB vaccine for the preferred vaccination program (Program #5)

Target Age/age-group (at first dose)	No. of primary doses	Schedule proposed	Booster dose requirement (age)
A) Routine vaccination program			
A1) Infants aged 2 months	3	At age 2,4,6 months	12 months; (15 years*)
A2) Adolescents aged 15 years	2	≥ 1 months apart	Not determined
B) Catch-up vaccination program			
B1) Infants >2–5 months	3	1-2 months apart (may include age 4,6 months)	12 months; (15 years*)
B2) Infants 6–8 months	2	≥ 2 months apart (may include age 6,12 months)	12 or 18 months; (15 years*)
B3) Infants 9–11 months	2	≥ 2 months apart (may include age 12 months)	18 months; (15 years*)
B4) Toddlers 12–below 24 months	2	≥ 2 months apart (may include age 12,18 months)	Not determined; (15 years*)
B5) Adolescents aged 16–19 years	2	≥ 1 months apart	Not determined

* provision of a booster dose (2 shots) is proposed for those who were vaccinated in childhood reaching the adolescent age at which the routine adolescent program targets.

Source: Table 1.1, p2 of the minor submission

- 2.5 The minor re-submission presented the following alternative vaccination schedules to also be considered:

Table 2: Proposed alternative vaccination programs (VP) for inclusion onto the Australian NIP schedule

Alternative Vaccination Programs	Target Age/age-group (at first dose) Vaccination program	Booster dose requirement (age)
#1. Infant only	A1) Infants aged 2 months	12 months; (15 years*)
#2. Infant + toddler catch-up	A1) Infants aged 2 months	12 months; (15 years*)
	B1) Infants >2–5 months	12 months; (15 years*)
	B2) Infants 6–8 months	12 or 18 months; (15 years*)
	B3) Infants 9–11 months	18 months; (15 years*)
#3. Adolescent only	B4) Toddlers 12–below 24 months	Not determined; (15 years*)
	A2) Adolescents aged 15 years	Not determined
#4. Alternate to preferred schedule: Adolescent + catch-up	A2) Adolescents aged 15 years	Not determined
	B5) Adolescents aged 16–19 years	

* provision of a booster dose (2 shots) is proposed for those who were vaccinated in childhood reaching the adolescent age at which the routine adolescent program targets.

Source: Table 1.2, p3 of the minor submission

- 2.6 Alternate vaccination program #1 and #2 are the closest programs to the schedule recommended in the UK of two primary doses at 2 and 4 months of age and one booster dose at 12 months of age (it was unknown whether a catch-up program would also be implemented).
- 2.7 The ATAGI post-submission advice provided at the November 2013 PBAC meeting stated that:
- The first priority of a 4CMenB program should be directed towards an ongoing primary program for infants.
 - The most preferable scenario would be one that includes the ongoing routine program components for infants as well as adolescents. This program is expected to provide direct protective benefit for those in the age groups of highest disease incidence.

- Programs involving the vaccination of infants only, would not cover the secondary peak incidence age group.
- Programs involving the vaccination of adolescents only would not cover infants where the highest disease burden lies.
- Occurrence of severe adverse events or high frequency of significant adverse events in infants may alter the assessment of preferences of these program model scenarios, and post-implementation surveillance of adverse events following 4CMenB would be essential.

2.8 An Australian School Vaccination Register has been announced and will be operational in the 2017 school year. Expanding the existing National Human papillomavirus Vaccine Register to become an 'Australian School Vaccination Register' to allow capture of all adolescent vaccines given through school-based programs. Some individuals in the proposed adolescent catch-up for 4CMenB vaccine cohort may be older than school age and their vaccinations would likely not be entered into this Register.

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

3 Background

- 3.1 4CMenB was TGA registered on 14 August 2013, and is indicated for active immunisation against disease caused by *Neisseria meningitidis* group B strains. It is indicated for vaccination of individuals from 2 months of age and older.
- 3.2 This was the third consideration by the PBAC.
- 3.3 The following table provides a summary of the key differences between the November 2013 and July 2014 submissions and this current minor re-submission, including PBAC comments on the November 2013 and July 2014 submissions.

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Table 3: Summary of the previous submission, what was considered at the PBAC meeting (given Pre-PBAC response) and minor re-submission

	4CMenB, November 2013		4CMenB, July 2014		Current minor re-submission
	Submission	Considered at PBAC meeting	Submission	Considered at PBAC meeting	
Requested NIP listing	The inclusion on the NIP Schedule for prevention of meningococcal B disease in infants and adolescents.		Unchanged		Unchanged
Requested price	\$█ per dose, plus █% discount in the catch-up program.	\$█ per dose.	\$█ per dose, plus █% discount in the catch-up program.	\$█ per dose, plus █% discount in the catch-up program, █.	\$█ per dose, plus █ should the preferred vaccination program be implemented (#5).
Main comparator	No vaccination. PBAC Comment: The PBAC agreed that the nominated comparator was appropriate (item 5.2).		Unchanged		Unchanged
Vaccination programs	#1. Routine infant schedule (four doses at 2, 4, 6 and 12 months); #2. Routine adolescent schedule (two doses at 15 years); #3. Routine infant and adolescent schedules; #4. Routine infant and adolescent schedules with catch-up for older infants and toddlers (two to three doses); #5. Routine infant and adolescent schedules with catch-up for adolescents (two doses); #6. Routine infant and adolescent with catch-up for older infants and toddlers and adolescents.		#1. Routine infant and adolescent with catch-up for older infants and toddlers and adolescents.		#1. Routine infant schedule (four doses at 2, 4, 6 and 12 months); #2. Routine infant schedule with catch-up for older infants and toddlers (two to three doses) (new); #3. Routine adolescent schedule (two doses at 15 years); #4. Routine adolescent with catch-up for adolescents (new); #5. Routine infant and adolescent with catch-up for older infants and toddlers and adolescents.
Clinical evidence	Clinical evidence presented: - Two RCTs comparing 4CMenB to placebo (Studies V72P12 and V72P13), in infants aged 2 months at entry, receiving 3 doses (primary vaccination). A meta-analysis of these studies. Three extension studies: Study V72P12 had one extension phase (E1) and Study V72P13 had two extension phases (E1 and E2). Evidence from Studies V72P12E1 and V72P13E1 were		Unchanged. Updated literature review, but identified no new studies. Additional data on: - Concomitant use of 4CMenB with rotavirus vaccine, based on subgroup analysis of studies V72P12 and V72P13. - Safety data from CDC report on use of 4CMenB among young adults to address two University-based Meningococcal B disease outbreaks in the US. Updated Safety Risk Management Plan.		Unchanged. Updated literature review, but identified no new studies. Additional safety data presented: - summary of routine pharmacovigilance (PV) data from spontaneous reporting within Australia, - Periodic Safety Update Report

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	4CMenB, November 2013		4CMenB, July 2014		Current minor re-submission
	Submission	Considered at PBAC meeting	Submission	Considered at PBAC meeting	
	<p>presented in support of a booster dose at 12 months.</p> <ul style="list-style-type: none"> - One RCT comparing 4CMenB to placebo (Study V72P10), in adolescents 11 to 17 years. One extension study, V72P10E1, to demonstrate persistence of effect. - One RCT that assessed the effect of 4CMenB (2 doses) on the reduction in meningococcal B nasopharyngeal carriage in university students aged 18-24 years in the UK (Study V72_29). 				<p>(PSUR4) covering the period 14th July 2014- 13 Jan 2015;</p> <ul style="list-style-type: none"> - preliminary surveillance report of the vaccination campaign with Bexsero in Saguenay Lac Saint Jean, Quebec, Canada ; - safety data from use of Bexsero in outbreaks at Princeton University and the University of California at Santa Barbara (UCSB) in 2014; - EU Risk Management Plan (RMP) version 5, 11th April 2014; and - Australian Specific Annex to the RMP, 27th June 2014.
Clinical claim	<p>The submission described 4CMenB as superior to non-vaccination in terms of comparative effectiveness, with an acceptable tolerability profile in infants and adolescents.</p> <p>PBAC Comment: There was a limited demonstration of and multiple uncertainties in relation to the clinical effectiveness of the vaccine against the disease when delivered in a vaccination program (item 7.2).</p>	<p>Unchanged.</p> <p>PBAC Comment: ... the clinical claim was highly uncertain because of the likely short persistence of the antibody response, uncertainty about the correlation between antibody responses and protection, the unknown effect on carriage of the bacteria, the overall uncertain long-term protective efficacy against infection and disease, and the unknown influence of projected herd immunity effects on overall disease burden (item 7.6).</p> <p>... the rates of fever in infant participants of the trials receiving the vaccine would indicate that prophylactic paracetamol would be appropriate so that the local transient reactogenicity of 4CMenB would not be different to routine vaccination. However, the PBAC also noted that the impact of, and compliance with, this recommendation is unknown, and that a wider loss of confidence in the National Immunisation Program may arise from concerns about increased rates of fever and convulsions. In the absence of effective prophylaxis, the relatively high frequency of adverse events reported in the</p>	Unchanged.	Unchanged.	

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	4CMenB, November 2013		4CMenB, July 2014		Current minor re-submission
	Submission	Considered at PBAC meeting	Submission	Considered at PBAC meeting	
			trials compared to the relatively low frequency of modelled benefits would suggest a less favourable balance of benefits and harms. From the table summarising the modelled benefits and harms observed in the trials, for every extra death averted over five years, there would be about 100 (272,224/2,500) febrile seizures, and for every case of IMD averted, there would be about 4 (10,532/2,500) febrile seizures. As suggested by ESC, the PBAC also noted that safety in adolescents appears acceptable (item 7.7).		
Economic evaluation	Cost-utility model with an ICER of \$15,000/QALY - \$45,000/QALY for Program #6 versus no vaccination.	Cost-utility model with an ICER of \$45,000/QALY - \$75,000/QALY for Program #6 versus no vaccination. PBAC Comment: The PBAC preferred model had an ICER of \$██████/QALY (item 6.37).	Cost-utility model with an ICER of more than \$200,000 in the base case. PBAC Comment: ... was unacceptably high and was based on uncertain and optimistic assumptions about the extent and duration of effect and herd immunity, noting particularly the ESC and ATAGI doubts about the vaccine's effectiveness against NHBA (one of 4 antigens in the vaccine).	Cost-utility model with an ICER of: Program #5 versus no vaccination: \$105,000/QALY - \$200,000/QALY (preferred program) Program #4 versus no vaccination: \$45,000/QALY - \$75,000/QALY (alternate to preferred program) Program #3 versus no vaccination: \$45,000/QALY - \$75,000/QALY (lowest ICER of the five programs)	
	Base case was based on a dynamic transmission model, which took hSBA outcomes extrapolated for 100 years (from up to 32 months in the trials) and applied utility weights from several published studies, differential annual discount rates of 5% p.a. for costs and 1.5% p.a. for health outcomes, a 50% for vaccine impact on carriage acquisition (herd immunity	A revised base case was presented, with differential annual discount rates of 5% p.a. for costs and 1.5% p.a. for health outcomes, a 12.6% for vaccine impact on carriage acquisition (herd immunity response), and \$██████/dose. PBAC Comment: The PBAC preferred model was based on the above but with	A revised base case was presented, with non-differential annual discount rates of 5% p.a. for costs and health outcomes. Sensitivity analysis on discount rates was also conducted for the following scenarios: 1) differential annual discount rates of 5% p.a. for costs and 1.5% p.a. for health outcomes; 2) stepped annual discount rates of 5% p.a. for costs and health outcomes in years 1 to 20, and 1.5% p.a. for costs and health outcomes thereafter; and 3) stepped and differential annual discount rates of 5% p.a. for costs and health outcomes in years 1 to 20, and 5% for costs and 1.5% p.a. for health outcomes thereafter. Additionally vaccine coverage (75.9%), projected births, deaths, and life expectancy were updated, and costs inflated using the CPI. Only one scenario was presented. The submission also clarified how vaccine	A revised base case was presented, with non-differential annual discount rates of 5% p.a. for costs and health outcomes in years 1 to 30, stepped to 1.5% p.a. for costs and health outcomes in years 31-100, vaccine coverage of 75%, and \$██████ per dose. Five vaccination schedules were presented.	

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	4CMenB, November 2013		4CMenB, July 2014		Current minor re-submission
	Submission	Considered at PBAC meeting	Submission	Considered at PBAC meeting	
	response), and \$█/dose. Six vaccination schedules were presented.	non-differential annual discount rates of 5% for costs and health outcomes (item 6.37).	efficacy and persistence was calculated. PBAC Comment: The PBAC reaffirmed its preference for applying a discount rate of 5% per annum for both costs and outcomes (item 7.9)		
Number of patients	Over 200,000 over 5 years.		Over 200,000 over 5 years.		Unchanged for Program #5.
Estimated cost to the NIP	More than \$100 million over the first 5 years of listing.	More than \$100 million over the first 5 years of listing	More than \$100 million over the first 5 years of listing.		Program #5: More than \$100 million over the first 5 years of listing. Program #4: More than \$100 million over the first 5 years of listing.
Risk-share scheme	A █% price reduction for 4CMenB under the catch-up programs for children and adolescents. Plus continuation of MATS analysis.	A █% price reduction for 4CMenB under the catch-up programs for children and adolescents. Plus conducting the following studies: - Continuation of MATS analysis. - Vaccine registry that enables identification of vaccinated cohorts for █, if necessary. - Carriage study at baseline and post NIP. - Independent research of discounting regarding future health benefits in certain circumstances. Plus suggested that either that regular updates of the	A █% price reduction for 4CMenB under the catch-up programs for children and adolescents. Plus a more detailed MES is proposed, including conducting the following studies: - An observational study of the incidence of IMD at baseline and post NIP (including establishing a vaccine registry and continuation of MATS analysis). - An analytic study to assess vaccine effectiveness in terms of IMD using case-control methods. - An observational study of nasopharyngeal carriage in adolescents at baseline and post NIP - Safety study using regular passive, enhanced and active pharmacovigilance. █, if necessary. PBAC Comments: The PBAC considered that the proposed MES would reduce uncertainty, especially in the context of internationally compatible studies. However, the PBAC noted the methodological reservations expressed by ATAGI and the ESC, particularly that the intermediate protective status of partially immunised participants was not adequately considered in the design of the proposed observational studies. Further, the PBAC acknowledged that if	█ should the preferred vaccination program be implemented (#5) (the █% price reduction for 4CMenB under the catch-up programs for children and adolescents is no longer proposed). No longer proposes a formal MES, but re-confirms that it will conduct the studies as was previously proposed under the MES proposed in the previous major submission.	

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	4CMenB, November 2013		4CMenB, July 2014		Current minor re-submission
	Submission	Considered at PBAC meeting	Submission	Considered at PBAC meeting	
		results of the observational study V72_38OB (using screening methods) be provided to ATAGI, or a similar study be conducted in Australia.	<p>twelve to eighteen months would be needed to extend the vaccination register as required for the MES studies, this would have consequences for the timing of implementing both an NIP listing and the studies. The PBAC concluded by anticipating that, even with highly favourable outcomes reported by all the studies, the reduction in the modelled ICER would be insufficient to address concerns regarding acceptable cost-effectiveness at the current requested price. Overall, the PBAC considered that, although important, the proposed MES was a secondary issue that only warranted further consideration if a price commensurate with an acceptable ICER is proposed to enable a recommendation to list on the NIP in the first place (item 7.11).</p> <p>The PBAC noted the post submission advice from ATAGI and the current lack of unanimous support from states and territories regarding potential implementation of a managed entry scheme for 4CMenB. If expected clinical benefits were not realised and/or the rate of fever-associated side-effects was significant, such that removal of the vaccine from the NIP had to be contemplated, there would be great difficulty associated with such a disinvestment, which may flow on to undermine public confidence in the NIP in general (item 7.12).</p>		
PBAC decision	Reject. There was a limited demonstration of and multiple uncertainties in relation to the clinical effectiveness of the vaccine against the disease when delivered in a vaccination program. In addition, the PBAC concluded that the ICER was unacceptably high and was based on uncertain assumptions about extent and duration of effect and herd immunity (item 7.1 and 7.2).		Reject. There was a limited demonstration of, and multiple uncertainties in relation to, the clinical effectiveness of the vaccine against the disease when delivered in a vaccination program, as well as an unacceptably high and uncertain ICER, including when based on optimistic assumptions about the extent and duration of effect and herd immunity (item 7.1 and 7.2).		

CPI = consumer price index; hSBA= human Serum Bactericidal Assay; ICER = incremental cost-effectiveness ratio; IMD= invasive meningococcal B disease; MATS= Meningococcal Antigen Typing System; MES = Managed Entry Scheme; QALY = quality adjusted life year. Source: Novartis Vaccines & Diagnostics (2013) Pre-PBAC response for multicomponent meningococcal group B vaccine-Bexsero®, item 5.10, PBAC (2013) PBAC Public Summary Document (PSD) November 2013, PBAC (2014) PBAC PSD July 2014 and compiled during the evaluation.

4 Clinical place for the proposed therapy

- 4.1 Invasive meningococcal B disease (IMD) is a rare disease caused by the bacterium *Neisseria meningitidis*. There were 184 cases (0.82 per 100,000) and approximately 11 deaths in 2011, around five of the deaths were in those aged less than five years old. Incidence is bimodal, with 20% of confirmed cases aged less than one year old, 22% aged one to four years old, and the next peak in later teens, with 17% aged 15-19 years old and 9% aged 20 to 24 years old between 1991 and 2011. IMD can also cause meningitis and sepsis, leading to long-term sequelae including: limb amputation, hearing loss, seizures, renal insufficiency, significant neurological deficits and skin scarring. In contrast to the incidence of IMD, asymptomatic carriage of meningococci (all serotypes) is common: from 4.5% in infants to a peak of 23.7% in 19-year olds (Christensen 2010).

5 Comparator

- 5.1 The previous major submission considered by the PBAC in July 2014 nominated no vaccination. This was unchanged in the minor re-submission.
- 5.2 In November 2013 the PBAC agreed that the nominated comparator was appropriate (item 5.2, PBAC PSD, November 2013).

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (14) via the Consumer Comments facility on the PBS website. The majority of comments supported listing of the vaccine due to perceived benefits of community protection, and potential to save lives and eradicate disease, although there was one comment that claimed that the significant financial costs, rarity of disease and absence of evidence demonstrating safety did not support listing of the vaccine.

Clinical trials

- 6.3 As a minor submission, no new clinical trials were presented in the minor re-submission.

Comparative effectiveness

- 6.4 In July 2014 the PBAC reaffirmed its November 2013 conclusion that the vaccine is effective in inducing antibodies against the component antigens of 4CMenB. However, in the context of a population-based intervention against IMD, the

Committee considered the clinical claim was highly uncertain because of the likely short persistence of the antibody response, uncertainty about the correlation between antibody responses and protection, the unknown effect on carriage of the bacteria, the overall uncertain long-term protective efficacy against infection and disease, and the unknown influence of projected herd immunity effects on overall disease burden.

- 6.5 The trial results remained unchanged from the previous major submission considered in July 2014.
- 6.6 The Pre-PBAC response provided observations comparing cases of serogroup B meningococcal disease notified in the Saguenay Lac Saint Jean region of Quebec to the rest of the province.

Comparative harms

- 6.7 In July 2014 the PBAC reaffirmed its November 2013 conclusion that the rates of fever in infant participants of the trials receiving the vaccine would indicate that prophylactic paracetamol would be appropriate so that the local transient reactogenicity of 4CMenB would not be different to routine vaccination. However, the PBAC also noted that the impact of, and compliance with, this recommendation is unknown, and that a wider loss of confidence in the National Immunisation Program may arise from concerns about increased rates of fever and convulsions. In the absence of effective prophylaxis, the relatively high frequency of adverse events reported in the trials compared to the relatively low frequency of modelled benefits would suggest a less favourable balance of benefits and harms. From the table summarising the modelled benefits and harms observed in the trials, for every extra death averted over five years, there would be about 100 (272,224/2,500) febrile seizures, and for every case of IMD averted, there would be about 4 (10,532/2,500) febrile seizures. As suggested by the ESC, the PBAC also noted that safety in adolescents appears acceptable (item 7.7, PBAC PSD, July 2014).
- 6.8 The estimates of comparative harms were unchanged from the previous submission. The minor re-submission also presented additional safety data:
- summary of routine pharmacovigilance (PV) data from spontaneous reporting within Australia;
 - Periodic Safety Update Report (PSUR4) covering the period 14th July 2014- 13 Jan 2015;
 - preliminary surveillance report of the vaccination campaign with Bexsero in Saguenay Lac Saint Jean, Quebec, Canada¹;
 - safety data from use of Bexsero in outbreaks at Princeton University and the University of California at Santa Barbara (UCSB) in 2014;
 - EU Risk Management Plan (RMP) version 5, 11th April 2014; and
 - Australian Specific Annex to the RMP, 27th June 2014.
- 6.9 According to the routine pharmacovigilance (PV) data from spontaneous reporting of adverse events within Australia:

¹ As described in the FDA Pharmacovigilance Plan Review Memo, Jan 23, 2015 (see the [FDA website](#) for a copy of the Review Memo).

- since launch 40,651 doses of Bexsero were distributed to general practice surgeries or pharmacies in Australia; and
- there were three cases requiring hospitalisation – all case hospitalisations were due to fever (ages of reported cases: 6mths, 10mths, <2 years).

The number of infants vaccinated was not reported to allow estimation of the rate of hospitalisations per infant vaccinated.

6.10 According to the preliminary surveillance report of a vaccination campaign in Canada:

- 43,740 individuals between the ages of 2 months and 20 years received an initial dose of the 4CMenB vaccine;
- 93% of children under 2 years of age received fever prophylaxis medication;
- one case of febrile seizure was identified in a 1-year-old child; and
- eight patients required hospitalization, of which 4 had a visit to the emergency room that lasted <12 hours and one was hospitalized outside the observation period (for otitis that began on day 7 with hospitalization on day 10). The three other hospitalizations were attributable to respiratory problems and did not appear related to vaccination.

The number of infants vaccinated was not reported to allow estimation of the rate of febrile seizures or hospitalisations per infant vaccinated.

Clinical claim

6.11 The re-submission described 4CMenB as superior in terms of comparative effectiveness, with an acceptable tolerability profile in infants and adolescents. This was unchanged from the previous submission.

6.12 The PBAC reaffirmed its November 2013 and July 2014 conclusion that the vaccine is effective in inducing antibodies against the component antigens of 4CMenB. However, in the context of a population-based intervention against IMD, the Committee considered the clinical claim was highly uncertain because of the likely short persistence of the antibody response in children, uncertainty about the correlation between antibody responses and protection, the uncertain effect on carriage of the bacteria, the overall uncertain long-term protective efficacy against infection and disease, and the unknown influence of projected herd immunity effects on overall disease burden. These issues were not addressed in the re-submission, although the PBAC acknowledged the limitations of the evidence base.

Economic analysis

6.13 The previous major submission considered by PBAC in July 2014 presented a cost-utility analysis of Program #5 against no vaccination. The PBAC considered the base case ICER of more than \$200,000/QALY to be unacceptably high and was based on uncertain and optimistic assumptions about the extent and duration of effect and herd immunity, noting particularly the ESC and ATAGI doubts about the vaccine's effectiveness against NHBA. The PBAC noted the sensitivity analysis based on a further highly optimistic scenario resulted in an ICER of \$105,000/QALY - \$200,000/QALY, which was also unacceptably high.

- 6.14 The minor re-submission claimed that it re-specified the best estimate of the base case ICER (to which the five vaccination programs were applied) by:
- Reducing the price to \$█ per dose (from \$█ per dose)²;
 - Applying discount rates of 5% p.a. for costs and health outcomes in years 1 to 30, and 1.5% p.a. for costs and health outcomes in years 31-100 (compared to 5% in all time periods in the previous submission); and
 - Reducing vaccine coverage (i.e. proportion of strains covered by 4CMenB) to 75% (from 75.9% in the previous submission).
- 6.15 Additionally, compared to the July 2014 re-submission, several spreadsheets of this re-submission's economic model were substantially changed³ and "initial implementation costs" for (Preferred) Program #5 was -\$█, rather than \$█ in the previous model. These changes to the model were not fully evaluated. The small variation in the ICERs when the re-specified variables, described above, were applied to the July 2014 economic model suggested that the changes to the spreadsheets and "initial implementation costs" in this economic model had a minor impact on the results (see Table 4).
- 6.16 In November 2013 the PBAC recalled that differential discounting rates were not used in the deliberation by the PBAC for recommending other vaccines for the NIP, such as for rotavirus (where immediate benefits were expected) and for HPV (where the major benefits begin to accrue approximately 20 years after immunisation) (Item 7.15, PBAC PSD November 2013). In both cases a constant 5% discount rate was applied for costs and health outcomes in all time periods.
- 6.17 In response, the minor re-submission argued that:
- The cost-effectiveness of most preventative programmes is highly sensitive to discounting because of the long time over which benefits accrue.
 - The benefits of avoiding death and significant disability [due to vaccination with 4CMenB] that last far into the future are discounted significantly in the economic model.
 - There were two rotavirus applications reviewed concurrently. One of these estimated the cost-effectiveness of rotavirus vaccination over a period of 5 years and consequently, discounting had limited impact on its results. The other application used a model with a 100 year time horizon which incorporated deaths due to rotavirus. With only 3 deaths due to rotavirus reported for the period 1998-2003, this claim could be considered uncertain and as very few would be prevented, the impact of discounting was low.
 - The benefits of HPV vaccination are impacted differently by discounting due to their epidemiology, with genital warts occurring earlier, and hence sooner after vaccination, than cervical cancer which occurs later in life. Discounting has limited impact on the value estimation of reduction in genital warts but does impact the value estimation of prevention of cervical cancer. However, the impact of HPV vaccination on cervical cancer prevention could be considered

² It is unclear whether the free vaccine to half of the adolescent catch-up cohort was included with regards to Program #5.

³ For example, additional columns Z:AM in sheet "Start" columns Z:AM, additional rows and check boxes in sheets "Vaccine inputs_St1" etc, additional input boxes in "Acute Care & Sequelae" and additional data in sheet "Output Summary".

uncertain due to potential changes in cervical screening practices following vaccination. If cervical screening frequency was significantly reduced in frequency following vaccination there could be potential harmful consequences (Gardasil public summary document, 2006).

- Thus, submission argued that discounting applied to the HPV vaccine impacted an uncertain outcome compared to the more certain impact resulting from meningococcal B vaccination. The submission therefore claimed it is justifiable to apply a different discount methodology to the meningococcal B vaccination program, with 5% costs/5% outcome up to 30 years, and 1.5% costs/1.5% outcome from years 31 onwards.

6.18 In the new base case presented in the submission, Program #3 resulted in the lowest ICER of \$45,000/QALY - \$75,000/QALY gained. The preferred vaccination program, Program #5, resulted in an ICER of \$105,000/QALY - \$200,000/QALY gained. The alternate to the preferred, Program #4 resulted in an ICER of \$45,000/QALY - \$75,000/QALY gained.

Table 4: Results of economic evaluation

	Incremental costs versus no vaccination, \$	Incremental outcome versus no vaccination	ICER versus no vaccination	ICER versus no vaccination using July 2014 model
Program #1	\$ [redacted]			
Cases averted		[redacted]	\$ [redacted]	
Deaths averted		[redacted]	\$ [redacted]	
Life years gained		[redacted]	\$ [redacted]	
QALYG		[redacted]	\$ [redacted]	\$ [redacted]
Program #2	\$ [redacted]			
Cases averted		[redacted]	\$ [redacted]	
Deaths averted		[redacted]	\$ [redacted]	
Life years gained		[redacted]	\$ [redacted]	
QALYG		[redacted]	\$ [redacted]	\$ [redacted]
Program #3	\$ [redacted]			
Cases averted		[redacted]	\$ [redacted]	
Deaths averted		[redacted]	\$ [redacted]	
Life years gained		[redacted]	\$ [redacted]	
QALYG		[redacted]	\$ [redacted]	\$ [redacted]
Program #4	\$ [redacted]			
Cases averted		[redacted]	\$ [redacted]	
Deaths averted		[redacted]	\$ [redacted]	
Life years gained		[redacted]	\$ [redacted]	
QALYG		[redacted]	\$ [redacted]	\$ [redacted]
Program #5 (preferred)	\$ [redacted]			
Cases averted		[redacted]	\$ [redacted]	
Deaths averted		[redacted]	\$ [redacted]	
Life years gained		[redacted]	\$ [redacted]	
QALYG		[redacted]	\$ [redacted]	\$ [redacted]

ICER, incremental cost-effectiveness ratio; QALYG, quality adjusted life years gained
 Source: Table 9.6, p31 of the minor re-submission.

6.19 The minor re-submission presented sensitivity analyses of the results to the discount rate and assumed herd effect (i.e. vaccine impact on nasopharyngeal carriage of meningococci).

Table 5: Sensitivity analyses

	ICER versus no vaccination (Cost per QALYG)	
Discounting (0%/0% - 5%/5%costs/outcomes)		
Program 1	\$	/ \$
Program 2	\$	/ \$
Program 3	\$	/ \$
Program 4	\$	/ \$
Program 5	\$	/ \$
Herd Effect ^a (0 - 67% herd)		
Program 1	\$	/ \$
Program 2	\$	/ \$
Program 3	\$	/ \$
Program 4	\$	/ \$
Program 5	\$	/ \$

^a a vaccine impact on nasopharyngeal carriage of meningococci

ICER, incremental cost-effectiveness ratio; QALYG, quality adjusted life years gained

Source: Table 9.7, p32 of the minor re-submission.

- 6.20 The model assumed that a herd effect of █.█%, based on Study V72_29. The reason for choosing the upper limit of █% herd immunity in the sensitivity analysis was not provided in the re-submission. This value is similar to the value of 66%, the reduction in nasopharyngeal carriage of meningococcal C across the UK at one year post the introduction of vaccination (Maiden & Stuart (2002)), which was relied upon for deriving the herd immunity applied in the economic model in the original November 2013 submission. The ATAGI and the PBAC considered that it was inappropriate to extrapolate data regarding meningococcal C conjugate vaccines to 4CMenB. Sensitivity analysis in the July 2014 re-submission included a highly optimistic scenario. In this highly optimistic scenario, the assumption for herd immunity was 50%.
- 6.21 The ICER of Program #3 increased to \$105,000/QALY - \$200,000/QALY and the ICER of Program #5 increased to more than \$200,000/QALY gained when a discount rate of 5% per annum for both costs and outcomes were applied in all time periods.
- 6.22 The PBAC reaffirmed the Committee's preference for a discount rate of 5% per annum for both costs and outcomes applied over the time horizon of the model. The PBAC considered:
- there is no intrinsic reason to treat the costs and health benefits of this intervention differently from any other intervention. The benefit of preventing meningococcal infection is saving lives and preventing future morbidity/mortality for individuals vaccinated now (and into the future). This is comparable to the benefit of preventing morbidity and mortality for other population preventative interventions including lipid-lowering and anti-hypertensive drugs and other vaccines.
 - that the arguments presented in the submission with respect to rotavirus and HPV vaccination do not negate the rationale for applying a consistent rate of time preference to costs and outcomes and across the time horizon, given that the opportunity cost of investing in this program is forgone investment in other health programs
 - that the phrase 'the more certain impact resulting from meningococcal B vaccination' in justifying the application of a stepped discounting method

differed from the view of the PBAC in July 2014, where the Committee considered that the clinical claim was highly uncertain.

- 6.23 The PBAC noted in this submission that a consequence of the methodology used to apply stepped discounting was that the value of benefits and costs in year 31 and beyond implausibly increased to a higher value than in year 30, because of the way the lower rate was applied in the model. This favours the vaccine in the model. The PBAC considered if a method of stepped discounting was applied to a model, that upon application of the lower discounting rate, the reduction of the cost and benefits should commence from the last value when the 5% rate was applied.
- 6.24 The PBAC noted that the submission had not addressed the previous concerns of the PBAC in regards to the model, namely uncertain and optimistic assumptions about the extent and duration of effect and herd immunity. The PBAC considered that none of the program options were cost-effective as presented in the submission.
- 6.25 In reaffirming the preferred constant discount rate of 5% for both costs and outcomes, the PBAC recalled at the July 2014 meeting that the Committee considered that before NIP listing could be reconsidered, there would have to be a proposal for a price that produces an acceptable ICER as a basis for a PBAC recommendation to list. At the July 2014 meeting, the PBAC agreed with the ESC that a reduction in price of the vaccine to align the ICER at no greater than the previous submission (i.e. \$ [REDACTED] /QALY) was likely to be the only available option for further PBAC consideration.
- 6.26 **Drug cost/patient/course:** \$ [REDACTED] per dose for routine vaccination. The number of vaccinations received depends on the age of the individual. If Program #5 is listed on the NIP, a child born after listing would receive six doses in total, four doses in infancy and two doses in adolescence.

Estimated PBS usage & financial implications

- 6.27 The minor re-submission estimated a net cost to the NIP of \$30 – \$60 million and a net cost to Government of \$60 – \$100 million in Year 5 of listing, with a total net cost to the NIP of more than \$100 million over the first 5 years of listing for Program #5 ([REDACTED]). This is summarised in the table below as well as the expected number of individuals vaccinated.
- 6.28 The minor re-submission also estimated a net cost to the NIP of \$10 - \$20 million and a net cost to Government of \$10 – 20 million in Year 5 of listing, with a total net cost to the NIP of more than \$100 million over the first 5 years of listing for the adolescent only (with catch up) Program #4 ([REDACTED]). This is summarised in the table below as well as the expected number of individuals vaccinated.
- 6.29 The minor re-submission did not estimate the net cost to the NIP for Program #3.

Table 6: Net cost of drug to the Australian Government (one year catch up)

Total cost	Year 1	Year 2	Year 3	Year 4	Year 5
Program #5 (preferred) ^{a,b}					
Individuals likely to be vaccinated					
Total vaccinations					
Total cost of vaccination (dispensed/supplied)	\$	\$	\$	\$	\$
Total net cost	\$	\$	\$	\$	\$
Implementation in schools	\$	\$	\$	\$	\$
Additional general practitioner visitation	\$	\$0	\$0	\$0	\$0
Overall net cost to Government Health Budget of listing drug	\$	\$	\$	\$	\$
Program #4 (alternate) ^b					
Individuals likely to be vaccinated					
Total vaccinations					
Total cost of vaccination (dispensed/supplied)	\$	\$	\$	\$	\$
Total net cost	\$	\$	\$	\$	\$
Implementation in schools	\$	\$	\$	\$	\$
Additional general practitioner visitation	\$	\$0	\$0	\$0	\$0
Overall net cost to Government Health Budget of listing drug	\$	\$	\$	\$	\$

Notes: a Assumes

b catch-up occurs over one year.

Source: Table 10.3 and Table 10.4, p36-7 of the minor re-submission and Attach 5 – Budget Impact Model.xls, Sheet "Epidemiology and Patient Numbers".

The redacted table above shows that the estimated use and financial implications of 4CMenB to the health budget for the prevention of meningococcal B disease in infants and adolescents. For Program #5 and Program #4 the estimated number of vaccinations is over 200,000 per year. The overall net cost is more than \$100 million in the first year for Program #5 and \$60 - \$100 million for the rest of the first five years of listing. The overall net cost is \$60 - \$100 million in the first year for Program #4 and \$10 - \$20 million for the rest of the first five years of listing.

6.30 The minor re-submission no longer proposed a formal Managed Entry Scheme, but re-confirmed that the sponsor would conduct the studies as was previously proposed under the Managed Entry Scheme proposed in the previous major submission. In particular, the following studies would be conducted:

- A population wide observational study of the change in the incidence of IMD from a pre-vaccination period to a post-vaccination period, including continuation of MATS analysis (observational study protocol V72_53OB).
- A vaccine effectiveness analytic study of 4CMenB in preventing IMD, including establishing a vaccine registry (observational study protocol V72_53OB). The impact of the recently announced Australian School Vaccination Register (to be operational in the 2017 school year) on this proposed study is unknown.
- A nasopharyngeal carriage survey of carriage of Neisseria meningitidis before and after the introduction of 4CMenB into the NIP (observational study protocol V72_73OB).
- A safety surveillance study, consisting of regular passive, enhanced and active pharmacovigilance.

- 6.31 The minor re-submission re-confirmed the sponsor's financial commitments to these studies.

Figure 1: Financial commitments for studies

[THIS FIGURE HAS BEEN REDACTED]

- 6.32 In July 2014 the PBAC considered that the proposed MES would reduce uncertainty, especially in the context of internationally compatible studies. However, the PBAC noted the methodological reservations expressed by ATAGI and the ESC, particularly that the intermediate protective status of partially immunised participants was not adequately considered in the design of the proposed observational studies. Further, the PBAC acknowledged that if twelve to eighteen months would be needed to extend the vaccination register as required for the MES studies, this would have consequences for the timing of implementing both an NIP listing and the studies. The PBAC concluded by anticipating that, even with highly favourable outcomes reported by all the studies, the reduction in the modelled ICER would be insufficient to address concerns regarding acceptable cost-effectiveness at the current requested price (Item 7.11, PBAC PSD, July 2014).
- 6.33 In July 2014 the PBAC also noted the post submission advice from ATAGI and the current lack of unanimous support from states and territories regarding potential implementation of a managed entry scheme for 4CMenB. If expected clinical benefits were not realised and/or the rate of fever-associated side-effects was significant, such that removal of the vaccine from the NIP had to be contemplated, there would be great difficulty associated with such a disinvestment, which may flow on to undermine public confidence in the NIP in general (Item 7.12, PBAC PSD, July 2014).

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

7 PBAC Outcome

- 7.1 The PBAC rejected the re-submission requesting listing of the 4CMenB vaccine on the National Immunisation Program Schedule for the prevention of meningococcal B disease in infants and adolescents. The basis of the rejection was that the re-submission did not address multiple uncertainties in relation to the clinical effectiveness of the vaccine against the disease when delivered in a vaccination program, that the optimistic assumptions about the extent and duration of effect and herd immunity raised by the PBAC in previous consideration of this vaccine were not addressed, and the unacceptably high and uncertain ICER, presented in the re-submission.
- 7.2 The PBAC noted that the proposed vaccination program of routine infant and adolescent with catch-up for older infants and toddlers and adolescents (program 5) was consistent with the November 2013 and July 2014 submissions. This minor re-submission proposed four other potential programs, including routine adolescent with catch-up for adolescents. The PBAC noted the advice from ATAGI on this item. ATAGI re-iterated that the optimal configuration of a 4CMenB program should include an ongoing primary program for infants and young children in addition to

adolescents. For an adolescent-only program, ATAGI supported the inclusion of a catch-up component that incorporates older adolescents at ages above that targeted for the routine ongoing primary program (aged 16–19 years), on the basis of expected direct benefit and for equity of access to the vaccine for this age group of higher incidence, noting potential challenges in implementation.

- 7.3 As previously agreed, the nominated comparator of no vaccination was considered appropriate.
- 7.4 The PBAC noted the additional safety data provided in the re-submission and that ATAGI had not identified any new safety concerns regarding the use of 4CMenB in adolescents as the vaccine is used in Australia and other countries. The PBAC recalled from the July 2014 consideration that the rates of fever in infant participants of the trials receiving the vaccine would indicate that prophylactic paracetamol would be appropriate so that the local transient reactogenicity of 4CMenB would not be different to routine vaccination. However, the PBAC also noted that the impact of, and compliance with, this recommendation is unknown. For this consideration, the PBAC noted the data from Canada provided in the submission and in the ATAGI advice, where the use of antipyretic prophylaxis varied by vaccination age group, including 51% (12–20 year olds) to 93% (children under 2 years of age). Further, the PBAC noted the rate of febrile seizures or hospitalisations per infant vaccinated could not be estimated from the submission as the number of infants vaccinated was not reported with the number of febrile seizures or hospitalisations presented in the re-submission. The impact or compliance with this recommendation may not be an issue for an adolescent only program, since, as previously noted by the PBAC, safety in adolescents appears acceptable.
- 7.5 The PBAC reaffirmed its November 2013 and July 2014 conclusion that the vaccine is effective in inducing antibodies against the component antigens of 4CMenB. However, in the context of a population-based intervention against IMD, the Committee considered the clinical claim was highly uncertain because of the likely short persistence of the antibody response in children, uncertainty about the correlation between antibody responses and protection, the uncertain effect on carriage of the bacteria, the overall uncertain long-term protective efficacy against infection and disease, and the unknown influence of projected herd immunity effects on overall disease burden. These issues were not addressed in the re-submission, although the PBAC acknowledged the limitations of the evidence base.
- 7.6 The PBAC noted that the changes to the economic model compared to previous submissions had not been evaluated but noted that there were only small ICER changes in this re-submission compared to updated assumptions in the model presented in the July 2014 re-submission. The PBAC recalled that the model was based on uncertain and optimistic assumptions about the extent and duration of effect and herd immunity. The PBAC also noted the ICER remains highly sensitive to the discount rates applied to costs and outcomes and reaffirmed the Committee's preference of annual discount rates of 5% p.a. for costs and health outcomes. The PBAC concluded that the re-submission's base case ICER of more than \$100,000/QALY for the vaccination program of infants and adolescents was unacceptably high. The PBAC noted of the 5 proposed programs, Program 3 (adolescents only) resulted in the lowest ICER of \$45,000/QALY - \$75,000/QALY, but even this ICER was not acceptable and likely underestimated given the use of

stepped discounting rates, and the apparent inconsistent benefit and cost values over time by the application of these stepped discounting rates.

- 7.7 The PBAC noted that the ATAGI's preferred program would include an ongoing primary program for infants and young children in addition to adolescents. The ATAGI advice stated that if such a universal program is not deemed cost-effective, ATAGI would support a program that targets population groups at higher risk of meningococcal B infection. The PBAC noted that this advice reiterated the view of ATAGI at the time of the November 2013 submission, where it was noted that there is a higher IMD burden in the Aboriginal and Torres Strait Islander population, particularly in children under 5 years of age, where confirmed cases were 3.8 times higher than their non-Indigenous counterparts for 2006-2011. The PBAC noted that this re-submission and previous submissions had not considered the clinical benefit or cost-effectiveness of targeting the vaccine to any high-risk population.
- 7.8 The PBAC noted the consumer comments on this item and agreed with the ATAGI that there is a clinical need for vaccination against meningococcal B disease. The PBAC agreed with ATAGI that if a program only targeted at adolescents was considered, it should include a catch-up component that incorporates older adolescents (aged 16-19 years).
- 7.9 The PBAC considered that any re-submission should be a major submission, so that the economic model could be fully evaluated.
- 7.10 The ATAGI advice outlined issues with the implementation of a program for 15-19 year olds, including:
- Additional service delivery resources would be required, as the proposed program would target adolescent age cohorts who are older than those currently targeted for the school-based vaccination program
 - Special provisions need to be made to enable delivery of the vaccine doses through alternate providers especially in primary care, such as general practitioners or clinics, to adolescents who do not attend school.
 - Based on previous experience of vaccination programmes, there is likely to be a trend of lower vaccine uptake with increasing age/school year with regard to the catch-up component of the program,
 - Accurate capture of vaccine uptake data will present challenges, as adolescents may receive the vaccine through a school-based program or through a primary care provider (or a combination of the two). This could lead to data collection in different registers that will necessitate cross linkage or transfer of records. ATAGI reiterates that accurate recording of vaccine uptake is essential for implementing a 4CMenB program on the NIP.

The PBAC considered that these issues should be explored in any future submission.

- 7.11 The PBAC noted the minor re-submission re-confirmed the sponsor's commitment to undertake post-NIP listing studies proposed in the July 2014 re-submission. The PBAC considered that a mechanism to monitor and report on the efficacy and safety of the vaccine in Australia would provide confidence to the Committee for the listing of 4CMenB on the NIP. This would require a financial commitment from the sponsor. In acknowledging the limitations of the evidence base, the PBAC considered that listing 4CMenB vaccine on the NIP would place considerable risk on the

Commonwealth, and there should be a risk sharing agreement between the Sponsor and the Commonwealth to address these uncertainties.

- 7.12 The PBAC noted that this submission is not eligible for an Independent Review, which is only applicable for submissions requesting PBS listing.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

GSK is disappointed with the PBACs decision. GSK believes that the PBAC's evaluation criteria (including a comparatively higher discount rate in the economic evaluation) have significantly undervalued the benefits of vaccination with 4CMenB compared with another major health technology review agency which has reimbursed the vaccine from September 2015.

GSK notes the advice from the Government's key clinical advisors on immunisation, the Australian Technical Advisory Group on Immunisation (ATAGI): that Meningococcal B vaccine is recommended for infants and young children under two years old and adolescents aged 15-19 years.

GSK believes that the application of the PBAC's current HTA evaluation criteria will prohibit the adoption of a vaccine that prevents a rare and unpredictable life threatening disease, with devastating impact in children, adolescents and their families. To this end, GSK supports the PBAC Guidelines review.