

## 7.05 MULTICOMPONENT MENINGOCOCCAL GROUP B VACCINE, Injection 0.5 mL, Bexsero<sup>®</sup>, GlaxoSmithKline Australia Pty Ltd.

### 1 Purpose of Application

- 1.1 The resubmission requested listing on the National Immunisation Program (NIP) for multicomponent meningococcal group B vaccine (4CMenB) for active immunisation against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* group B strains, in individuals from 2 month of age and older. Previous submissions for 4CMenB included a major submission in November 2013, major resubmission in July 2014 and a minor resubmission in July 2015.
- 1.2 The resubmission requested a listing based on cost-effectiveness compared with no vaccine. The key components of the resubmission are presented in Table 1.

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

Component	Description
Population	All infants/toddlers and adolescents for the prevention of IMD caused by <i>Neisseria meningitidis</i> .
Intervention	4CMenB vaccine suspension for injection 0.5mL pre-filled syringe. There are four vaccine antigens NHBA, NadA, fHbp and OMV. The proposed additions to the NIP Schedule as follows: Infants: routine doses at 2, 4 and 12 months (2 +1). Adolescents: routine vaccination in school year 10, two doses ≥ 8 weeks apart. <u>Catch-up schedule</u> Infants and toddlers: a catch-up program aged < 2 years. Aboriginal and Torres Strait Islander: a catch-up program for children / adolescents aged < 20 years. Medical high risk groups: age appropriate dosing for the population as defined by The Australian Immunisation Handbook.
Comparator	No vaccination.
Outcomes	Vaccine impact and vaccine effectiveness. Reactivity and adverse events. Immunogenicity for persistence over longer-term follow-up. Cross-protection against gonorrhoea caused by related bacteria <i>Neisseria gonorrhoea</i> .
Clinical claim	In infants, children and adolescents, 4CMenB is more effective than no Men B vaccination in preventing IMD. In adolescents, 4CMenB is more effective than no Men B vaccination in preventing gonorrhoea.

Abbreviations: 4CMenB= multicomponent meningococcal group B vaccine; ATAGI= Australian Technical Advisory Group on Immunisation; fHbp= factor H binding protein; IMD = invasive meningococcal disease; Men B= Meningococcal B; NadA= Neisseria Adhesin A; NHBA= Neisseria Heparin Binding Antigen; OMV= Outer Membrane Vesicles;

Source: Table 1.1, p.35 of the resubmission.

## 2 Requested listing

2.1 The proposed listing was consistent with ATAGI advice (ATAGI pre-submission advice, June 2019) and the product information (PI) (4CMenB PI, p. 2). The requested restriction is summarised in Table 2.

**Table 2: Essential elements of the requested listing**

Name, restriction, manner of administration, form	Nationally negotiated price	Proprietary name and manufacturer
Multicomponent meningococcal group B vaccine (4CMenB), 1 x 0.5 mL syringe	\$■	Bexsero®, GSK
National Immunisation Program		
<ul style="list-style-type: none"> <li>• Two primary doses at 2 and 4 months and a booster dose at 12 months for infants aged 2 months</li> <li>• Two primary doses ≥ 1 month apart for adolescents aged 15 years (School Year 10)</li> <li>• Three primary doses at 2, 4 and 6 months with 8 weeks between doses and a booster at 12 months for infants with medical conditions<sup>a</sup> known to increase risk of IMD</li> </ul>		

Abbreviations: GSK= GlaxoSmithKline; 4CMenB= Multicomponent Meningococcal B Vaccine; NIP= National Immunisation Program;

Note: <sup>a</sup>Includes those with a specified medical condition associated with increased risk of meningococcal disease, including inherited defects or deficiency of properdin or complement components, current or future treatment with eculizumab, functional or anatomical asplenia, HIV infection and haematopoietic stem cell transplant.

Source: p. 61 of the resubmission.

2.2 In addition to the routine vaccination schedule included in Table 2, the resubmission proposed a time-limited catch-up for infants, toddlers (under 2 years of age), Aboriginal and Torres Strait Islander people (under 20 years of age) and all people with medical conditions known to increase the risk of IMD (as defined by the Australian Immunisation Handbook).

2.3 The ATAGI considered the vaccination of people with high-risk conditions should be part of a routine, ongoing program rather than a time-limited catch-up program (ATAGI post-submission advice). Additionally, the vaccination of Aboriginal and Torres Strait Islander people should also be routine and ongoing but if this was not considered cost-effective, it may be appropriate to limit it to a catch-program of at least 2 years duration. The ATAGI considered a catch-up program in adolescents would also be desirable (ATAGI post-submission advice) and the pre-PBAC response was supportive of this should the PBAC recommend implementation.

2.4 Table 3 provides a summary of the requested prices and corresponding schedule costs in the previous and current (re)submission.

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Table 3: Requested pricing from previous and current (re)submissions

	November 2013 major submission	July 2014 major resubmission	July 2015 minor resubmission	Current major resubmission
Requested NIP listing	Prevention of Men B disease in infants and adolescents.	Unchanged.	Unchanged.	Addition of infants with medical conditions <sup>b</sup> known to increase the risk of IMD. Addition of catch-up in Aboriginal and Torres Strait Islander people aged 2-19 y.o.
Requested price	Proposed in submission: \$■ per dose, plus ■% discount in the catch-up program.	Proposed in submission: \$■ per dose, plus ■% discount in the catch-up program.	\$■ per dose, plus free vaccine to half of the adolescent catch-up cohort for program 5 <sup>a</sup> .	\$■ per dose. No adolescent catch-up program.
	Considered at PBAC meeting: \$■ per dose	Considered at PBAC meeting: \$■ per dose, plus ■% discount in the catch-up program, plus free vaccine to half of the adolescent catch-up cohort.		
Schedule cost	Proposed in submission: Infant schedule (3+1): \$■ Adolescent schedule (2 doses): \$■	Infant schedule (3+1): \$■ Adolescent schedule (2 doses): \$■	Infant schedule (3+1): \$■ Adolescent schedule (2 doses): \$■ Total infant and adolescent schedule: \$■	Infants schedule (2+1): \$■ Adolescent schedule (2 doses): \$■ Total infant and adolescent schedule: \$■
	Considered at PBAC meeting: Infant schedule (3+1): \$■ Adolescent schedule (2 doses): \$■			

Abbreviations: NIP= National Immunisation Program; IMD= invasive meningococcal disease; PBAC= Pharmaceutical Benefit Advisory Committee; y.o = year olds.

Note: <sup>a</sup> Preferred program of routine infant and adolescent with catch-up for older infants and toddlers and adolescents; <sup>b</sup>Includes inherited defects or deficiency of properdin or complement components, current or future treatment with eculizumab, functional or anatomical asplenia, HIV infection and haematopoietic stem cell transplant.

Source: paragraph 3, 4CMenB minutes, July 2015 PBAC meeting; p.61-62 of the resubmission.

2.5 The requested NIP listing is consistent with the infant target population in the UK Public Health England (PHE) Vaccination program. The UK PHE Vaccination program does not provide vaccination for adolescents.

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

### **3 Background**

#### ***Registration status***

- 3.1 4CMenB was registered by the TGA on 14 August 2013 for active immunisation against invasive disease caused by *Neisseria meningitidis* group B strains in individuals from 2 months of age and older. An abbreviated infant schedule consisting of two primary doses followed by a booster (2 + 1) was approved on 24 May 2019.

#### ***Previous PBAC consideration***

- 3.2 Table 4 summarises previous concerns and how these were addressed in the current resubmission.

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Table 4: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
Effectiveness	The PBAC stated that an ICER >\$200,000/QALY 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. (paragraph 7.8, 4CMenB PSD, July 2014 PBAC meeting).	The resubmission relied on VE estimates based on a 3-year observational study of routine infant 4CMenB vaccination program in the UK. The ESC noted VE was appropriately based on real world evidence rather than relying on immunogenicity data.
Herd immunity	Uncertain and optimistic assumptions about..... herd immunity (paragraph 7.8, 4CMenB PSD, July 2014 PBAC meeting).	No herd effect in Section 3 based on the change in carriage from the South Australian 'B Part of It' Study (0% reduction).The impact of herd immunity was tested in a sensitivity analysis only. The ESC considered this was appropriate.
Persistence	Uncertain and optimistic assumptions about the .....duration of effect .....(paragraph 7.8, 4CMenB PSD, July 2014 PBAC meeting)..	Longer-term immunogenicity persistence data (2-3 y for infants and 7.5 y for adolescents) from two immunogenicity studies (V72_28 and V72_28E1) was used. The ESC considered this was appropriate.
Infant fever	High incidence of fever in infants (based on immunogenicity studies). The PBAC acknowledged that the higher rates of fever in infants would indicate that prophylactic paracetamol would be appropriate, noting that the impact of, and compliance with, this recommendation was unknown (paragraph 7.4, 4CMenB PSD, July 2015 PBAC meeting)	The incidence of infant fever from the real world data presented in the resubmission was: <ul style="list-style-type: none"> <li>• 0.05% per dose (11/23,500 in South Australian Meningococcal B vaccination program</li> <li>• 0.01% of doses (364/3,000,000) in UK PHE study</li> </ul> The resubmission relied on the UK PHE study completion rate of the 2+1 Men B course (86.7%) to support that there was no loss of confidence in the program due to infant fever
Discounting rate	The July 2015 resubmission applied a 5% discount rate for costs and outcomes in year 1-30 and 1.5% for costs and outcomes in years 31-100. 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 IMD is saving lives and preventing future morbidity/mortality for individuals vaccinated now (and into the future) (paragraph 6.22, 4CMenB PSD, July 2015 PBAC meeting). The PBAC reaffirmed its preference that a 5% pa discount rate apply to costs and outcomes (paragraph 7.6, 4CMenB PSD, July 2015 PBAC meeting)	The model base case assumed a 3.5% discount rate. This is inconsistent with the PBAC guidelines.

Abbreviations: 4CMenB= Multicomponent Meningococcal B Vaccine; IMD= invasive meningococcal disease; PBAC= Pharmaceutical Benefit Advisory Committee; PHE= Public Health England; PSD= public summary document; QALY= quality adjusted life year; UK PHE= United Kingdom Public Health England; VE= vaccine effectiveness; VI= vaccine impact

Source: Table 1.2, p.36 of the resubmission; paragraph 2.1, 4CMenB minutes, July 2015 PBAC meeting.

3.3 The main differences between the current resubmission and the previous (re)submissions are: real world evidence was used as the main source to derive VE (instead of immunogenicity data), proposed a 2 + 1 schedule (instead of a 3 + 1), no

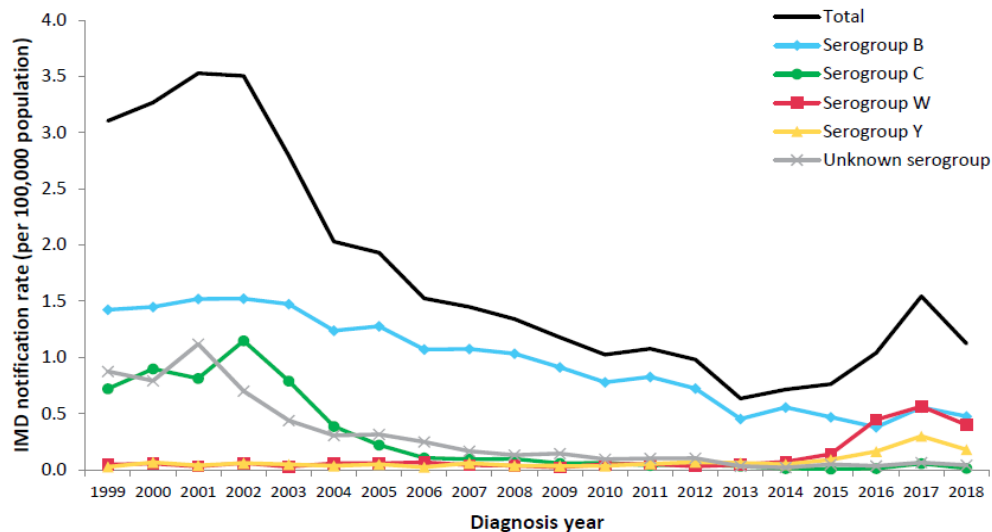
catch-up program for adolescents (except for Aboriginal and Torres Strait Islander adolescents), no herd immunity was assumed in the base case, a constant 3.5% discount rate was assumed for costs and health benefits, additional IMD sequelae and other indirect costs and consequences were incorporated into the economic model and a separate economic model was provided to model the Aboriginal and Torres Strait Islander population.

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

## **4 Population and disease**

- 4.1 IMD is a rare disease caused by the bacterium *Neisseria meningitidis*. From a public health perspective it is a disease of particular importance due to its potential to cause epidemics for which a causal relationship has been established for six of the twelve known serogroups, A, B, C, W, X and Y. The geographic distribution and epidemic potential differs depending on the serogroup. In Australia, the incidence of IMD has varied throughout the years with serogroup B the dominant strain, however with an observed decline since 2003-2004 (Figure 1). The epidemiology of serogroup B IMD also varies by region, with a higher incidence observed in South Australia compared with other jurisdictions.

Figure 1. IMD notification rates by serogroup and year, Australia, 1999–2018\*



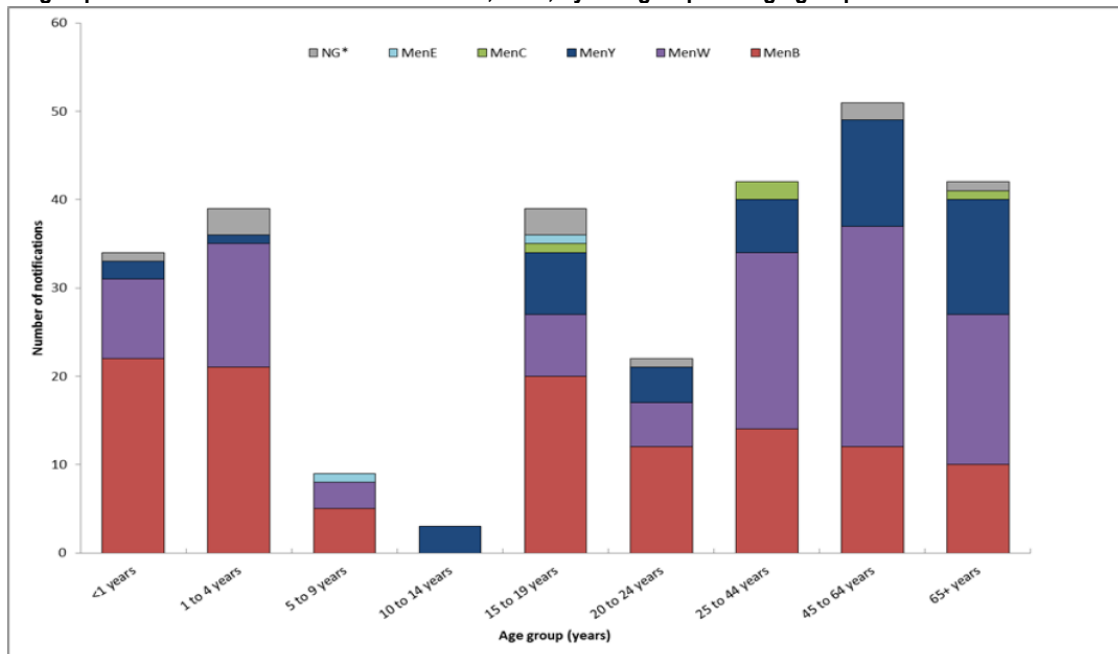
Abbreviations: IMD= invasive meningococcal disease.

Note: \*Data (NNDSS) shown is for cases with a diagnosis date from 1 January 1999 to 31 December 2018. Cases from 1999–2007 were extracted in March 2018; cases from 2008 onwards were extracted in February 2019. Unknown serogroup encompasses both ungrouped and non-groupable IMD. Trends not shown for serogroups A (n=5), E (n=2) and X (n=2).

Source: Figure 1, ATAGI pre-submission advice, June 2019, p. 5

- 4.2 The key clinical manifestation of IMD are meningitis and septicaemia. Depending on age and serogroup, up to 15% of patients may die with some deaths occurring within 24 to 48 hours after the onset of symptoms. Around one-third of survivors develop permanent sequelae including limb deformity, vision or hearing difficulties, arthritis, or learning difficulties.
- 4.3 The incidence of IMD is bimodal, with most cases occurring before 4 years of age and peaking again between 15-19 years of age (Figure 2).

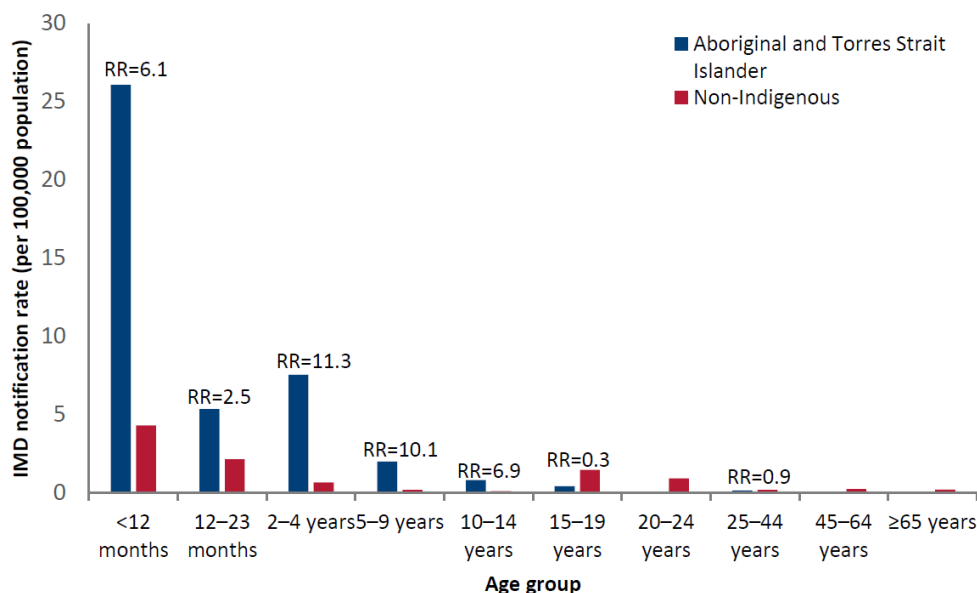
Figure 2. Age-specific notifications of IMD in Australia, 2018, by serogroup and age group



Abbreviations: IMD= invasive meningococcal disease.  
Source: Figure 1.5, p. 43 of the resubmission.

- 4.4 In 2018, there were 281 IMD cases; Men B was established as the cause for 119 cases (42.3%) and Men W in 100 cases (36%). There were 16 deaths attributable to IMD with 4 due to Men B and 10 due to Men W. A vaccination to prevent Men W (Men ACWY) was included on the NIP for infants in July 2018 and for adolescents in April 2019.
- 4.5 The burden of IMD caused by Men B is higher in Aboriginal and Torres Strait Islander children aged < 15 years compared with non-Indigenous children (Figure 3). However, there is no disparity observed in adolescents and young adults aged 15 to 24 years of age. The PBAC noted the average annual rate of serogroup B IMD notifications in Aboriginal and Torres Strait Islander children under 5 years of age between 2016 and 2018 was 11.0 per 100,000 population compared to 1.7 per 100,000 in non-Indigenous children (rate ratio = 6.6) (ATAGI pre submission advice, June 2019).

Figure 3. Average annual rates of serogroup B IMD notifications and rate ratio (RR) for notifications in Aboriginal and Torres Strait Islander and non-Indigenous persons, by age group, 2016 to 2018



Source: Figure 5, ATAGI pre submission advice, June 2019, , p.10

- 4.6 4CMenB is proposed to be included in the NIP and was assumed to replace the current private uptake of the vaccine and the existing South Australian Government program (implemented due to the higher incidence IMD caused by Men B observed in South Australia).
- 4.7 The submission provided additional evidence to support a secondary superiority clinical claim for the prevention of gonorrhoea.

## 5 Comparator

- 5.1 The resubmission nominated no vaccine as the main comparator. The PBAC previously considered the nominated comparator was appropriate as no vaccine against Men B infection was available at the time (paragraph 5.2, 4CMenB Public Summary Document (PSD), November 2013 PBAC meeting). An additional meningococcal group B vaccine was registered by the TGA in September 2017 for use in children aged  $\geq 10$  years for the prevention of *Neisseria meningitidis* serogroup B (MenB-fHbp). The resubmission argued that this was not interchangeable with 4CMenB because it did not target infants/toddlers and did not have cross-protection against gonorrhoea in adolescents. The Pre-Sub-Committee Response (PSCR) stated that cross-protection against gonorrhoea is specific to the antigenic composition of 4CMenB and therefore MenB-fHbp should not be considered a near-market comparator for children aged  $\geq$

10 years. The PBAC considered MenB-fHbp may be considered an alternative vaccine for children and adolescents aged  $\geq 10$  years.

## **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 individuals (201), health care professionals (28) and organisations (6) via the Consumer Comments facility on the PBS website. The comments described the devastating, often life-long consequences of IMD and the high impact on the quality of life of families that are affected. Many comments raised the equity issues associated with the affordability of the vaccine with some families not offered the vaccine due to the high cost. Many comments related to the difficulty in diagnosing IMD and the speed with which the condition can progress. Respondents commented that children and adolescents should be protected against all strains of IMD and Men B is the only strain not currently covered. There was a perception amongst some respondents that vaccination provided 100% protection from IMD and provided protection for unvaccinated individuals (i.e., herd immunity), however the clinical evidence indicates that the vaccine is not 100% effective with IMD having been reported in vaccinated individuals and that only vaccinated individuals are protected.

### ***Clinical trials***

6.3 The resubmission presented four real world evidence studies to support the clinical claim of superior effectiveness compared to no vaccination. The main study was the UK PHE Vaccination Program that vaccinated infants against IMD caused by Men B. Three other studies, the Quebec Regional Vaccination Program, the Portugal PT-BEST study and the 'South Australia B part of it' were also presented as supporting evidence. These studies had not previously been considered by the PBAC.

6.4 The resubmission presented 6 immunogenicity randomised controlled trials (RCTs) as supportive evidence of the efficacy of 4CMenB [V72\_28, V72\_28E1, V72\_56, V72P12E2, V72\_41, V72\_75]. These studies had not previously been considered by the PBAC. Of these, only 3 (V72\_28, V72\_28E1 and V72\_75) were considered relevant to the evaluation. The studies excluded by the evaluation assessed concomitance of 4CMenB with a vaccine not listed in the NIP, additional doses beyond the proposed schedule and one that assessed the safety and immunogenicity of 4CMenB when formulated with the outer membrane vehicle antigen manufactured at two different manufacturing sites.

- 6.5 The resubmission also presented three real world evidence studies to support the clinical claim of superior effectiveness compared to no vaccination against *Neisseria gonorrhoea* in adolescents. The evaluation considered that one of these studies was relevant as the other two did not provide evidence on cross-protection of 4CMenB against *Neisseria gonorrhoea*.
- 6.6 Details of the real world evidence trials presented in the submission to support the clinical effectiveness claim are provided in the table below.

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**Table 5: Real-world evidence and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
UK PHE Vaccination Program	<p>Pariikh S, Campbell H, Andrews, Ribeiro S, White J, Ramsay M et al. Progress report on 4CMenB (Bexsero®) vaccine coverage and effectiveness in England; 3rd annual report 01 September 2015-31 August 2018</p> <p>Pariikh SR, Andrews NJ, Beebeejaun K, Campbell H, Ribeiro S, Ward C et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study</p> <p>Bryan P, Seabroke S, Wong J, Donegan K, Webb E, Goldsmith C. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study.</p>	<p>Not published</p> <p><i>Lancet</i> 2016; 388(10061), 2775-2782</p> <p><i>Lancet Child Adolesc Health</i> 2018, 2(6), 395-403</p>
Quebec regional vaccination program	<p>De Serres G, Billard M, Gariepy M, Rouleau I, Yoth E et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada.</p> <p>De Wals P, Deceuninck G, Lefebvre B, Tsang R, Law D, De Serres G et al. Impact of an Immunization Campaign to Control an Increased Incidence of Serogroup B Meningococcal Disease in One Region of Quebec, Canada.</p> <p>De Wals P, Deceuninck G, Lefebvre B, Tsang R, Belinga JB, De Serres G. Epidemiological impact of the vaccination campaign against serogroup B meningococcal disease in the Saguenay - Lac-Saint-Jean region in 2014: report of 30 June 2018 [English translation].</p> <p>Deceuninck G, Lefebvre B, Tsang R, Betala-Beling JF, De Serres G, De Wals P. Impact of a mass vaccination campaign against Serogroup B meningococcal disease in the Saguenay-Lac-Saint-Jean region of Quebec four years after its launch.</p> <p>De Serres G, Billard MN, Gariepy MC, Roy MC, Boucher FD, Gagne H, Belley S, Toth E, et al. Nephrotic syndrome following four-component meningococcal B vaccination: Epidemiologic investigation of a surveillance signal.</p>	<p><i>Vaccine</i> 2018; 36(52), 8039-8046.</p> <p><i>Clin Infect Dis</i> 2017; 64(9), 1263-1267</p> <p>Not published</p> <p><i>Vaccine</i> 2019; 37: 4243-4245.</p> <p><i>Vaccine</i> 2019; 37: 4996-5002.</p>
PT-BEST	<p>Rodrigues F, Marlow R, Ladhani S, Simões MJ and Finn A. Preliminary data from the Portuguese Meningococcus Group B Vaccine Effectiveness Study (PT-BEST)– Preliminary results.</p>	<p>15th Congress of The European Meningococcal and Haemophilus Disease Society (EMGM), Lisbon, May 2019 (powerpoint slides)</p>

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Trial ID	Protocol title/ Publication title	Publication citation
South Australia B Part of it	Marshall HS, McMillan M, Koehler A, Lawrence A, MacLennan J, Maiden MCJ et al. B Part of It protocol: a cluster randomised controlled trial to assess the impact of 4CMenB vaccine on pharyngeal carriage of <i>Neisseria meningitidis</i> in adolescents.	<i>BMJ Open</i> 2018; 8(7): e020988. doi: 10.1136/bmjopen-2017-020988
	Marshall H, Koehler A, Pratt N, Quinn H, Ahoure M, Crawford N et al. Enhanced passive surveillance of adverse events following implementation of a meningococcal B vaccine herd immunity study "B Part Of It" in senior school students in Australia.	36th Annual Meeting of the European Society for Paediatric Infectious Diseases, Malmö, Sweden May 2018
	Marshall H, McMillan M, Lee S, Rokkas S, Koehler A, Lawrence A et al. B Part Of It: SA Men B Vaccine Herd Immunity Study	International Pathogenic <i>Neisseria</i> Conference (IPNC), California, USA September 2018
	Marshall HS (2019) B Part of It study: Impact of 4CMenB vaccine on carriage of <i>Neisseria meningitidis</i> in adolescents	The European Meningococcal and <i>Haemophilus</i> Disease Society. May 2019. Lisbon, Portugal (powerpoint slides).
	Marshall HS, McMillan M, Koehler A, Lawrence A, MacLennan J, Maiden M, Ramsay M, Ladhani SN, et al. B Part of It School leaver protocol: An observational repeat cross-sectional study to assess the impact of a meningococcal serogroup B (4CMenB) vaccine programme on carriage of <i>Neisseria meningitidis</i> .	<i>BMJ Open</i> 2019; 9: e027233.
	McMillan M, Walters L, Mark T, Lawrence A, Leong LEX, Sullivan T, Rogers GB, Andrews RM, Marshall HS. B Part of It study: a longitudinal study to assess carriage of <i>Neisseria meningitidis</i> in first year university students in South Australia.	Human vaccines and Immunotherapeutics 2019; 15: 987-994

Source: Table 2-10, p.73-74 of the resubmission.

6.7 The evaluation rated the risk of bias of the real world evidence studies using the ROBINS-1 tool which is designed for assessing bias in observational studies, and the studies were considered to have a low to medium risk of bias (Table 6). However, the PBAC did not agree with the evaluation and noted that evidence from observational studies is generally associated with a high risk of bias compared to evidence from randomised controlled trials. Specifically, the observational studies are at high risk of confounding due to underlying differences between vaccinated and unvaccinated children, and due to temporal changes in the incidence of disease unrelated to the vaccination program.

**Table 6: Key features of the included evidence**

Trial	Program	Design/ duration	Risk of bias (observational studies)	Patient population	Outcome(s)	Use in modelled evaluation
UK PHE Vaccination Program	Population based	Observational cohort study 3 years	Low	UK infants/toddlers	VE and VI.	Used to model the VE.
Quebec Regional Vaccination Program	Population based in response to outbreak	Vaccination impact study 2 years	Low	2 m - 20 years of age residing or attending school in the SLSJ region	VI and safety	Not used
Portugal PT-BEST	Private use	Case control study 4.5 years	Medium	Children and adolescents (2 m to 18 years) with IMD; for each case, two controls identified.	VE for protection against IMD B. VE for protection against all IMD.	Used to assess VE in the sensitivity analysis.
South Australia B Part of it	Carriage study	Parallel cluster RCT 1 year	Low	Students in Years 10, 11 and 12 attending school.	VI, safety and difference in carriage	Used to support herd immunity assumption in Section 3.

Abbreviations: IMD = invasive meningococcal disease; m= months; Men B = meningococcal B; RCT= randomised controlled trial; SLSJ = Saguenay-Lac-Saint-Jean; UK PHE= United Kingdom Vaccination Program by Public Health England; VE= vaccine effectiveness; VI= vaccine impact.

Note: The ROBINS-1 tool was used to assess the risk of bias of observational studies.

Source: Table 2.11, p. 77 of the resubmission.

6.8 Vaccine effectiveness (VE) is estimated by comparing the proportion of cases who are vaccinated with the proportion of cases in the population eligible for vaccination (rather than only unvaccinated cases) (ATAGI pre-submission advice, June 2019). Generally, VE is estimated using the screening method especially when data on the vaccination status of cases only are available. The screening method for calculating VE may not provide a reliable estimate if (1) the disease is rare, (2) the vaccine coverage is high and (3) the vaccine is effective as these three properties may lead to small frequencies for the number of vaccinated cases, or unvaccinated cases, or both. The PBAC noted that although there is no intrinsic bias in VE estimates from the screening method attributable to these three factors, it acknowledged that VE estimates will be uncertain if the total number of cases is small. The PBAC noted that despite the uncertainty in the VE estimate from the UK PHE study, the data were most consistent with a VE of 58.9% while the upper bound of the 95% confidence interval suggests the data were not consistent with a VE of greater than 87.1%.

6.9 Vaccine impact (VI) refers to the overall effect of a vaccination program and is measured by comparing one population in which the vaccination is implemented to a reference population without the vaccination program.

6.10 VI for the UK PHE vaccination program was estimated using a Poisson model constructed based on the incidence rates ratio (IRR) adjusted by year, age and vaccine

eligible period. The IRR was calculated relative to the baseline of the non-vaccine eligible cohort. This was used to produce an interrupted time series model with IRR in the non-vaccinated targeted aged group used to predict changes in the vaccine targeted ages. The PBAC noted the modelling used to estimate VI captures the change in disease incidence beyond that explainable by random variation, after taking into consideration the change in incidence over time and in unvaccinated age groups. The PBAC noted that any changes in incidence over time may be due to factors other than the vaccine program, and therefore attributing 100% of the apparent reduction to vaccine impact was very uncertain. This uncertainty extends to extrapolation of VE from the VI.

### **Comparative effectiveness**

- 6.11 Previous submissions relied on immunogenicity data with the hSBA titre used as a surrogate for VE (derived from study V72P6) which reached 98% when a full schedule (3+1) was assumed. The current resubmission relied on estimates of VE and VI calculated from the UK PHE Vaccination program using a 2+1 infant schedule. The ESC acknowledged that calculating VE using data from the UK PHE Vaccination program was preferable to using immunogenicity data.
- 6.12 The resubmission argued that the standard method for estimating VE (screening method) led to inaccurate results and wide confidence intervals because Men B was a rare disease, the vaccination coverage was high and the vaccine was effective. An alternative method of calculating VE was proposed with the adjusted VE calculated directly from [REDACTED]. The calculation relies on the [REDACTED]. The economic model in the resubmission relied on the adjusted VE.
- 6.13 The adjustment [REDACTED] the VE from 58.9% (95% CI: -31.5, 87.1) to [REDACTED]% (95% CI: [REDACTED], [REDACTED]). The ATAGI considered this adjustment inappropriate because methodological details had not been peer-reviewed nor published, uncertainties in some parameters, assumptions and potential errors in the estimation of VI. The PBAC considered that the screening method resulted in imprecise estimates of VE, especially when a disease is rare, coverage is very high, or the true VE is modest. The PBAC did not agree with the resubmission that these factors resulted in unreliable VE estimates per se, although noted that confounding caused by differences between vaccinated and unvaccinated children could bias the VE estimate (in either direction). The PBAC noted that the alternative approach to estimating VE [REDACTED] was also associated with significant uncertainty [REDACTED] and therefore the PBAC did not accept that it represented a more reliable estimate of the VE. The PBAC noted that the two VE estimates were inconsistent, noting that the point estimate of the adjusted VE ([REDACTED]%) was poorly consistent with

the number of cases observed among vaccinated children (25 of 29), being ██████████ ██████████ for the VE using the screening method (87.1%). On balance, the PBAC considered the true VE was likely to lie between the VE calculated using the screening method (58.9%) and the adjusted VE (██████████%).

6.14 The estimates of VE calculated from the evidence presented in the resubmission are summarised in the table below.

**Table 7: Results of vaccine effectiveness across the real-world evidence**

Trial ID	Age group	Number of IMD cases, n	Coverage	Vaccination status	VE against Men B disease
UK PHE	Cases aged ≥ 12 months	29 total, 25 in vaccinated, 4 unvaccinated	92.6%	2 + 1	58.9% (95% CI: -31.5, 87.1)
UK PHE adjusted	Cases aged ≥ 12 months	-	95.1%	2 + 1	██████████% (95% CI: ██████████, ██████████)
	18 to 52 week cohort	-	95.1%	2 + 0	██████████% (95% CI: ██████████, ██████████)
Quebec	> 2 months to 20 years	5 total, 1 vaccinated and 4 unvaccinated	83%	At least one dose	Over 4 years 79% (95% CI: -231, 99)
PT-BEST	2 months to < 18 years	NR	< 4 y.o 57% in 2018	Fully vaccinated	██████████% (95% CI: ██████████, ██████████)
	2 months to < 18 years	NR	-	Partially vaccinated (> 1 dose)	██████████% (95% CI: ██████████, ██████████)

Abbreviations: CI = confidence interval; IMD = invasive meningococcal disease; Men B = meningococcal B; n = number of participants with event (case); NR= not reported; PT-BEST= Portuguese Meningococcus Group B Vaccine Effectiveness Study; UK PHE= United Kingdom Public Health England; y.o = year olds.

Note: bold text indicates statically significant differences.

Source: p.91, p.94, p.97, p.98 and Table 2.27, p.100; Table 2.23, p.92, Table 2.24, p.94 of the resubmission.

6.15 The estimates of VI presented in the resubmission are summarised in the table below.

**Table 8: Results of vaccine impact across the real-world evidence**

Study ID	Age group	Cases, n	N	Vaccination status	Men B disease
UK PHE	1 year	13.75 in 2017/2018 vs. 71.25 in 2014/2015	1.29 million infants	2 + 1	<b>80% (95% CI: 64, 89)</b>
	Age 18+ weeks	Difference in expected and observed was 277 cases	NR	eligible for 2 + 1	<b>74% (95% CI: 65, 81)</b>
Quebec	> 2 months to 20 years	2 in target group	59,433	At least one dose	<b>96% (95% CI: NR, NR), p&lt;0.0013</b>
	All ages	5 post 2014	NR	NR	<b>87% (95% CI: NR, NR), p&lt;0.0001</b>
South Australia B Part of it	17-19 years	0	26,153	Appropriately vaccinated (92% of students from participating schools across South Australia from 15-18 years)	<b>71.4% (95% CI:29.0, 96.3)</b>

Abbreviations: CI = confidence interval; IMD = invasive meningococcal disease; Men B = meningococcal B; n = number of participants with event (case); NR= not reported; PT-BEST= Portuguese Meningococcus Group B Vaccine Effectiveness Study; UK PHE= United Kingdom Public Health England; y.o = year olds.

Note: bold text indicates statically significant differences.

Source: p.88, p.96, p.103. p.100 and Table 2.20, p.88 of the resubmission.

### **Comparative harms**

- 6.16 The UK PHE Vaccination Program implemented the Yellow Card Scheme safety surveillance system to monitor the occurrence of AEs of which fever, seizures, local reactions, Kawasaki disease, and sudden death were pre-specified as outcomes of interest for assessment. From 1 Sept 2015 to 31 May 2017, 1.29 million infants were vaccinated and 902 yellow card reports were received. Of these, 366 (41%) AEs were related to local reactions, described as a persistent nodule at the site of injection, usually without other local symptoms and 364 (40%) AEs were related to fever (including pyrexia, body temperature, feeling hot).
- 6.17 The prospective surveillance study for the UK PHE Vaccination Program noted there was incomplete reporting of the actual magnitude or severity of fever in the Yellow Card reports, those that were reported as serious tended to refer to a high fever, with some reporting a temperature of more than 40°C. There was insufficient information about paracetamol use in these reports. However, this study concluded that there were no significant safety concerns from the vaccination program and that the vaccine appears to have been well accepted by parents (Bryan et al. 2018<sup>1</sup>).
- 6.18 The ATAGI noted that there was evidence of an acceptable safety profile, albeit with an increased risk of fever in infants, which can be mitigated by the prophylactic use of

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<sup>1</sup> Bryan, P., Seabroke, S., Wong, J. & et al, 2018. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. *Lancet Child Adolesc Health*, 2(6), pp. 395-403.

paracetamol with vaccine administration in young children aged < 2 years (ATAGI pre-submission advice, June 2019).

- 6.19 One immunogenicity study (V72\_28) provided evidence comparing the proposed 2 + 1 schedule versus the previously assessed 3 + 1 schedule. Results showed that infants vaccinated with a 2+1 schedule were at a higher risk of developing fever. There were statistically significantly higher fever events at the 5 month dose in the 2 + 1 schedule versus the 3 + 1 schedule with a risk difference of 17% (9%, 25%) between the dosing schedules.

### **Benefits/harms**

- 6.20 Between 2013 and 2017 there were approximately 400 cases of IMD caused by Men B in people under 23 years of age. A vaccination program with 4CMenB may have prevented around half of these cases and approximately 8 deaths.

### **Clinical claim**

- 6.21 The resubmission described 4CMenB as superior in terms of effectiveness and non-inferior in terms of safety compared with no vaccination. The evaluation noted the following issues with regards to the effectiveness and safety of 4CMenB:
- VE was based on real-world evidence from the UK PHE Vaccination Program. In this program, VE was not statistically significant (58.9%; 95% CI -31.5, 87.1), however the resubmission relied on an adjusted VE estimate which may [REDACTED] the VE ([REDACTED]%; 95% CI [REDACTED], [REDACTED]). The ESC considered the use of the adjusted VE was reasonable although may be associated with some uncertainty. The ESC noted the adjusted VE was lower than the VE applied in previous submissions (98%) which was based on immunogenicity studies.
  - The waning of the vaccine, which reflects the persistence of effect reported as the time (in months) of sufficient antibody response, was estimated in a similar manner to the previous (re)submissions. The results from the extension study V12PE1 were broadly consistent with the previous (re)submission in infants and toddlers but the duration of effect was shorter and more conservative in the adolescent population. The ATAGI noted the reliance on studies of antibody persistence to infer duration of protection and the lack of data from population use. The ATAGI considered the duration of protection afforded by 4CMenB to be an area of uncertainty (ATAGI pre-submission advice, June 2019).
  - The UK PHE Vaccination Program showed the most common AE were local reactions and fever. The ATAGI considered that there is evidence of an acceptable safety profile, albeit with an increased risk of fever in infants, which can be mitigated with the prophylactic use of paracetamol in young children aged <2 years (ATAGI pre submission advice, June 2019). The ESC agreed with the ATAGI that the safety profile of 4CMenB is acceptable.

- The resubmission described 4CMenB as superior in terms of effectiveness against gonorrhoea prevention compared with no vaccination in adolescents. The ESC agreed with the ATAGI that while there may be some emerging evidence of a potential positive effect of 4CMenB in preventing gonorrhoea, there are limitations in applying it to the proposed use of 4CMenB in Australia (ATAGI pre-submission advice, June 2019). The pre-PBAC asserted the supplementary benefit of cross-protection against gonorrhoea provided substantial public health benefits and even a small protective benefit could be significant in view of the increasing notification rate of gonorrhoea.
- 6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though the magnitude and duration of benefit were uncertain.
- 6.23 The PBAC did not accept the claim of non-inferior comparative safety but considered the safety profile of 4CMenB was acceptable.

### ***Economic analysis***

- 6.24 The economic evaluation presented was a cost-utility analysis and this is unchanged from the previous resubmission. Although the methodological modelling approach is consistent with the previous submission, the structure is substantially different. The resubmission included two economic models identical in structure, one for the General population and one for the Aboriginal and Torres Strait Islander population (which is a subset of the general population) to account for the difference in incidence of IMD caused by Men B.

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**Table 9: Summary of model structure and rationale**

Component	Approach in July 2014 resubmission	Approach in resubmission
Type of analysis	Cost-utility analysis	Unchanged.
Outcomes	IMD infections, and IMD-related deaths and sequelae avoided, quality-adjusted life years	Unchanged.
Time horizon	Life-time horizon (100 years)	Unchanged.
Perspective	Modified societal/health system perspective with indirect costs and benefit beyond the patient.	Broader societal perspective compared to previous resubmission.
Discounting	5% in years 1-30, stepped to 1.5% in years 31-100.	3.5%. This is not consistent with PBAC guidelines.
Epidemiology	Average cases of meningococcal B from 2000-2011 from the NNDSS, confirmed cases plus imputation rule of probable, and not-determined.	Average cases of Men B from 2001-2017 from the NNDSS plus 68.5% of the pool IMD cases classified as 'Others'.
Methods used to generate results	Step 1: DTM Step 2: Decision tree model to account for the number of deaths and cases of IMD survivors with sequelae.	Unchanged however 16 sequelae were included (12 physical/neurological and 4 psychological/behavioural).
Costs (direct)	Administration costs, treatment of 8 sequelae and adverse events.	No administration costs for 4CMenB. Additional costs to account for the additional 8 sequelae.
Costs (indirect)	Productivity costs due to IMD as a scenario analysis. Indirect medical costs of special education associated with sequelae and public health response in the base case.	Unchanged except that productivity costs due to IMD were included in the base case.
Health states	DTM: nine mutually-exclusive states. All vaccine-preventable strains were grouped together hence all transmission and infection parameters were assumed to represent an average across all vaccine-preventable strains." (paragraph 10, 4CMenB PSD, July 2014 PBAC meeting).	DTM: eight mutually-exclusive compartments were defined in terms of susceptible, carriage of Men B, Men ACWY or 'Other' serogroups, and vaccination status; further stratified by age and time of vaccination given (vaccinated as infant vs toddler).
Cycle length	Monthly	Unchanged.
Software package	Excel 2010 with Visual Basic	R with Excel interface
Effectiveness against Men B IMD	Based on the V72P6 immunogenicity study the VE for 3 + 1 dose in infants was 98%	Adjusted VE data from UK PHE study.
Persistence	Average waning for all antigens.	Waning relied on fHbp (ignoring NHBA, NadA and PorA) which was appropriate and tested in sensitivity analyses.
Herd effect	12.6% carriage reduction based on V72_29.	0% carriage reduction based on South Australian adolescent study, B Part of It.

Abbreviations: ESC= Economic Sub-Committee; fHbp = factor H binding protein; IMD = invasive meningococcal disease; Men ACWY = meningococcal serogroups A,C,W and Y; Men B = meningococcal B; NadA = Neisseria adhesin A; NHBA = Neisseria heparin binding antigen; PHE = Public Health England; PorA = Porin A; UK = United Kingdom; VE = vaccine effectiveness; VI = vaccine impact.  
Source: Table 3.1-3.2, p.140, 143-144 of the resubmission; p.147, p.240 of the resubmission. ; paragraph 6.16, 4CMenB PSD, July 2014 PBAC meeting; Table D.3.6, pD-31 of the July 2014 resubmission; 4CMenB submission, July 2014, Table D.3.6, pD-31. Table 4.4, p.c-29 Section C of the July 2014 resubmission.

6.25 The resubmission justified the use of the lower discount rate and broader societal perspective based on a policy paper entitled 'The Value of Vaccines' that suggests a new evaluation framework for vaccines.

- 6.26 Based on the PBAC guidelines (Version 5.0, section 3.A.15), lower discount rates can be considered in a sensitivity analysis rather than the base case. The sponsor agreed with the principle of discounting in its PSCR, however considered the 5% compounding rate too high and that this disproportionately disadvantages preventive treatments such as vaccines, particularly those such as 4CMenB that realise the majority of the utility benefit and cost offsets in the longer term but incur the cost of the vaccine immediately, compared to chronic preventative interventions whose ongoing cost is discounted. The ESC considered it was appropriate to apply a 5% discount rate in the base case analysis and use a lower discount rate in a sensitivity analysis. The ESC noted the ICER was highly sensitive to the discount rate.
- 6.27 Including productivity in economic evaluations raises important equity issues as it implies interventions that improve the health of people in the workforce (or those who earn more) are of a higher value than other interventions. Additionally, there are methodological issues with incorporating productivity which may increase the uncertainty of an evaluation. The PBAC guidelines (Version 5.0, Appendix 6) state that changes in productivity should not be included in the base case but can be included in supplementary (sensitivity) analyses. The ESC considered it was appropriate to include productivity in sensitivity analysis and noted the sensitivity of the base case ICER to the inclusion of productivity.
- 6.28 Over a period of 5 years, the model predicted a total of 1,134 cases in the no vaccination scenario and 941 cases in the vaccinated scenario which led to approximately 193 cases and 6 deaths potentially avoided.
- 6.29 The PBAC noted the background incidence of IMD caused by Men B was a major driver of the model. The base case used the average number of cases reported from 2001-2017 however the annual incidence has progressively declined since the early 2000's. Using the average number of cases reported from 2010-2017 increased the base case ICER from \$15,000/QALY - \$45,000/QALY to \$105,000/QALY - \$200,000/QALY gained. Applying the same assumption to the Aboriginal and Torres Strait Islander population model increased the ICER from less than \$15,000/QALY gained to \$15,000/QALY - \$45,000/QALY gained. The PBAC noted that the ATAGI considered the use of data from 2001-2017 to model the disease incidence to be acceptable (ATAGI pre-submission advice, June 2019). The PBAC considered the use of data from 2001-2017 will likely overestimate the future incidence of IMD caused by Men B.
- 6.30 The model incorporated a Quality of Life Adjustment Factor (QAF) with a value of three (3) for all long-term sequelae into the economic evaluation. The resubmission justified this based on the UK's Joint Committee on Vaccination and Immunisation (JCVI) recommendation to include the QAF of three "In response to concerns raised on how the quality of life losses of IMD had not been fully captured within the cost-effectiveness analysis due to limitations of the EQ-5D questionnaire used in the MOSAIC study [case-control study in UK children who survived IMD caused by Men B],

and wider concerns regarding the measurement of the impact of IMD in children and the innovative nature of the 4CMenB, as well as the differential societal value of equal QALY measures of severe and relatively mild disease". It was not reported how a QAF of three was derived. This argument for using a QAF may possibly be reasonable in a context where, like the UK, a fixed ICER threshold is used (the ESC noted the JCVI requires vaccine ICERs to be less than £20,000), however, this is not the case in Australia and varying ICERs are accepted to enable consideration of different factors (e.g. severity of the disease, rarity or limitations of the quality of life instrument). The PBAC agreed with the ESC that use of a QAF was not appropriate in either the base case or in a sensitivity analysis as it was not relevant to the Australian context.

- 6.31 The inclusion of the costs and disutilities for the additional sequelae not considered in the previous submissions also had a large impact on the ICER. In particular, the inclusion of the psychological and behavioural sequelae anxiety, separation anxiety and attention deficient hyperactivity disorder (ADHD) had a greater impact on the ICER compared to the physical and neurological sequelae. These additional sequelae were identified from a systematic literature review of observational studies. Given the nature of the background evidence, observational studies which are prone to confounding, it is unclear whether there is a causal relationship between the new proposed sequelae and IMD or it is purely an association. In addition, by adding these sequelae, there is a considerable risk of double counting the disutility as patients with other physical sequelae, for example amputation, may also suffer from anxiety or any other psychological or behavioural sequelae which had already been accounted for. The PSCR acknowledged the difficulty in accounting for the psychological consequence of physical sequelae but maintain the approach taken in the resubmission is appropriate and conservative. The PSCR stated that the model conservatively assumed a disutility loss of zero for skin scarring (the most common sequelae) and that the probability of depression occurring was assumed to be zero. Further, the PSCR provided information that showed that utility loss per Men B survivor was higher in the 2014 submission (0.3) as compared to the current submission (0.16). The pre-PBAC response provided additional support for including psychological sequelae in the economic model and further noted the conservative assumption regarding the incidence of depression included in the model.
- 6.32 The key drivers of the economic model are summarised in the table below.

Table 10: Key drivers of the model

Description	Method/Value	Impact from the General population model \$ [REDACTED]/QALY gained	Impact from the Aboriginal and Torres Strait Islander population model \$ [REDACTED]/QALY gained
Background IMD incidence	IMD incidence= average for the 2001-2017 period	High. Decreasing the incidence to the average reported in 2010-2017 increased the ICER to \$ [REDACTED]/QALY gained. Increasing the incidence by a factor of 2 results in 4CMenB being dominant.	High. Decreasing the incidence to the average reported in 2010-2017 increased the ICER to \$ [REDACTED]/QALY gained. Increasing the incidence by a factor of 2 results in 4CMenB being dominant.
Quality of life adjustment factor	QAF set to 3 in base case	High, favours 4CMenB. Removal of QAF (=1) results in ICER of \$ [REDACTED]/QALY gained.	High, favours 4CMenB. Removal of QAF (=1) results in ICER of \$ [REDACTED]/QALY gained.
Discount rate	3.5% p.a. for costs and health outcomes	High, favours 4CMenB. Discount rate of 5% p.a. results in ICER of \$ [REDACTED]/QALY gained.	Moderate, favours 4CMenB. Discount rate of 5% p.a. results in ICER of \$ [REDACTED]/QALY gained.
Vaccine effectiveness	[REDACTED]% for 2+ 1 dose from adjusted UK PHE Vaccination Program	High, favours 4CMenB. Use of unadjusted VE point estimate from UK PHE Vaccination Program resulted in ICER of \$ [REDACTED]/QALY gained.	High, favours 4CMenB. Use of unadjusted VE point estimates from UK PHE Vaccination Program resulted in ICER of \$ [REDACTED]/QALY gained.
Inclusion of additional sequelae	Additional sequelae blindness/severe visual impairment; Hearing loss - moderate bilateral; Hearing loss - unilateral/hearing impairment; Speech or communication problems; Mental retardation/low IQ; Motor deficits; Depression; Anxiety; Separation anxiety; ADHD	High, removal of additional sequelae resulted \$ [REDACTED]/QALY gained.	High, removal of additional sequelae resulted \$ [REDACTED]/QALY gained.

Abbreviations: 4CMenB= Multicomponent Meningococcal B Vaccine; ICER= incremental cost effectiveness ratio; p.a.= per annum; QAF= quality of life adjustment factor; QALY= quality adjusted life years; UK PHE= United Kingdom Public Health England.

Source: Section 3.9 of the resubmission and compiled during the evaluation.

6.33 The results of the stepped economic evaluation in the General population and the Aboriginal and Torres Strait Islander population are presented in Table 11 and Table 12 respectively. The impact of adjusting the life years gained (LYG) for quality of life leads to a decrease in the ICER from more than \$200,000/LYG to \$15,000/QALY - \$45,000/QALY in the General population. Similarly, the ICER decreased from \$105,000/LYG - \$200,000/LYG to less than \$15,000/QALY in the Aboriginal and Torres Strait Islander population. These results show that the assumed utilities are a driver of the results.

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Table 11: Results of the stepped economic evaluation – General population (2,938,932 people vaccinated over model duration)

Step and component	Base case vaccination strategy	No vaccination	Increment
<b>Step 1: 5-year costs and outcomes for IMD avoided (no discounting)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
IMD cases	[redacted]	[redacted]	- [redacted] <sup>a</sup>
Incremental cost/per IMD case avoided			\$ [redacted]
<b>Step 2: time horizon extended to 100 years (no discounting)</b>			
Costs	\$ [redacted]	\$ [redacted]	-\$ [redacted]
IMD cases	[redacted]	[redacted]	- [redacted] <sup>a</sup>
Incremental cost/per IMD case avoided			Dominant
<b>Step 3: time horizon 100 years, discounting (3.5%)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
IMD cases	[redacted]	[redacted]	- [redacted] <sup>a</sup>
Incremental cost/per IMD case avoided			\$ [redacted]
<b>Step 4: time horizon 100 years, deaths avoided, discounting (3.5%)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Deaths	[redacted]	[redacted]	- [redacted] <sup>a</sup>
Incremental cost/per death avoided			\$ [redacted]
<b>Step 5: time horizon 100 years, LYG, discounting (3.5%)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life years lost	[redacted]	[redacted]	- [redacted] <sup>a</sup>
Incremental cost per LYG			\$ [redacted]
<b>Step 6: utility weights applied, time horizon 100 years, QALY avoided, discounting (3.5%)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs lost	[redacted]	[redacted]	- [redacted] <sup>a</sup>
<b>Incremental cost/QALY gained (base case)</b>			\$ [redacted]

Abbreviations: IMD = invasive meningococcal disease; LYG = life-year gained; Men = meningococcal; QALY = quality adjusted life year.  
 Note: Total IMD cases, life years and QALYs include Men B, Men ACWY and Other Men. Base case defined as infant vaccination and adolescent Vaccination in the General Population with one year catch-up for 12 month to 2 years. Adolescents received one dose only if previously vaccinated as an infant (i.e. after 15 years of the model);

<sup>a</sup> Given that the intervention prevents disease, a negative health outcome represents fewer individuals being diagnosed with IMD, and hence a health benefit gain.

Source: Table 3.80-Table 3.83, p.281-283 of the resubmission. Extracted from sheet 'CE Table' and 'Health Outcomes & Cost' from Excel spreadsheet 'Workbook i General Population Model 190701' of the resubmission.

6.34 The results of the stepped economic evaluation in the Aboriginal and Torres Strait Islander population are presented in Table 12.

**Table 12: Results of the stepped economic evaluation – Aboriginal and Torres Strait Islander population (176,847 people vaccinated over model duration)**

Step and component	Base case vaccination strategy	No vaccination	Increment
<b>Step 1: 5-year costs and outcomes for IMD avoided (no discounting)</b>			
Costs	\$	\$	\$
IMD cases			- <sup>a</sup>
Incremental cost/per IMD case avoided			\$
<b>Step 2: time horizon extended to 100 years (no discounting)</b>			
Costs	\$	\$	-\$
IMD cases			- <sup>a</sup>
Incremental cost/per IMD case avoided			Dominant
<b>Step 3: time horizon 100 years, discounting (3.5%)</b>			
Costs	\$	\$	\$
IMD cases			- <sup>a</sup>
Incremental cost/per IMD case avoided			\$
<b>Step 4: time horizon 100 years, death avoided, discounting (3.5%)</b>			
Costs	\$	\$	-\$
Deaths			- <sup>a</sup>
Incremental cost/per death avoided			\$
<b>Step 5: time horizon 100 years, LYG, discounting (3.5%)</b>			
Costs	\$	\$	\$
Life years lost			- <sup>a</sup>
Incremental cost per LYG			\$
<b>Step 6: utility weights applied, time horizon 100 years, QALY avoided, discounting (3.5%)</b>			
Costs	\$	\$	\$
QALYs lost			- <sup>a</sup>
<b>Incremental cost/extra QALY gained (base case)</b>			\$

Abbreviations: IMD = invasive meningococcal disease; LYG = life-year gained; Men = meningococcal; QALY = quality adjusted life year.

Note: Total cases, life years and QALYs include Men B, Men ACWY and Other Men.

<sup>a</sup> Given that the intervention prevents disease, a negative health outcome represents fewer individuals being diagnosed with IMD, and hence a health benefit gain.

Source: 3.88, p.288 of the resubmission, Extracted from sheet 'CE Table' and 'Health Outcomes & Cost' from Excel spreadsheet 'Workbook ii Indigenous Population 190701' of the resubmission.

6.35 During the evaluation it was considered that there is an overestimation of the incidence of IMD (all serogroups) partly due to the imputation of cases defined as “not groupable” to the various serogroups. Removing the assumption that 68.93% (average proportion of Men B cases from 2001-2017) of “not groupable” cases were Men B cases, resulted in an ICER of \$45,000 - \$75,000 per QALY gained. The ESC considered the imputation of cases that were “not groupable” may be reasonable, provided the strain distribution does not differ between the cases that were serotyped and the “not groupable” cases.

6.36 The resubmission presented one-way and multi-way sensitivity analysis. During the evaluation several additional one-way and multi-way sensitivity analysis were conducted. The impact of assuming a scenario aligned with the PBAC guidelines (multivariate sensitivity analysis) resulted in an ICER of more than \$200,000/QALY gained compared to the base case ICER of \$15,000/QALY - \$45,000/QALY gained. Similarly, the ICER increased from less than \$15,000/QALY gained to \$105,000/QALY - \$200,000/QALY in the Aboriginal and Torres Strait Islander model.

- 6.37 In the General population, the ICER for vaccinating infants only was \$45,000/QALY - \$75,000/QALY gained and for vaccinating adolescents only<sup>2</sup> was \$15,000/QALY - \$45,000/QALY gained (Table 13). The difference is largely due to the different number of doses required (three doses in the infant population and two doses in the adolescent only population). In contrast, in the Aboriginal and Torres Strait Islander population model, the ICER for vaccinating infants only was less than \$15,000/QALY gained and for vaccinating adolescents only was \$105,000/QALY - \$200,000/QALY gained. The difference reflects the substantially higher incidence of IMD caused by Men B in the infant compared with the adolescent population. The PBAC noted no cost for the administration of 4CMenB was included for infants or adolescents. The PBAC considered that while this may be reasonable for the infant doses and the first adolescent dose as vaccination with 4CMenB was likely to take place at the same time as current NIP vaccinations, it may not be reasonable for the second adolescent dose which does not coincide with any current NIP vaccinations.
- 6.38 Table 13 summarises the sensitivity analysis for the General population model. The background incidence of IMD caused by Men B was the parameter that had the largest impact on the results (paragraph 6.29). The resubmission modelled a hyperendemic scenario assuming an incidence multiplier of 3. For this scenario vaccination with 4CMenB was dominant for the General population and the Aboriginal and Torres Strait Islander population. The ATAGI considered an incidence multiplier of 3 could represent a hypothetical hyperendemic scenario, the occurrence of which it considered plausible though unlikely (ATAGI post-submission advice, October 2019). The ATAGI noted however, it is uncertain whether the particular clone or strain of the serogroup B meningococcus responsible for a hyperendemic scenario would be covered by 4CMenB (ATAGI post-submission advice, October 2019).

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<sup>2</sup> Adolescents in the base case model receive 2 doses of 4CMenB for the first 15 years of the model (i.e., the cohort that were not vaccinated as infants) and 1 dose for the remaining 85 years. In the adolescent only model, they receive 2 doses for the duration of the model.

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Table 13: Results of one-way and multivariate sensitivity analyses – General population

	Incremental cost	Incremental QALY <sup>a</sup>	ICER (\$/QALY gained)
<b>One-way sensitivity analysis</b>			
Base case	\$ [redacted]	- [redacted]	\$ [redacted]
Model time horizon (base case 100 years)			
25 years	\$ [redacted]	- [redacted]	\$ [redacted]
50 years	\$ [redacted]	- [redacted]	\$ [redacted]
VE (base case adjusted VE from UK PHE study, [redacted]%)			
VE Portugal PT-BEST ([redacted]%)	\$ [redacted]	- [redacted]	\$ [redacted]
VE upper bound PHE data (87.1%)	\$ [redacted]	- [redacted]	\$ [redacted]
VE point estimate PHE data (58.9%)	\$ [redacted]	- [redacted]	\$ [redacted]
Incidence of IMD caused by Men B (base case 2001-2017)			
Incidence 2001 to 2003	\$ [redacted]	- [redacted]	\$ [redacted]
Incidence multiplier set to 2 <sup>b</sup> (Men B only)	\$ [redacted]	- [redacted]	Dominant
Incidence multiplier set to 3 <sup>c</sup> (Men B only)	\$ [redacted]	- [redacted]	Dominant
No redistribution of “Not Groupable” cases to Men B	\$ [redacted]	- [redacted]	\$ [redacted]
Incidence 2010-2017	\$ [redacted]	- [redacted]	\$ [redacted]
Cross-protection against non-Men B strains <sup>d</sup>	\$ [redacted]	- [redacted]	\$ [redacted]
Herd immunity against Men B 12.6%	\$ [redacted]	- [redacted]	Dominant
Productivity losses excluded	\$ [redacted]	- [redacted]	\$ [redacted]
Discount rate 5%	\$ [redacted]	- [redacted]	\$ [redacted]
No QAF	\$ [redacted]	- [redacted]	\$ [redacted]
Population vaccinated (base case infants + adolescents)			
Infants only	\$ [redacted]	- [redacted]	\$ [redacted]
Adolescents only	\$ [redacted]	- [redacted]	\$ [redacted]
<b>Multi-variate sensitivity analysis</b>			
Caregiver utility weight = 1, family and network utility loss factor when child survives and has sequelae =0 family and network utility loss factor for bereaved family =1	\$ [redacted]	- [redacted]	\$ [redacted]
Removal of costs and utility from additional sequelae (set prob. to among survivors to 0% for blindness/severe visual impairment; Hearing loss - moderate bilateral; hearing loss - unilateral/hearing impairment; Speech or communication problems; mental retardation/low IQ; motor deficits; depression; anxiety; separation anxiety; ADHD)	\$ [redacted]	- [redacted]	\$ [redacted]
Scenario consistent with PBAC guidelines <ul style="list-style-type: none"> <li>Discount rate = 5% costs and benefits</li> <li>Removal productivity loss for patient = \$0</li> <li>Removal of productivity loss for family = \$0</li> <li>Removal special education costs = \$0</li> <li>Removal of long-term caregiving costs = \$0</li> <li>Removal QAF = 1</li> <li>Removal of family and network utility loss factor when child survives and has sequelae = 0</li> <li>Family and network utility loss factor for bereaved family = 1</li> <li>Removal professional caregiver’s utility decrement = 1</li> </ul>	\$ [redacted]	- [redacted]	\$ [redacted]

Abbreviations: ICER=incremental cost effectiveness ratio; prob= probability; QAF = quality adjustment factor; QALY=quality adjusted life year; VE = vaccine effectiveness.

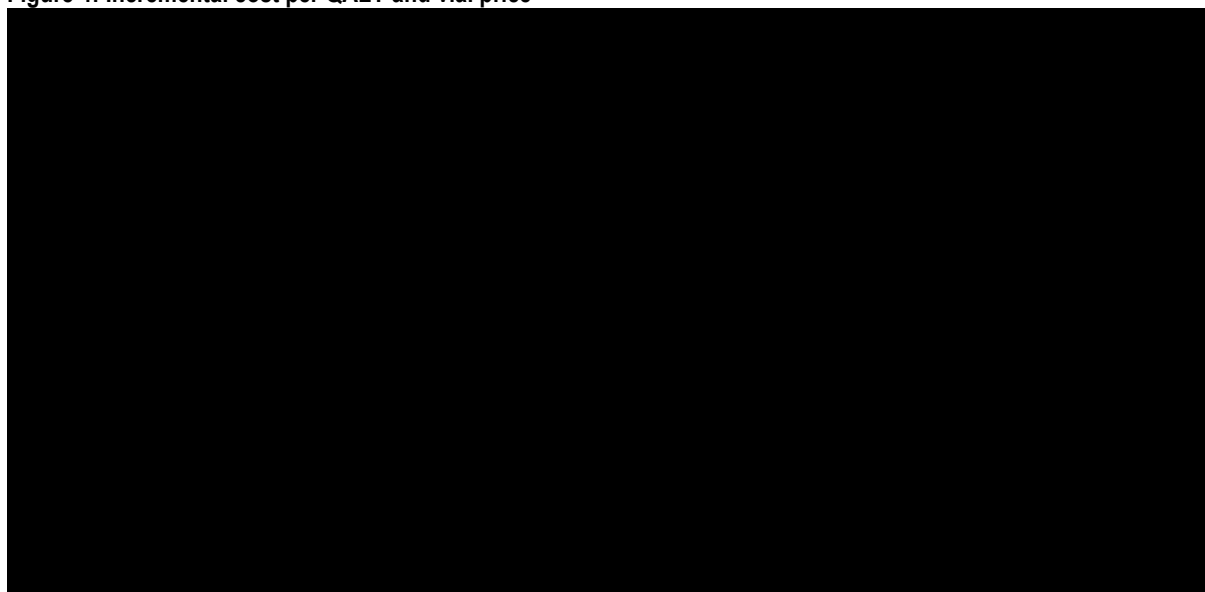
Note: <sup>a</sup> Given that the intervention prevents disease, the health gain represents less loss from fewer individuals being diagnosed with IMD; <sup>b</sup> Results in a similar disease incidence as observed in 2001 to 2003; <sup>c</sup> considered by ATAGI to represent a hyperendemic scenario; <sup>d</sup>Could not be verified during the evaluation ICER returned \$ [redacted] when 93% for protection of infant against ACWY and Protection against carriage against ACWY was 26.5%.

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Source: p.297-302 of the resubmission. Compiled during the evaluation using Excel spreadsheet 'Workbook i General Population Model 190701'.

- 6.39 The ESC considered that including outcomes beyond the health outcomes of the patient receiving the intervention and beyond the health care system was not appropriate in the base case. However, inclusion of these outcomes in sensitivity analyses would be informative.
- 6.40 The ESC considered the scenario aligned with the PBAC guidelines (paragraph 6.36) provided a more reasonable and consistent base case economic analysis. The ESC considered a modified PBAC guidelines scenario that included utility loss for family and network, long-term special education costs, long-term caregiving costs and a discount rate of 3.5% could be considered as a sensitivity analysis. These ICERs for the General population and the Aboriginal and Torres Strait Islander population are summarised in Table 14.
- 6.41 The ESC considered it was informative to see the relationship between the incremental cost per QALY and the price per vial of 4CMenB (Figure 4).

**Figure 4: Incremental cost per QALY and vial price**



**Table 14: PBAC guidelines scenario (revised base case) and modified PBAC Guidelines scenario (sensitivity analysis), infants and adolescents, infants only and adolescents only**

	General population			Aboriginal and Torres Strait Islander population		
	I + A	I	A	I + A	I	A
Base case as per submission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Base case as per submission with productivity assumptions equivalent between General and Aboriginal and Torres Strait Islander population	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	Dominant	Dominant	\$ [REDACTED]
<b>PBAC guidelines scenario (revised base case)</b> • Discount rate = 5% costs and benefits • Removal productivity loss for patient = \$0 and productivity loss for family = \$0 • Removal special education costs = \$0 and long-term caregiving costs = \$0 • Removal QAF = 1 • Removal of family and network utility loss factor when child survives and has sequelae = 0 • Family and network utility loss factor for bereaved family = 1 • Removal professional caregiver's utility decrement = 1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Modified PBAC Guidelines scenario</b> • Discount rate = 3.5% costs and benefits • Addition of long-term caregiving costs • Addition special education costs • Addition of family and network utility loss factor when child survives and has sequelae	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Abbreviations: A=adolescent; I=infants; I+A =infant and adolescents; PBAC= Pharmaceutical Benefits Advisory Committee; QAF=quality adjustment factor

**Vaccine cost/patient/dose**

- 6.42 The proposed price of 4CMenB was \$ [REDACTED] per dose.
- 6.43 The proposed price equates to a schedule cost of \$ [REDACTED] for infants (2 + 1 schedule, 3 doses in total), \$ [REDACTED] for adolescents (2 doses in total) and \$ [REDACTED] for high risk infants (3 + 1 schedule, 4 doses in total). The economic modelling assumed that if an individual was previously vaccinated as an infant with the full 2+1 schedule, they would only require 1 dose as an adolescent.

**Estimated NIP usage & financial implications**

- 6.44 This submission was not considered by DUSC. The resubmission used an epidemiological approach.
- 6.45 The number of doses required varied by age and IMD risk factors. Infants with no risk factor require 3 doses, infants with a high-risk medical condition for IMD require 4 doses and all adolescents require 2 doses. Over the time frame of the financial estimates, no adolescent would have received vaccination as an infant.

6.46 The total cost to the NIP over 6 years for the General population was more than \$100 million and for the Aboriginal and Torres Strait Islander population was \$30 - \$60 million (Table 15).

**Table 15: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number vaccinated General population <sup>a</sup>	991,392	1,043,689	862,705	876,668	887,387	900,565
Number vaccinated Aboriginal and Torres Strait Islander population	292,590	61,885	50,294	51,062	51,942	52,567
Vaccinations General population <sup>a</sup>	████████	████████	████████	████████	████████	████████
Vaccinations Aboriginal and Torres Strait Islander population	████████	████████	████████	████████	████████	████████
<b>Estimated financial implications of 4CMenB</b>						
Cost to NIP General population	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Cost to MBS General population	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Cost to NIP Aboriginal and Torres Strait Islander population	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Cost to MBS Aboriginal and Torres Strait Islander population	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
<b>Net financial implications</b>						
Net cost to NIP/MBS – General population <sup>a</sup>	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Net cost to NIP/MBS Aboriginal and Torres Strait Islander population	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████

Abbreviations: GP = general practitioner; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program NR= not reported.

Note: <sup>a</sup>Did not include the catch-up program for Aboriginal and Torres Strait Islander adolescents aged 16 to 19 years and aged 2 to 14 years in Year 1;

Source: Table 4.6, p. 316; Table 4.7, p. 317; Table 4.8, p. 318; Table 4.9, p. 319; Table 4.14, p.328; Table 4.15, p.328; Table 4.17 and Table 4.18, p. 323 of the resubmission and calculated during the evaluation

6.47 The evaluation considered the main issues regarding the financial estimates that may have underestimated the cost to the NIP were:

- The resubmission did not propose a catch-up program for adolescents, whereas ATAGI recommended an ongoing catch-up program for all adolescents aged 15–19 years.
- The resubmission did not consider the additional administration costs required to provide the second dose for adolescents in a school based program.
- The financial estimates for the General population did not include the catch-up program for Aboriginal and Torres Strait Islander people (under 20 years of age).
- The financial estimates included a one year catch-up program for people with high-risk medical conditions. The ATAGI considered a routine ongoing program is necessary for this population (ATAGI post-submission advice, October 2019).

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended the listing of multicomponent meningococcal group B vaccine (4CMenB, Bexsero®), on the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) (the Determination), for the prevention of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* group B strain in Aboriginal and Torres Strait Islander children. The PBAC noted the cost-effectiveness of the vaccine was highly dependent on the incidence of IMD caused by the group B strain and the incidence was more than 6 times higher in Aboriginal and Torres Strait Islander children under 5 years of age compared with non-Indigenous children. The PBAC considered 4CMenB was cost-effective for the routine vaccination of Aboriginal and Torres Strait Islander infants at the price proposed in the resubmission. The PBAC also recommended implementation of a catch-up program for Aboriginal and Torres Strait Islander children up to 2 years of age. The PBAC considered 4CMenB was likely to be cost-effective in children and adults with medical conditions associated with increased risk of IMD (specifically, people with asplenia and hyposplenia, complement deficiency and those undergoing treatment with eculizumab) and recommended listing on the NIP for routine vaccination of this population. The PBAC did not recommend listing for the general population of infants or for adolescents as 4CMenB was not cost-effective at the price proposed in the resubmission.
- 7.2 The PBAC noted the large number of consumer comments (paragraph 6.2) supporting inclusion of 4CMenB on the National Immunisation Program (NIP) to prevent IMD caused by the group B strain of *Neisseria meningitidis*.
- 7.3 The PBAC noted the resubmission included evidence from four real world evidence (observational) studies to support the clinical claim of superior effectiveness compared to no vaccination. The PBAC considered that although there is a risk of bias with observational studies, the clinical evidence provided in the resubmission was a more appropriate and reliable evidence-base than the immunogenicity studies which formed the basis of the clinical claim in previous submissions.
- 7.4 The pivotal study informing vaccine effectiveness (VE) was the UK PHE Vaccination Program, which provided routine vaccination for 1.29 million infants. The PBAC noted the VE calculated directly from the study (using the screening method) was 58.9% (95% CI: -31.5, 87.1). The PBAC noted vaccine coverage in the study was 92.6% and a total of 29 cases of IMD caused by Men B were reported (25 cases in vaccinated children and 4 cases in unvaccinated children). The PBAC noted the high vaccine coverage and the low number of cases of IMD caused by Men B resulted in the VE calculated using the screening method being imprecise.
- 7.5 The PBAC noted the resubmission proposed an alternative method of calculating VE with the adjusted VE calculated directly from [REDACTED]

██████████. The PBAC considered the adjusted VE proposed by the resubmission was highly dependent on the assumption implicit in the VE calculation that any change in ██████████ ██████████, and considered this assumption to be highly uncertain. The PBAC noted the point estimate for the adjusted VE (██████%) ██████████ to the upper bound of the 95% CI for the VE calculated directly from the study (87.1%) and therefore considered the adjustment likely resulted in VE being overestimated.

7.6 Evidence from three supportive studies, the Quebec Regional Vaccination Program, the Portugal PT-BEST study and the 'South Australia B part of it' were also included in the resubmission. The PBAC noted the following:

- The Portuguese-BEST study reported a VE of ███████% (95%CI: █████, █████). This study was not a population-based study and data was only available as a conference presentation. No information was provided on strategies used to mitigate confounding and other biases.
- The Quebec study reported a VE of 79% (95%CI: -231, 99). This study vaccinated fewer than 60,000 children and adolescents and 5 cases of IMD caused by Men B were reported which resulted in an imprecise estimate of VE.
- The South Australian study did not report VE and was primarily designed to assess the impact of 4CMenB on nasopharyngeal carriage of disease-causing *Neisseria meningitidis* genogroups. The study vaccinated 26,153 adolescents and found that 4CMenB had no impact on nasopharyngeal carriage and hence indicates that vaccination protects the individual vaccinated but not the broader community through herd immunity.

7.7 The PBAC considered the real world evidence provided in the resubmission supported the benefit of vaccinating infants with 4CMenB in the short-term, although noted there is still uncertainty about the size of the benefit and the duration of protection. The PBAC noted that the studies which informed VE were conducted in infants only and in the economic model it was assumed that the VE in adolescents would be the same as in infants. The PBAC noted assumptions regarding waning of effect are based on immunogenicity studies, and while longer term immunogenicity data was provided in the resubmission, considered that the duration of protection afforded by 4CMenB is uncertain.

7.8 The base case incremental cost effectiveness ratio (ICER) as presented in the resubmission for the routine vaccination of infants and adolescents was \$15,000/QALY - \$45,000/QALY in the General population and less than \$15,000/QALY in the Aboriginal and Torres Strait Islander population. The PBAC noted the base case ICERs incorporated a broader perspective than is usually considered by the PBAC (by inclusion of outcomes and costs beyond the patient and the health system), a Quality

Adjustment Factor (QAF) (which is not appropriate in the context of PBAC decision making) and a lower discount rate than recommended in the PBAC Guidelines.

- 7.9 The PBAC considered the use of a QAF was not appropriate in the base case economic evaluation (or in a sensitivity analysis) as it was not relevant to the Australian context. The PBAC noted that the QAF was sourced from the UK analysis for 4CMenB, however unlike in the UK where vaccines are assessed against a fixed ICER threshold, there is no fixed threshold for PBAC decisions and the PBAC accepts varying ICERs to account for factors such as severity or rarity of the disease, equity, clinical need, public health considerations and other relevant factors.
- 7.10 The PBAC noted the cost-effectiveness of 4CMenB was sensitive to the incidence of IMD caused by Men B. Applying the incidence observed in 2001 to 2003 (i.e., the peak incidence, Figure 1) decreased the resubmission base case ICER from \$15,000/QALY - \$45,000/QALY to less than \$15,000/QALY and applying the average incidence observed from 2010 to 2017 (i.e., excluding the peak incidence, Figure 1) increased the ICER to \$105,000/QALY - \$200,000/QALY.
- 7.11 The PBAC noted the cost-effectiveness of 4CMenB was sensitive to the inclusion of the costs and utilities for the eight additional sequelae that were not included in previous submissions. Excluding the additional sequelae increased the resubmission base case ICER from \$15,000/QALY - \$45,000/QALY to \$105,000/QALY - \$200,000/QALY in the General population and from less than \$15,000/QALY to \$45,000/QALY - \$75,000/QALY in the Aboriginal and Torres Strait Islander population. The PBAC considered there was a risk of double counting the disutility for some of the additional sequelae. For example, patients with physical sequelae, such as amputation, may also suffer from the additional psychological and behavioural sequelae that were included, such as anxiety.
- 7.12 The PBAC considered the ICER for the scenario consistent with the PBAC guidelines (General population more than \$200,000/QALY, Aboriginal and Torres Strait Islander population \$105,000/QALY - \$200,000/QALY) generated as part of the evaluation was most relevant for decision-making, although the ICER for the modified PBAC guidelines scenario (General population \$105,000/QALY - \$200,000/QALY, Aboriginal and Torres Strait Islander population \$45,000/QALY - \$75,000/QALY) (incorporating a 3.5% discount rate, long-term caregiving costs, special education costs, family and network utility loss due to sequelae) was also informative. Given the very high ICER, the lack of herd effects, the lack of evidence about the duration of clinical protection, and the lack of any clinical effectiveness data for adolescents, the PBAC considered the proposed price for 4CMenB was not acceptable for the general population of children or for adolescents under either of these scenarios.
- 7.13 The PBAC considered the base case ICER in the resubmission (paragraph 7.8) and the revised base case ICER (paragraph 7.12) were uncertain due to the likely overestimate

of VE (paragraph 7.5), unknown future incidence of IMD due to Men B (paragraph 7.10) and inclusion of additional sequelae (paragraph 7.11).

- 7.14 The PBAC noted the ICER for the scenario consistent with the PBAC guidelines for Aboriginal and Torres Strait Islander children was \$105,000/QALY - \$200,000/QALY and for the modified PBAC guidelines scenario (as defined in paragraph 7.12) was \$15,000/QALY - \$45,000/QALY. The PBAC considered that, in the context of the extreme disparity in disease rates compared to non-Indigenous children (6-fold higher incidence) and relatively small opportunity cost, 4CMenB was of acceptable cost-effectiveness in Aboriginal and Torres Strait Islander children and recommended the inclusion of routine vaccination of infants on the NIP with a catch-up program for children up to 2 years of age. The PBAC noted the lack of any data on clinical effectiveness among adolescents and therefore considered the cost effectiveness of 4CMenB to be unacceptably high and uncertain in Aboriginal and Torres Strait Islander adolescents at the price proposed in the resubmission.
- 7.15 The PBAC considered that 4CMenB was likely to be cost-effective in children and adults with medical conditions associated with increased risk of IMD, and was supportive of a listing for routine vaccination of this population. The PBAC recalled it had recommended funding of Men ACWY in people with asplenia and hyposplenia, complement deficiency and those undergoing treatment with eculizumab due to the high clinical need for vaccination in these populations (published outcomes for the May 2019 PBAC meeting). The PBAC considered it would be appropriate to provide routine vaccination with 4CMenB for the same high-risk populations. The PBAC noted there is some uncertainty regarding the duration of protection provided by 4CMenB and considered this population may require revaccination in 5 to 10 years.
- 7.16 The PBAC considered that, given the high (paragraph 7.12) and uncertain (paragraph 7.13) ICER, the lack of herd protective effects, the lack of data on the duration of clinical protection, and the absence of data on clinical effectiveness for adolescent vaccination, circumstances that could enhance the acceptability of the cost-effectiveness would include arrangements resulting in a reduction in effective price and a sharing of the cost of delivery of an adolescent program for the general population.
- 7.17 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listings.

**Outcome:**

Recommended.

## **8 Recommended listing**

- 8.1 Add new item:

**Essential elements of the requested listing**

Name, restriction, manner of administration, form	Nationally negotiated price	Proprietary name and manufacturer
Multicomponent meningococcal group B vaccine, 1 x 0.5 mL syringe	\$■	Bexsero®, GSK
National Immunisation Program		
<ul style="list-style-type: none"> <li>• Two primary doses at 2 and 4 months and a booster dose at 12 months for Aboriginal and Torres Strait islander infants*</li> <li>• Three primary doses at 2, 4 and 6 months with 8 weeks between doses and a booster at 12 months for Aboriginal and Torres Strait Islander infants with medical conditions<sup>1</sup> known to increase risk of IMD*</li> <li>• For people with specified medical conditions known to increase the risk of IMD2: infants 6 weeks to 5 months at start of vaccine course- three primary doses with 8 weeks between doses and a booster at 12 months; children between 6 and 11 months at start of vaccine course - two primary doses with 8 weeks between doses and a booster at 12 months; over 12 months of age at start of vaccine course - two primary doses with 8 weeks between doses</li> </ul>		

\* With a 3 year catch-up program for children aged under 2 years old

1. As defined by the Australian Immunisation Handbook

2. People with asplenia and hyposplenia, complement deficiency and those undergoing treatment with eculizumab

## 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

GSK welcomes the PBAC recommendation to list the meningococcal B vaccine, Bexsero, on the National Immunisation Program (NIP) for people with specified medical conditions and for Aboriginal and Torres Strait Islander infants. This is a much-needed step towards reducing the burden of meningococcal B disease in two groups of Australians who are at a higher risk for this rare but potentially deadly disease.

However, GSK disagrees with the PBAC decision not to recommend meningococcal B vaccination on the NIP for all Australian infants and adolescents, as requested in our submission.

Significant real-world evidence has been generated since the previous submission which GSK believes addresses most of the key clinical uncertainties upon which the prior three rejections were based. From a clinical and public health perspective, the Australian Technical Advisory Group on Immunisation (ATAGI) considered that inclusion of meningococcal B (MenB) vaccines in the NIP was warranted for the requested populations included in the submission.

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GSK believes the PBAC's current decision-making framework and criteria is prohibitive to obtaining public subsidy for this clinically recommended vaccine in all infants and adolescents for the prevention of a rare and unpredictable life-threatening disease, with devastating impact in children, adolescents and their families. Consequently, GSK cannot see a path forward to enable this vaccine to be widely available on the NIP beyond the current PBAC recommendation.

The Value of Vaccines paper referred to in paragraph 6.25 of the Public Summary Document is available from the GSK Australia website (<https://au.gsk.com/>) and can be found by searching 'value of vaccines'.